HETEROCYCLES, Vol. 71, No. 1, 2007, pp. 87 - 104. © The Japan Institute of Heterocyclic Chemistry
Received, 11th October, 2006, Accepted, 31st October, 2006, Published online, 2nd November, 2006. COM-06-10908

# TRI- AND TETRACYCLIC HETEROAROMATIC SYSTEMS: SYNTHESIS OF NOVEL BENZO-, BENZOTHIENO- AND THIENO-FUSED PYRANO[2,3-*c*]PYRAZOL-4(1*H*)-ONES‡

**Gernot A. Eller,* Andreas W. Haring, Barbara Datterl, Maryam Zwettler, and Wolfgang Holzer***

Department of Drug Synthesis, Faculty of Life Sciences, University of Vienna, Althanstrasse 14, A-1090 Vienna, Austria
E-mail: gernot.eller@univie.ac.at, wolfgang.holzer@univie.ac.at

**Abstract** – A straightforward, two-step synthesis of chromeno[2,3-*c*]pyrazol-4(1*H*)-ones, thieno[2',3':5,6]pyrano[2,3-*c*]pyrazol-4(1*H*)-ones, and [1]benzothieno[2',3':5,6]pyrano[2,3-*c*]pyrazol-4(1*H*)-ones, respectively, is presented. Hence, treatment of 1-substituted or 1,3-disubstituted 2-pyrazolin-5-ones with 2-fluorobenzoyl chloride, 2-chlorobenzoyl chloride, 3-chlorothiophene-2-carbonyl chloride, or 3-chloro-1-benzothiophene-2-carbonyl chloride using calcium hydroxide in refluxing 1,4-dioxane gave the corresponding 4-aroylpyrazol-5-ols, which were successfully cyclized into the fused ring systems (NaH/DMF). The *N*-unsubstituted title compounds were obtained upon treatment of 1-(4-methoxybenzyl) protected congeners with trifluoroacetic acid. Detailed NMR spectroscopic investigations ($^{1}$H, $^{13}$C, $^{15}$N) with the obtained compounds were undertaken.

## INTRODUCTION

With regard to the importance of the xanthone core as a partial structure of numerous biologically active compounds,[1] heterocyclic analogues of this system seem to be of high interest. Thus, a series of tricyclic moieties have been synthesized so far, in which one or both benzene rings of the dibenzo-γ-pyrone system had been replaced with different heteroaromatic rings.[2] Some compounds containing such cores showed interesting biological activities, to the point of the anti-ulcer agent amlexanox (Aphthasol™), which is

‡ Dedicated with best personal wishes to Prof. Christian R. Noe on the occasion of his 60th anniversary.

currently on the market (Figure 1).[3] The $A_2$-subtype specific adenosine receptor antagonist (**A**) – containing a substituted pyrazole system – may serve as another example (Figure 1).[4]

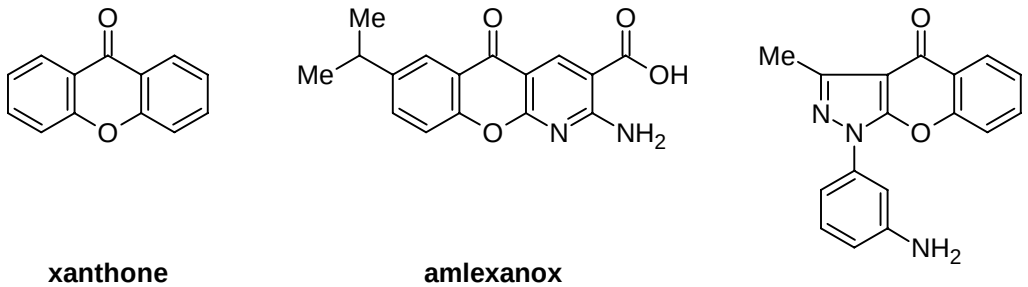
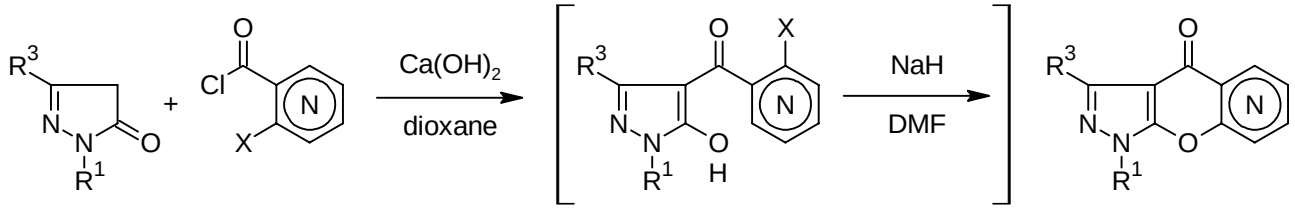



Figure 1

In the course of our investigations on the synthetic versatility of 4-acylpyrazolones, we recently reported an efficient synthesis of all possible pyrido[5,6]pyrano[2,3-*c*]pyrazol-4(1*H*)-ones by the reaction of 1-substituted or 1,3-disubstituted 2-pyrazolin-5-ones with different *o*-halopyridinecarbonyl chlorides under the conditions of the 'Jensen'-reaction (calcium hydroxide, refluxing 1,4-dioxane, Scheme 1).[5] According to this approach, most of the tricyclic target compounds were obtained in one reaction step, as the intermediate 4-acylpyrazolones spontaneously underwent pyrane ring closure under these acylation conditions. Only in the cases where the leaving halogen atom was situated in the less reactive 3-position to the pyridine nitrogen atom, an additional reaction step was necessary. However, transformation of these isolated 4-acylpyrazolones into the corresponding tricyclic compounds was smoothly achieved by treatment with sodium hydride in DMF (Scheme 1).

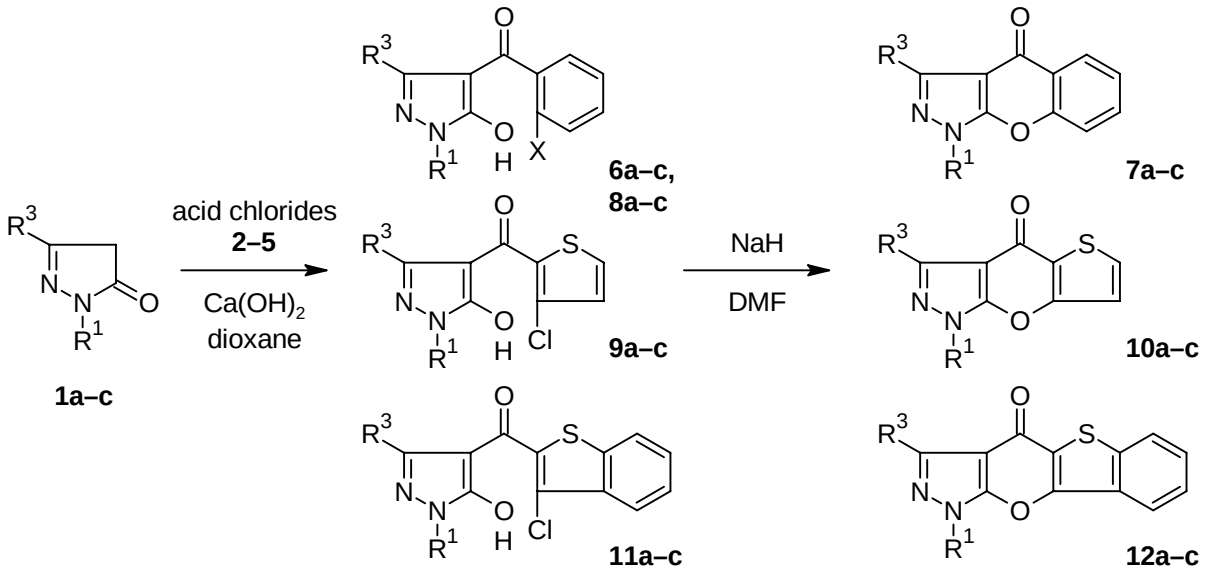



Scheme 1

In the course of our ongoing interest in new heterocyclic scaffolds, we here present the first synthesis of pyrano[2,3-*c*]pyrazol-4(1*H*)-ones with a thieno- (**10a**–**d**) or a [1]benzothieno system (**12a**–**d**) condensed to the pyrane ring, using a similar approach. In addition, also the previously unknown benzo[5,6]-annulated compound (**7c**) is described.

## RESULTS AND DISCUSSION

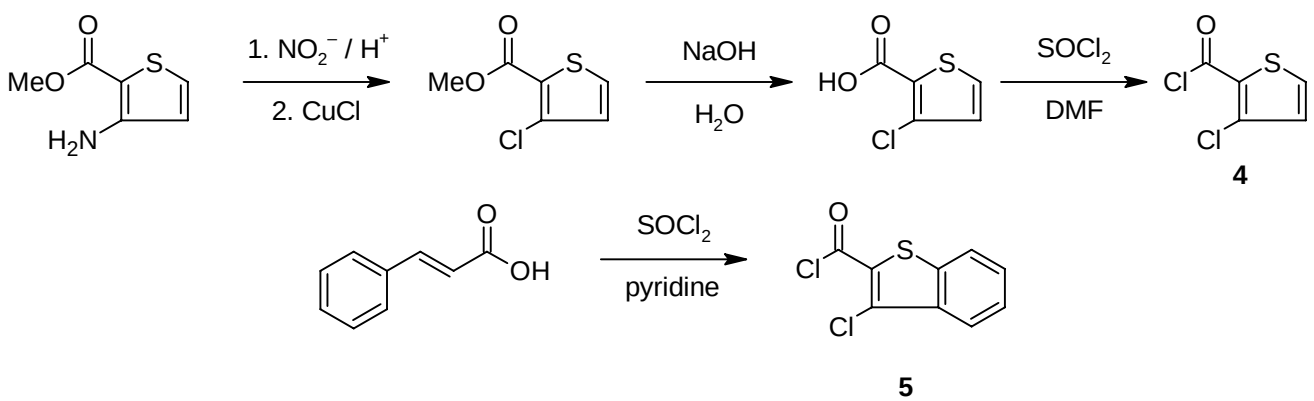
The synthesis of the title compounds (**7**), (**10**), and (**12**) was planned similarly to a two-step method which had been described by Sarenko et al.[2a] for the preparation of compound (**7a**). Thus, 2-pyrazolin-5-ones (**1**) (tautomer to 5-hydroxypyrazoles)[6] were *C*4-acylated with the appropriate carboxylic acid chlorides (**2**–**5**) in the presence of excess calcium hydroxide in boiling 1,4-dioxane ('Jensen'-method)[7] to yield the desired 4-(*o*-haloaroyl)pyrazol-5-ols of type (**6**), (**8**), (**9**), and (**11**), respectively, in good yields (Scheme 2).




**a**: $R^1$ = Ph, $R^3$ = Me; **b**: $R^1$ = Ph, $R^3$ = H; **c**: $R^1$ = *p*-methoxybenzyl, $R^3$ = H; **6**: X = F; **8**: X = Cl

Scheme 2

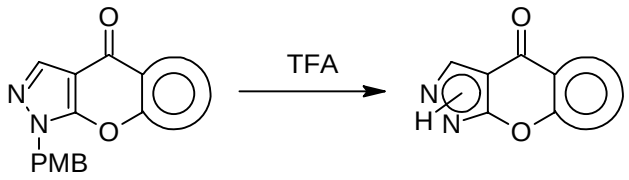
All used starting materials (**1**–**5**) were commercially available and/or were easily prepared in multi-gram quantities according to known procedures. The route to acid chlorides (**4**) and (**5**) is sketched in Scheme 3.




Scheme 3

For the subsequent cyclization reaction – an intramolecular nucleophilic substitution of the aryl halogenide [F in compounds (**6**) or Cl in compounds (**8**), (**9**), and (**11**)] – NaH in refluxing DMF proved to be advantageous to the reaction conditions reported by Sarenko et al.[2a] (aqueous KOH in boiling $H_2O$/DMF).

The synthesis of the unsubstituted title compounds of type (**d**) was easily achieved by treatment of the *N*1 PMB (*p*-methoxybenzyl) protected congeners of type (**c**) with trifluoroacetic acid (TFA) (Scheme 4). This multi-talented group served successfully in protection of hydroxyl functions[8] as well as in azol chemistry.[2b,9] Recently, we described its convenient application in the synthesis of *N*1-unprotected 4-acylpyrazol-5-ols[10] and *N*1-unprotected pyrano[2,3-*c*]pyrazol-4(1*H*)-ones.[11]




**7c, 10c, 12c** **7d, 10d, 12d**

Scheme 4

Detailed NMR spectroscopic analyses for all prepared compounds are reported. Full and unambiguous assignment for all proton, carbon, and nitrogen resonances was achieved by combined application of standard NMR spectral techniques,[12] such as NOE-difference experiments, fully $^1$H-coupled $^{13}$C-NMR spectra, APT, HMQC and HMBC spectra as well as experiments with selective excitation such as 1D-TOCSY,[13] 1D-HETCOR[14] and selective long-range INEPT.[15] The $^{15}$N-NMR spectra were mainly recorded using the gradient selected, sensitivity enhanced HMBC sequence.[16] The obtained data show a high degree of consistency and are summarized in Table 1 ($^1$H-NMR), Table 2 ($^{15}$N-NMR shifts), Table 3 ($^{13}$C-NMR shifts), and Table 4 ($^{13}$C,$^1$H coupling constants).

## EXPERIMENTAL

Melting points were determined on a Reichert–Kofler hot-stage microscope and are uncorrected. Mass spectra were obtained on a Shimadzu QP 1000 instrument (EI, 70 eV) and on a Finnigan MAT 8230 instrument (EI, 70 eV, HRMS). IR spectra were recorded on a Perkin-Elmer FTIR 1605 spectrophotometer or on a Perkin-Elmer FTIR spectrum 1000 spectrometer. Elemental analyses were performed at the Microanalytical Laboratory, University of Vienna. $^1$H- and $^{13}$C-NMR spectra were recorded on a Varian UnityPlus 300 spectrometer at 28 °C (299.95 MHz for $^1$H, 75.43 MHz for $^{13}$C) or on a Bruker Avance 500 spectrometer at 293 K (500.13 MHz for $^1$H, 125.77 MHz for $^{13}$C). The centre of the

Table 1. $^{1}$H-NMR data of **7a**–**d**, **10a**–**d**, and **12a**–**d**

| Compd | Solvent | H of $R^3$ / H-3 | H-5 | H-6 | H-7 | H-8 | H-9 | H of $R^1$ |
|---|---|---|---|---|---|---|---|---|
| **7a** | $CDCl_3$ | 2.69 (Me) | 8.33 | 7.43 | 7.68 | 7.51 | – | Ph: 7.87 (2,6), 7.54 (3,5), 7.38 (4) |
| **7b** | $CDCl_3$ | 8.26 (H-3) | 8.38 | 7.47 | 7.73 | 7.56 | – | Ph: 7.92 (2,6), 7.57 (3,5), 7.43 (4) |
| **7c** | $CDCl_3$ | 8.07 (H-3) | 8.36 | 7.44 | 7.70 | 7.51 | – | Ph: 7.31 (2,6), 6.88 (3,5); 5.39 ($CH_2$), 3.78 (OMe) |
| **7d** | DMSO-$d_6$ | 8.61 (H-3) | 8.15 | 7.43 | 7.80 | 7.63 | – | 13.79 (NH) |
| **10a** | $CDCl_3$ | 2.68 (Me) | – | 7.73[a] | 7.19[a] | – | – | Ph: 7.84 (2,6), 7.53 (3,5), 7.39 (4) |
| **10b** | $CDCl_3$ | 8.24 (H-3) | – | 7.78[a] | 7.24[a] | – | – | Ph: 7.88 (2,6), 7.57 (3,5), 7.44 (4) |
| **10c** | $CDCl_3$ | 8.05 (H-3) | – | 7.72[b] | 7.18[b] | – | – | Ph: 7.29 (2,6), 6.87 (3,5); 5.37 ($CH_2$), 3.78 (OMe) |
| **10d** | DMSO-$d_6$ | 8.56 (H-3) | – | 8.18[c] | 7.42[c] | – | – | 13.78 (NH) |
| **12a** | $CDCl_3$ | 2.69 (Me) | – | 7.86 | 7.55 | 7.51 | 8.01 | Ph: 7.92 (2,6), 7.59 (3,5), 7.43 (4) |
| **12b** | $CDCl_3$ | 8.26 (H-3) | – | 7.90 | 7.54 | 7.52 | 8.05 | Ph: 7.96 (2,6), 7.62 (3,5), 7.47 (4) |
| **12c** | $CDCl_3$ | 8.10 (H-3) | – | 7.91 | 7.59 | 7.55 | 8.06 | Ph: 7.37 (2,6), 6.91 (3,5); 5.48 ($CH_2$), 3.78 (OMe) |
| **12d** | DMSO-$d_6$ | 8.65 (H-3) | – | 8.15 | 7.68 | 7.61 | 8.19 | 13.94 (NH) |

[a] $^{3}J$(H-6,H-7) = 5.3 Hz. [b] $^{3}J$(H-6,H-7) = 5.5 Hz. [c] $^{3}J$(H-6,H-7) = 5.4 Hz.

Table 2. $^{15}$N-NMR Chemical Shifts of **7a**–**d**, **10a**–**d**, and **12a**–**d** (Solvents as in Table 1)

| Compd | N-1 | N-2 | Compd | N-1 | N-2 | Compd | N-1 | N-2 |
|---|---|---|---|---|---|---|---|---|
| **7a** | –193.2 | –96.2 | **10a** | –193.4 | –94.3 | **12a** | –192.9 | –94.0 |
| **7b** | –187.0 | –88.8 | **10b** | –187.3 | –87.4 | **12b** | –187.0 | –87.1 |
| **7c** | –192.4 | –88.1 | **10c** | –192.5 | –86.6 | **12c** | –191.9 | –86.0 |
| **7d** | –178.0[a] | | **10d** | not found | not found | **12d** | not found | not found |

[a] Only one N-signal found.

Table 3. $^{13}$C-NMR Shifts of **7a**–**d**, **10a**–**d**, and **12a**–**d** (Solvents as in Table 1)

| Compd | C-3 | C-3a | C-4 | C-4a | C-5 / C-5a | C-6 | C-7 | C-7a / C-8 | C-8a / C-9 | C-9a | C-9b | C-10a | C of $R^1$ | C of $R^3$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **7a** | 148.1 | 104.9 | 173.5 | 123.3 | 126.8 | 125.2 | 133.7 | 117.6 | 154.5 | 152.9 | – | – | Ph: 137.0 (1), 129.4 (3,5), 127.3 (4), 121.2 (2,6) | 14.1 (Me) |
| **7b** | 136.8 | 106.8 | 172.8 | 123.0 | 127.1 | 125.4 | 134.1 | 117.7 | 154.5 | 152.8 | – | – | Ph: 137.0 (1), 129.5 (3,5), 127.8 (4), 121.5 (2,6) | – |
| **7c** | 135.9 | 105.6 | 172.7 | 123.1 | 127.2 | 125.1 | 133.8 | 117.5 | 154.4 | 153.3 | – | – | Ph: 159.7 (4), 129.4 (2,6), 127.0 (1), 114.3 (3,5); 55.3 (OMe), 51.0 ($CH_2$) | – |
| **7d** | 128.7 | 105.4 | 173.8 | 121.8 | 126.1 | 124.0 | 134.6 | 118.1 | 155.3 | 161.1 | – | – | – | – |
| **10a** | 147.3 | 105.6 | 170.1 | 124.5 | – | 132.1 | 117.3 | 155.5 | 153.7 | – | – | – | Ph: 137.0 (1), 129.4 (3,5), 127.5 (4), 121.3 (2,6) | 14.0 (Me) |
| **10b** | 135.9 | 107.6 | 169.2 | 124.2 | – | 132.7 | 117.3 | 155.6 | 153.5 | – | – | – | Ph: 136.9 (1), 129.5 (3,5), 127.9 (4), 121.5 (2,6) | – |
| **10c** | 134.9 | 106.4 | 169.2 | 124.1 | – | 132.2 | 117.2 | 155.4 | 154.0 | – | – | – | Ph: 159.7 (4), 129.3 (2,6), 126.8 (1), 114.3 (3,5); 55.3 (OMe), 51.3 ($CH_2$) | – |
| **10d** | 127.7[a] | 105.8 | 170.2 | 121.3 | – | 134.0 | 118.5 | 157.5 | 162.0[a] | – | – | – | – | – |
| **12a** | 147.2 | 106.4 | 170.7 | 123.8 | 139.3 | 123.9 | 128.6 | 125.3 | 121.5 | 128.3 | 149.7 | 153.3 | Ph: 137.0 (1), 129.5 (3,5), 127.5 (4), 121.1 (2,6) | 14.1 (Me) |
| **12b** | 135.9 | 108.4 | 169.8 | 123.7 | 139.4 | 124.0 | 128.8 | 125.4 | 121.5 | 128.2 | 149.8 | 153.2 | Ph: 137.1 (1), 129.6 (3,5), 128.0 (4), 121.3 (2,6) | – |
| **12c** | 134.8 | 107.2 | 170.0 | 123.5 | 139.4 | 124.0 | 128.7 | 125.3 | 121.5 | 128.4 | 149.7 | 153.8 | Ph: 159.8 (4), 129.6 (2,6), 126.6 (1), 114.4 (3,5); 55.3 (OMe), 51.8 ($CH_2$) | – |
| **12d** | 127.8 | 106.6 | 171.0 | 120.5 | 138.3 | 124.2 | 129.2 | 125.7 | 122.1 | 128.6 | 151.6 | 161.9 | – | – |

[a] Broad signal.

signal was used as an internal standard which was related to TMS with δ = 7.26 ppm ($^1$H in $CDCl_3$), δ = 2.49 ppm ($^1$H in DMSO-$d_6$), δ = 77.0 ppm ($^{13}$C in $CDCl_3$), and δ = 39.5 ppm ($^{13}$C in DMSO-$d_6$). $^{15}$N-NMR spectra were obtained on a Bruker Avance 500 instrument with a 'directly' detecting broadband observe probe and were referenced against external nitromethane (coaxial capillary). The starting materials were commercially available and/or prepared similarly to literature procedures: (**1b**),[17] (**1c**).[10] Yields of products were not optimized.

## Preparation of the acid chlorides

### Methyl 3-chlorothiophene-2-carboxylate[18]

This compound was prepared from methyl 3-aminothiophene-2-carboxylate (4.72 g, 30 mmol) similarly to a known procedure.[18] Yield after flash chromatography ($CH_2Cl_2$–hexanes, 1:1): 3.71 g (70%); colourless, slowly crystallizing oil. Mp 33–34 °C, (lit.,[18] mp 34–35 °C). $^1$H-NMR (300 MHz, $CDCl_3$): δ (ppm) 7.47 (d, $^3J$(H-5,H-4) = 5.3 Hz, 1H, H-5), 7.02 (d, $^3J$(H-4,H-5) = 5.3 Hz, 1H, H-4), 3.90 (s, 3H, $CH_3$). $^1$H-NMR (300 MHz, DMSO-$d_6$): δ (ppm) 7.98 (d, $^3J$(H-5,H-4) = 5.3 Hz, 1H, H-5), 7.23 (d, $^3J$(H-4,H-5) = 5.3 Hz, 1H, H-4), 3.81 (s, 3H, $CH_3$); $^{13}$C-NMR (75 MHz, $CDCl_3$): δ (ppm) 161.0 (CO), 131.6 (C-3), 130.4 (CH), 130.1 (CH), 125.5 (C-2), 52.1 ($CH_3$); $^{13}$C-NMR (75 MHz, DMSO-$d_6$): δ (ppm) 160.2 (CO), 132.8 (C-5, $^1J$ = 192.0 Hz), 130.25 (C-3), 130.18 (C-4, $^1J$ = 177.1 Hz), 124.8 (C-2), 52.3 ($CH_3$, $^1J$ = 148.0 Hz); MS (*m/z*, %): 178 ($M^+$, 9), 176 ($M^+$, 23), 147 (37), 145 (100), 82 (19), 81 (14), 73 (23), 45 (25).

### 3-Chlorothiophene-2-carboxylic acid[18]

This compound was prepared from methyl 3-chlorothiophene-2-carboxylate (2.65 g, 15 mmol) similarly to a known procedure.[18] Yield: 2.34 g (96%); colourless crystals. Mp 185–186, (lit.,[18] mp 187–188 °C). $^1$H-NMR (300 MHz, DMSO-$d_6$): δ (ppm) 13.37 (s, 1H, OH), 7.92 (d, $^3J$(H-5,H-4) = 5.3 Hz, 1H, H-5), 7.19 (d, $^3J$(H-4,H-5) = 5.3 Hz, 1H, H-4); $^{13}$C-NMR (75 MHz, DMSO-$d_6$): δ (ppm) 161.2 (CO), 132.0 (C-5, $^1J$ = 191.6 Hz, $^2J$(C-5,H-4) = 6.1 Hz), 130.1 (C-4, $^1J$ = 176.5 Hz, $^2J$(C-4,H-5) = 4.5 Hz), 129.4 (C-3, $^2J$(C-3,H-4) = 2.2 Hz, $^3J$(C-3,H-5) = 12.6 Hz), 126.6 (C-2, $^3J$(C-2,H-4) = 7.1 Hz, $^3J$(C-2,H-5) = 4.7 Hz); MS (*m/z*, %): 164 ($M^+$, 26), 162 ($M^+$, 70), 147 (43), 145 (100).

### 3-Chlorothiophene-2-carbonyl chloride (4)[19]

Similarly to a known procedure,[19] a suspension of 3-chlorothiophene-2-carboxylic acid (488 mg, 3 mmol) in toluene (30 mL), 3 droplets of DMF, and excess $SOCl_2$ (10 mL) was refluxed for 3 h. Then the solvent and excess $SOCl_2$ were removed under reduced pressure, additional toluene (20 mL) was added, and the solvent was removed again under reduced pressure. The remaining acid chloride (**4**) was used immediately and without further purification in the next reaction step.

Table 4. Selected $^{13}C,^{1}H$ Spin-Coupling Constants (Hz) of **7a**–**d**, **10a**–**d**, and **12a**–**d** (Solvents as in Table 1)

| Compd | *J* of C-3 | *J* of C-3a | other couplings |
|---|---|---|---|
| **7a** | $^{2}J$(3-Me) = 7.2 | $^{3}J$(3-Me) = 2.7 | $^{1}J$(3-Me) = 129.2, $^{3}J$(C-4,H-5) = 4.1, $^{4}J$(C-4,H-8) = 1.4 |
| **7b** | $^{1}J$ = 194.3 | $^{2}J$(H-3) = 10.1 | $^{3}J$(C-9a,H-3) = 4.9, $^{3}J$(C-4,H-5) = 4.1, $^{4}J$(C-4,H-8) = 1.4 |
| **7c** | $^{1}J$ = 193.9 | $^{2}J$(H-3) = 10.3 | $^{1}J$(OMe) = 143.9, $^{1}J(CH_2)$ = 140.8, $^{3}J(CH_2,H\text{-}2,6)$ = 4.6 |
| **7d** | [a] | $^{2}J$(H-3) = 8.6 | – |
| **10a** | $^{2}J$(3-Me) = 7.2 | $^{3}J$(3-Me) = 2.7 | $^{1}J$(C-6) = 188.2, $^{1}J$ (C-7) = 174.8, $^{1}J$(3-Me) = 129.3, $^{2}J$(C-6,H-7) = 5.0, $^{2}J$(C-7,H-6) = 4.4, $^{3}J$(C-7a,H-6) = 13.0, $^{3}J$(C-4a,H-7) = 5.7, $^{3}J$(C-4a,H-6) = 4.5 |
| **10b** | $^{1}J$ = 194.7 | $^{2}J$(H-3) = 10.2 | $^{1}J$(C-6) = 188.4, $^{1}J$(C-7) = 175.1, $^{2}J$(C-6,H-7) = 5.0, $^{2}J$(C-7,H-6) = 4.4, $^{2}J$(C-7a,H-7) = 1.0, $^{3}J$(C-7a,H-6) = 13.1, $^{3}J$(C-4a,H-7) = 5.7, $^{3}J$(C-8a,H-3) = 4.8, $^{3}J$(C-4a,H-6) = 4.6 |
| **10c** | $^{1}J$ = 194.2 | $^{2}J$(H-3) = 10.2 | $^{1}J$(C-6) = 188.2, $^{1}J$(C-7) = 174.8, $^{1}J$(OMe) = 144.0, $^{1}J(CH_2)$ = 140.9, $^{2}J$(C-6,H-7) = 5.0, $^{2}J$(C-7,H-6) = 4.4, $^{2}J$(C-7a,H-7) = 1.1, $^{3}J$(C-7a,H-6) = 13.0, $^{3}J$(C-4a,H-7) = 5.7, $^{3}J$(C-8a,H-3) = 4.8, $^{3}J$(C-4a,H-6) = 4.6, $^{3}J(C\text{-}8a,CH_2)$ = 2.7 |
| **10d** | $^{1}J$ = 195.3 | $^{2}J$(H-3) = 8.2 | $^{1}J$(C-6) = 191.5, $^{1}J$(C-7) = 175.8, $^{2}J$(C-6,H-7) = 5.8, $^{2}J$(C-7,H-6) = 4.7, $^{2}J$(C-7a,H-7) = 1.0, $^{3}J$(C-7a,H-6) = 12.9, $^{3}J$(C-4a,H-7) = 5.7, $^{3}J$(C-4a,H-6) = 4.4 |
| **12a** | $^{2}J$(3-Me) = 7.1 | $^{3}J$(3-Me) = 2.7 | $^{1}J$(3-Me) = 129.4, $^{3}J$(C-9b,H-9) = 3.3 |
| **12b** | $^{1}J$ = 195.0 | $^{2}J$(H-3) = 10.1 | $^{3}J$(C-10a,H-3) = 5.0, $^{3}J$(C-9b,H-9) = 3.2 |
| **12c** | $^{1}J$ = 194.4 | $^{2}J$(H-3) = 10.2 | $^{1}J$(OMe) = 144.0, $^{1}J(CH_2)$ = 140.7, $^{3}J$(C-10a,H-3) = 5.2, $^{3}J(CH_2,H\text{-}2,6)$ = 4.4, $^{3}J(C\text{-}10a,CH_2)$ = 2.5 |
| **12d** | [a] | $^{2}J$(H-3) = 8.5 | – |

[a] Not unambiguously assigned or not found.

**3-Chloro-1-benzothiophene-2-carbonyl chloride (5)**[20]

Similarly to a known procedure,[20] a suspension of *trans*-cinnamic acid (29.63, 0.20 mol), chlorobenzene (150 mL), and $SOCl_2$ (119.0 g, 1 mol) was stirred at room temperature for 30 min. Then, pyridine (1.58 g,

0.02 mol) was carefully added and the reaction mixture was refluxed for 72 h. The solvent and excess $SOCl_2$ were distilled off and the resulting residue was suspended in hot cyclohexane (400 mL) and immediately filtered. Upon staying at room temperature overnight, the title compound crystallized as yellowish needles. Yield: 21.99 g (48%). Mp 113–114, (lit.,[20] mp 112–114 °C). $^1$H-NMR (300 MHz, $CDCl_3$): δ (ppm) 7.99 (m, 1H, H-4), 7.84 (m, 1H, H-7), 7.62 (m, 1H, H-6), 7.54 (m, 1H, H-5); $^{13}$C-NMR (75 MHz, $CDCl_3$): δ (ppm) 158.2 (CO), 140.4 (C-7a), 137.1 (C-3a), 130.6 (C-3), 129.7 (C-6), 129.6 (C-2), 126.2 (C-5), 124.7 (C-4), 122.8 (C-7).

**Acylations of Pyrazolones (1): General Procedure for the Synthesis of 6a–c, 8a–c, 9a–c, and 11a–c.** Under anhydrous conditions, to a suspension of pyrazolone (**1a**–**c**) and $Ca(OH)_2$ (2 equiv) in dry 1,4-dioxane (2 mL per mmol of pyrazolone) a solution/suspension of the corresponding acid chloride (**2**–**5**) (1 equiv) in dry 1,4-dioxane (2 mL per mmol) was added. The reaction mixture was heated at reflux for 3 h under stirring. After cooling to room temperature, the mixture was treated with 2 N HCl (4 mL per mmol), stirred for 15 min, and poured into $H_2O$ (10 mL per mmol). After 30 min, the solid products were filtered off, washed with $H_2O$, and recrystallized. The oily compounds (**6c**) and (**8c**) were isolated by extraction (3 times) of the aqueous reaction mixture with $CH_2Cl_2$, washing the combined organic layers subsequently with saturated $NaHCO_3$ solution and water, drying ($Na_2SO_4$) and evaporation of the solvent under reduced pressure. The obtained residues were used without further purification in the next reaction step.

**(2-Fluorophenyl)(5-hydroxy-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)methanone (6a)**

Starting from pyrazolone (**1a**) (871 mg, 5 mmol) and 2-fluorobenzoyl chloride (**2**) (793 mg, 5 mmol) 985 mg (67%) of compound (**6a**) were obtained as colourless crystals. Mp 113–117 °C (aqueous EtOH). $^1$H-NMR (500 MHz, DMSO-$d_6$): δ (ppm) 7.67 (m, 2H, NPh H-2,6), 7.51 (m, 1H, Ph H-4), 7.5–5.5 (br s, 1H, OH), 7.44 (m, 2H, NPh H-3,5), 7.42 (m, 1H, Ph H-6), 7.27 (m, 1H, NPh H-4), 7.25 (m, 1H, Ph H-5), 7.24 (m, 1H, Ph H-3), 2.21 (br s, 3H, Me); $^{13}$C-NMR (125 MHz, DMSO-$d_6$): δ (ppm) 185.2 (CO), 159.0 (Ph C-2, $^1J$(C-2,F) = 247.4 Hz), 158.4 (C-5), 150.1 (C-3), 136.8 (NPh C-1), 131.9 (Ph C-4, $^3J$(C-4,F) = 7.9 Hz), 129.4 (Ph C-6, $^3J$(C-6,F) = 3.1 Hz), 129.1 (Ph C-1, $^2J$(C-2,F) = 16.1 Hz), 129.0 (NPh C-3,5), 126.0 (NPh C-4), 124.3 (Ph C-5, $^4J$(C-5,F) = 2.7 Hz), 120.9 (NPh C-2,6), 115.6 (Ph C-3, $^2J$(C-3,F) = 21.6 Hz), 105.0 (C-4), 14.1 (Me); IR (KBr): ν ($cm^{-1}$) 1624; MS (*m/z*, %): 297 ($M^+$ + 1, 20), 296 ($M^+$, 100), 295 ($M^+$ – 1, 25), 201 (15), 200 (53), 123 (59), 95 (20), 91 (24), 77 (17). *Anal*. Calcd for $C_{17}H_{13}N_2O_2F \cdot 0.25\ H_2O$: C, 67.88; H, 4.52; N, 9.31. Found: C, 67.76; H, 4.39; N, 9.25.

**(2-Fluorophenyl)(5-hydroxy-1-phenyl-1*H*-pyrazol-4-yl)methanone (6b)**

Starting from pyrazolone (**1b**) (801 mg, 5 mmol) and 2-fluorobenzoyl chloride (**2**) (793 mg, 5 mmol) 1.10 g (78%) of compound (**6b**) were obtained as colourless crystals. Mp 151 °C (aqueous EtOH). $^1$H-NMR (500 MHz, $CDCl_3$): δ (ppm) 10.99 (s, 1H, OH), 7.88 (m, 2H, NPh H-2,6), 7.80 (d, *J*(H-3,F) = 3.5 Hz),[21] 7.73 (m, 1H, Ph H-6), 7.57 (m, 1H, Ph H-4), 7.49 (m, 2H, NPh H-3,5), 7.34 (m, 1H, NPh H-4), 7.31 (m, 1H, Ph H-5), 7.23 (m, 1H, Ph H-3); $^{13}$C-NMR (125 MHz, $CDCl_3$): δ (ppm) 186.6 (CO, $^3J$(CO,F) = 4.3 Hz), 159.7 (C-5, $^3J$(C-5,H-3) = 4.6 Hz), 159.7 (Ph C-2, $^1J$(C-2,F) = 254.2 Hz), 140.0 (C-3, $^1J$ = 192.0 Hz, *J*(C-3,F) = 9.7 Hz),[22] 137.2 (NPh C-1), 133.9 (Ph C-4, $^3J$(C-4,F) = 8.7 Hz), 130.3 (Ph C-6, $^3J$(C-6,F) = 2.6 Hz), 129.2 (NPh C-3,5), 127.1 (NPh C-4), 125.4 (Ph C-1, $^2J$(C-1,F) = 13.8 Hz), 124.6 (Ph C-5, $^4J$(C-5,F) = 3.5 Hz), 121.1 (NPh C-2,6), 116.7 (Ph C-3, $^2J$(C-3,F) = 22.2 Hz), 104.8 (C-4, $^2J$(C-4,H-3) = 10.5 Hz, $^4J$(C-4,F) = 1.0 Hz); $^{15}$N-NMR (50 MHz, $CDCl_3$): δ (ppm) –97.1 (N-2), –185.8 (N-1); IR (KBr): ν ($cm^{-1}$) 1611; MS (*m/z*, %): 283 ($M^+$ + 1, 19), 282 ($M^+$, 99), 187 (24), 186 (71), 123 (100), 95 (32), 77 (37). *Anal*. Calcd for $C_{16}H_{11}N_2O_2F$: C, 68.08; H, 3.93; N, 9.92. Found: C, 67.83; H, 4.05; N, 9.76.

**(2-Fluorophenyl)[5-hydroxy-1-(4-methoxybenzyl)-1*H*-pyrazol-4-yl]methanone (6c)**

Starting from pyrazolone (**1c**) (1.02 g, 5 mmol) and 2-fluorobenzoyl chloride (**2**) (793 mg, 5 mmol) 1.28 g (79%) of compound (**6c**) were obtained as an oil. $^1$H-NMR (500 MHz, $CDCl_3$): δ (ppm) 9.85 (br s, 1H, OH), 7.65 (m, 1H, Ph H-6), 7.61 (d, *J*(H-3,F) = 3.2 Hz, H-3),[21] 7.52 (m, 1H, Ph H-4), 7.31 (m, 2H, NBn H-2,6), 7.25 (m, 1H, Ph H-5), 7.18 (m, 1H, Ph H-3), 6.87 (m, 2H, NBn H-3,5), 5.12 (s, 2H, $CH_2$), 3.78 (s, 3H, OMe); $^{13}$C-NMR (125 MHz, $CDCl_3$): δ (ppm) 187.1 (CO), 159.6 (Ph C-2, $^1J$(C-2,F) = 254.2 Hz), 159.5 (NBn C-4), 158.7 (C-5), 139.4 (C-3, *J*(C-3,F) = 8.5 Hz),[22] 133.6 (Ph C-4, $^3J$(C-4,F) = 8.6 Hz), 130.2 (Ph C-6, $^3J$(C-6,F) = 2.8 Hz), 129.6 (NBn C-2,6), 127.4 (NBn C-1), 125.8 (Ph C-1, $^2J$(C-1,F) = 13.8 Hz), 124.4 (Ph C-5, $^4J$(C-5,F) = 3.6 Hz), 116.6 (Ph C-3, $^2J$(C-3,F) = 22.0 Hz), 114.2 (NBn C-3,5), 103.9 (C-4, $^4J$(C-4,F) = 0.8 Hz), 55.3 (OMe), 49.7 ($CH_2$).

**(2-Chlorophenyl)(5-hydroxy-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)methanone (8a)**

Starting from pyrazolone (**1a**) (871 mg, 5 mmol) and 2-chlorobenzoyl chloride (**3**) (875 mg, 5 mmol) 1.25 g (80%) of compound (**8a**) were obtained as colourless crystals. Mp 148–150 °C (aqueous EtOH), (lit.,[2a] mp 150–152 °C). $^1$H-NMR (300 MHz, $CDCl_3$): δ (ppm) 9.52 (s, 1H, OH), 7.86 (m, 2H, NPh H-2,6), 7.50 (m, 1H, Ph H-3), 7.47 (m, 2H, NPh H-3,5), 7.45 (m, 1H, Ph H-4), 7.40 (m, 1H, Ph H-5), 7.36 (m, 1H, Ph H-6), 7.32 (m, 1H, NPh H-4), 1.85 (Me); $^{13}$C-NMR (75 MHz, $CDCl_3$): δ (ppm) 190.7 (CO, $^3J$(CO, H-6) = 3.8 Hz), 159.9 (C-5), 148.6 (C-3, $^2J$(C-3,Me) = 6.9 Hz), 137.7 (Ph C-1), 137.0 (NPh C-1), 131.3 (Ph C-4), 130.4 (Ph C-2), 130.0 (Ph C-3), 129.1 (NPh C-3,5), 127.8 (Ph C-6), 127.0 (Ph C-5), 126.9 (NPh C-4), 120.9 (NPh C-2,6), 104.4 (C-4, $^3J$(C-4,Me) = 2.6 Hz), 13.7 (Me, $^1J$ = 128.9 Hz); $^{15}$N-NMR (50 MHz, $CDCl_3$): δ (ppm) –101.7 (N-2), –190.3 (N-1); IR (KBr): ν ($cm^{-1}$) 1631; MS (*m/z*, %): 314 ($M^+$, 13), 312

($M^+$, 37), 278 (20), 277 (100), 200 (16), 139 (37), 111 (18), 77 (36).

**(2-Chlorophenyl)(5-hydroxy-1-phenyl-1*H*-pyrazol-4-yl)methanone (8b)**

Starting from pyrazolone (**1b**) (801 mg, 5 mmol) and 2-chlorobenzoyl chloride (**3**) (875 mg, 5 mmol) 1.12 g (75%) of compound (**8b**). Mp 99 °C (diisopropyl ether), 101–102 °C (aqueous EtOH). $^1$H-NMR (500 MHz, $CDCl_3$): δ (ppm) 10.17 (s, 1H, OH), 7.87 (m, 2H, NPh H-2,6), 7.60 (s, 1H, H-3), 7.54 (m, 1H, Ph H-6), 7.52 (m, 1H, Ph H-3), 7.49 (m, 2H, NPh H-3,5), 7.47 (m, 1H, Ph H-4), 7.40 (m, 1H, Ph H-5), 7.35 (m, 1H, NPh H-4); $^1$H-NMR (300 MHz, DMSO-$d_6$): δ (ppm) 8.13 (s, 1H, OH), 7.71 (m, 2H, NPh H-2,6), 7.56 (m, 1H, Ph H-3), 7.51 (s, 1H, H-3), 7.51 (m, 1H, Ph H-4), 7.51 (m, 1H, Ph H-6), 7.50 (m, 2H, NPh H-3,5), 7.45 (m, 1H, Ph H-5), 7.36 (m, 1H, NPh H-4); $^{13}$C-NMR (125 MHz, $CDCl_3$): δ (ppm) 190.1 (CO), 158.9 (C-5, $^3J$(C-5,H-3) = 4.7 Hz), 140.2 (C-3, $^1J$ = 191.2 Hz), 137.1 (NPh C-1), 136.5 (Ph C-1), 132.0 (Ph C-4), 131.3 (Ph C-2), 130.8 (Ph C-3), 129.3 (Ph C-6), 129.2 (NPh C-3,5), 127.3 (NPh C-4), 126.9 (Ph C-5), 121.2 (NPh C-2,6), 104.7 (C-4, $^2J$(C-4,H-3) = 10.5 Hz); $^{13}$C-NMR (75 MHz, DMSO-$d_6$): δ (ppm) 186.5 (CO), 155.4 (C-5, $^3J$(C-5,H-3) = 4.6 Hz), 141.6 (C-3, $^1J$ = 189.2 Hz), 138.9 (Ph C-1), 137.2 (NPh C-1), 131.2 (Ph C-4), 129.9 (Ph C-3), 129.5 (Ph C-2), 129.0 (NPh C-3,5), 128.7 (Ph C-6), 127.2 (Ph C-5), 127.0 (NPh C-4), 122.2 (NPh C-2,6), 105.6 (C-4, $^2J$(C-4,H-3) = 9.7 Hz); $^{15}$N-NMR (50 MHz, $CDCl_3$): δ (ppm) –97.3 (N-2), –184.9 (N-1); IR (KBr): ν ($cm^{-1}$) 1616; MS (*m/z*, %): 300 ($M^+$, 13), 298 ($M^+$, 36), 263 (100), 139 (49), 111 (22), 77 (25). *Anal*. Calcd for $C_{16}H_{11}N_2O_2Cl$: C, 64.33; H, 3.71; N, 9.38. Found: C, 63.94; H, 3.91; N, 9.26.

**(2-Chlorophenyl)[5-hydroxy-1-(4-methoxybenzyl)-1*H*-pyrazol-4-yl]methanone (8c)**

Starting from pyrazolone (**1c**) (1.02 g, 5 mmol) and 2-chlorobenzoyl chloride (**3**) (875 mg, 5 mmol) 857 mg (50%) of compound (**8c**) were obtained as an oil. $^1$H-NMR (300 MHz, $CDCl_3$): δ (ppm) 9.42 (s, 1H, OH), 7.47 (m, 1H, Ph H-3), 7.46 (m, 1H, Ph H-4), 7.45 (m, 1H, Ph H-6), 7.43 (s, 1H, H-3), 7.36 (m, 1H, Ph H-5), 7.32 (m, 2H, NBn H-2,6), 6.89 (m, 2H, NBn H-3,5), 5.13 (s, 2H, $CH_2$), 3.79 (s, 3H, OMe); $^{13}$C-NMR (75 MHz, $CDCl_3$): δ (ppm) 190.1 (CO), 159.6 (NBn C-4), 158.2 (C-5, $^3J$(C-5,H-3) = 4.7 Hz, $^3J$(C-5,$CH_2$) = 2.4 Hz), 139.6 (C-3, $^1J$ = 190.7 Hz), 136.9 (Ph C-1), 133.1 (Ph C-4), 131.2 (Ph C-2), 130.7 (Ph C-3), 129.7 (NBn C-2,6), 129.2 (Ph C-6), 127.3 (NBn C-1), 126.8 (Ph C-5), 114.2 (NBn C-3,5), 103.9 (C-4, $^2J$(C-4,H-3) = 10.4 Hz), 55.3 (OMe, $^1J$ = 143.9 Hz), 49.9 ($CH_2$, $^1J$ = 140.6 Hz, $^3J$($CH_2$,H-2,6) = 4.5 Hz). HRMS Calcd for $C_{18}H_{15}N_2O_3Cl$: 342.0771. Found: 342.0776.

**(3-Chloro-2-thienyl)(5-hydroxy-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)methanone (9a)**

Starting from pyrazolone (**1a**) (523 mg, 3 mmol) and 3-chlorothiophene-2-carbonyl chloride (**4**) (543 mg, 3 mmol) 552 mg (58%) of compound (**9a**) were obtained. Mp 143–147 °C (aqueous EtOH). $^1$H-NMR

(300 MHz, $CDCl_3$): δ (ppm) 9.92 (br s, 1H, OH), 7.85 (m, 2H, Ph H-2,6), 7.52 (d, $^3J$(H-5,H-4) = 5.1 Hz, 1H, thiophene H-5), 7.47 (m, 2H, Ph H-3,5), 7.32 (m, 2H, Ph H-4), 7.03 (d, $^3J$(H-4,H-5) = 5.1 Hz, 1H, thiophene H-4), 2.17 (s, 3H, Me); $^{13}$C-NMR (75 MHz, $CDCl_3$): δ (ppm) 183.4 (CO), 160.0 (C-5), 148.5 (C-3, $^2J$(C-3,Me) = 6.8 Hz), 137.0 (Ph C-1), 132.5 (thiophene C-2, $^3J$(C-2,H-4) = 7.3 Hz, $^3J$(C-2,H-5) = 4.4 Hz), 129.1 (Ph C-3,5), 128.6 (thiophene C-4, $^1J$ = 175.8 Hz, $^2J$(C-4,H-5) = 4.4 Hz), 128.2 (thiophene C-5, $^1J$ = 189.3 Hz, $^2J$(C-5,H-4) = 6.4 Hz), 127.0 (Ph C-4), 126.1 (thiophene C-3, $^2J$(C-3,H-4) = 2.2 Hz, $^3J$(C-3,H-5) = 13.1 Hz), 105.2 (C-4, $^3J$(C-4,Me) = 2.6 Hz), 14.0 (Me, $^1J$ = 128.9 Hz); $^{15}$N-NMR (50 MHz, $CDCl_3$): δ (ppm) –100.9 (N-2), –190.3 (N-1); IR (KBr): ν ($cm^{-1}$) 1613; MS (*m/z*, %): 320 ($M^+$, 3), 318 ($M^+$, 8), 283 (16), 200 (100), 91 (53). *Anal*. Calcd for $C_{15}H_{11}N_2O_2ClS$: C, 56.62; H, 3.48; N, 8.79. Found: C, 56.39; H, 3.65; N, 8.64.

**(3-Chloro-2-thienyl)(5-hydroxy-1-phenyl-1*H*-pyrazol-4-yl)methanone (9b)**

Starting from pyrazolone (**1b**) (481 mg, 3 mmol) and 3-chlorothiophene-2-carbonyl chloride (**4**) (543 mg, 3 mmol) 481 mg (53%) of compound (**9b**) were obtained. Mp 138–139 °C (aqueous EtOH). $^1$H-NMR (300 MHz, $CDCl_3$): δ (ppm) 10.33 (br s, 1H, OH), 8.11 (s, 1H, H-3), 7.87 (m, 2H, Ph H-2,6), 7.61 (d, $^3J$(H-5,H-4) = 5.1 Hz, 1H, thiophene H-5), 7.49 (m, 2H, Ph H-3,5), 7.35 (m, 1H, Ph H-4), 7.12 (d, $^3J$(H-4,H-5) = 5.1 Hz, 1H, thiophene H-4); $^{13}$C-NMR (75 MHz, $CDCl_3$): δ (ppm) 180.6 (CO), 159.8 (C-5, $^3J$(C-5,H-3) = 4.6 Hz), 139.5 (C-3, $^1J$ = 191.2 Hz), 137.1 (Ph C-1), 131.8 (thiophene C-2, $^3J$(C-2,H-4) = 7.3 Hz, $^3J$(C-2,H-5) = 4.3 Hz), 130.6 (thiophene C-4, $^1J$ = 176.1 Hz, $^2J$(C-4,H-5) = 4.1 Hz), 130.3 (thiophene C-5, $^1J$ = 189.4 Hz, $^2J$(C-5,H-4) = 6.2 Hz), 129.9 (thiophene C-3, $^2J$(C-3,H-4) = 2.2 Hz, $^3J$(C-3,H-5) = 12.4 Hz), 129.2 (Ph C-3,5), 127.3 (Ph C-4), 103.5 (C-4, $^2J$(C-4,H-3) = 10.9 Hz); $^{15}$N-NMR (50 MHz, $CDCl_3$): δ (ppm) –98.3 (N-2), –185.4 (N-1); IR (KBr): ν ($cm^{-1}$) 1596; MS (*m/z*, %): 306 ($M^+$, 8), 304 ($M^+$, 19), 269 (37), 186 (100), 147 (17), 145 (52), 91 (39), 77 (55). *Anal.* Calcd for $C_{14}H_9N_2O_2ClS$: C, 55.18; H, 2.98; N, 9.19. Found: C, 54.93; H, 3.03; N, 9.05.

**(3-Chloro-2-thienyl)[5-hydroxy-1-(4-methoxybenzyl)-1*H*-pyrazol-4-yl]methanone (9c)**

Starting from pyrazolone (**1c**) (613 mg, 3 mmol) and 3-chlorothiophene-2-carbonyl chloride (**4**) (543 mg, 3 mmol) 481 mg (52%) of compound (**9c**) were obtained. Mp 132–133 °C (aqueous EtOH). $^1$H-NMR (300 MHz, $CDCl_3$): δ (ppm) 9.32 (br s, 1H, OH), 7.91 (s, 1H, H-3), 7.55 (d, $^3J$(H-5,H-4) = 5.2 Hz, 1H, thiophene H-5), 7.30 (m, 2H, Ph H-2,6), 7.08 (d, $^3J$(H-4,H-5) = 5.2 Hz, 1H, thiophene H-4), 6.88 (m, 2H, Ph H-3,5), 5.11 (s, 2H, $CH_2$), 3.79 (s, 3H, OMe); $^{13}$C-NMR (75 MHz, $CDCl_3$): δ (ppm) 180.6 (CO), 159.5 (Ph C-4), 159.1 (C-5, $^3J$(C-5,H-3) = 4.7 Hz), 138.8 (C-3, $^1J$ = 190.5 Hz), 131.9 (thiophene C-2, $^3J$(C-2,H-4) = 7.3 Hz, $^3J$(C-2,H-5) = 4.3 Hz), 130.5 (thiophene C-4, $^1J$ = 175.9 Hz, $^2J$(C-4,H-5) = 4.2 Hz), 129.9 (thiophene C-5, $^1J$ = 189.3 Hz, $^2J$(C-5,H-4) = 6.2 Hz), 129.7 (thiophene C-3, $^2J$(C-3,H-4) = 2.1 Hz, $^3J$(C-

3,H-5) = 12.5 Hz), 129.6 (Ph C-2,6), 127.3 (Ph C-1), 114.2 (Ph C-3,5), 102.8 (C-4, $^2J$(C-4,H-3) = 11.0 Hz), 55.3 (OMe, $^1J$ = 143.9 Hz), 49.8 ($CH_2$, $^1J$ = 140.6 Hz, $^3J$($CH_2$,H-2,6) = 4.6 Hz); $^{15}$N-NMR (50 MHz, $CDCl_3$): δ (ppm) –98.3 (N-2), –189.2 (N-1); IR (KBr): ν ($cm^{-1}$) 1610; MS (*m/z*, %): 350 ($M^+$, 3), 348 ($M^+$, 8), 313 (28), 121 (100). *Anal*. Calcd for $C_{16}H_{13}N_2O_3ClS \cdot 0.2\ H_2O$: C, 54.53; H, 3.83; N, 7.95. Found: C, 54.47; H, 3.56; N, 7.79.

**(3-Chloro-1-benzothien-2-yl)(5-hydroxy-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)methanone (11a)**

Starting from pyrazolone (**1a**) (2.61 g, 15 mmol) and 3-chloro-1-benzothiophene-2-carbonyl chloride (**5**) (3.47 g, 15 mmol) 4.76 g (86%) of compound (**11a**) were obtained as dark red powder. Mp 114–116 °C (toluene–hexanes). $^1$H-NMR (500 MHz, $CDCl_3$): δ (ppm) 9.27 (s, 1H, OH), 7.94 (m, 1H, benzothiophene H-4), 7.86 (m, 1H, benzothiophene H-7), 7.86 (m, 2H, Ph H-2,6), 7.55 (m, 1H, benzothiophene H-5), 7.53 (m, benzothiophene H-6), 7.48 (m, 2H, Ph H-3,5), 7.33 (m, 1H, Ph H-4), 2.12 (s, 3H, Me); $^{13}$C-NMR (125 MHz, $CDCl_3$): δ (ppm) 184.1 (CO), 159.8 (C-5), 148.7 (C-3, $^2J$(C-3,Me) = 7.0 Hz), 137.8 (benzothiophene C-7a), 136.8 (Ph C-1), 135.9 (benzothiophene C-3a), 132.0 (benzothiophene C-2), 129.1 (Ph C-3,5), 127.2 (benzothiophene C-6), 127.0 (Ph C-4), 125.7 (benzothiophene C-5), 123.0 (benzothiophene C-4), 122.9 (benzothiophene C-7), 121.0 (Ph C-2,6), 121.0 (benzothiophene C-3, $^3J$(C-3,H-4) = 3.9 Hz), 105.4 (C-4, $^3J$(C-4,Me) = 2.7 Hz), 13.8 (Me, $^1J$ = 129.1 Hz); $^{15}$N-NMR (50 MHz, $CDCl_3$): δ (ppm) –101.0 (N-2), –190.2 (N-1); IR (KBr): ν ($cm^{-1}$) 1603; MS (*m/z*, %): 371 ($M^+$, 1), 368 ($M^+$, 8), 334 (20), 333 (100), 200 (56), 195 (26), 167 (17), 91 (30), 77 (38). *Anal.* Calcd for $C_{19}H_{13}N_2O_2ClS \cdot 0.25\ H_2O$: C, 61.12; H, 3.64; N, 7.50. Found: C, 61.00; H, 3.53; N, 7.57.

**(3-Chloro-1-benzothien-2-yl)(5-hydroxy-1-phenyl-1*H*-pyrazol-4-yl)methanone (11b)**

Starting from pyrazolone (**1b**) (1.60 g, 10 mmol) and 3-chloro-1-benzothiophene-2-carbonyl chloride (**5**) (2.31 g, 3 mmol) 2.94 g (83%) of compound (**11b**) were obtained as dark red powder. Mp 156–157 °C (toluene–hexanes). $^1$H-NMR (500 MHz, $CDCl_3$): δ (ppm) 9.73 (s, 1H, OH), 8.19 (s, 1H, H-3), 8.04 (m, 1H, benzothiophene H-4), 7.89 (m, 1H, benzothiophene H-7), 7.88 (m, 2H, Ph H-2,6), 7.58 (m, 1H, benzothiophene H-6), 7.55 (m, benzothiophene H-5), 7.50 (m, 2H, Ph H-3,5), 7.36 (m, 1H, Ph H-4); $^{13}$C-NMR (125 MHz, $CDCl_3$): δ (ppm) 181.7 (CO), 159.7 (C-5), 139.8 (C-3), 138.3 (benzothiophene C-7a), 137.0 (Ph C-1), 136.9 (benzothiophene C-3a), 131.2 (benzothiophene C-2), 129.2 (Ph C-3,5), 128.3 (benzothiophene C-6), 127.3 (Ph C-4), 125.9 (benzothiophene C-5), 125.1 (benzothiophene C-3), 123.9 (benzothiophene C-4), 122.8 (benzothiophene C-7), 121.2 (Ph C-2,6), 104.3 (C-4); $^{15}$N-NMR (50 MHz, $CDCl_3$): δ (ppm) –97.6 (N-2), –185.3 (N-1); IR (KBr): ν ($cm^{-1}$) 1600; MS (*m/z*, %): 356 ($M^+$, 3), 354 ($M^+$, 7), 320 (23), 319 (100), 195 (14), 186 (14), 167 (8), 91 (11), 77 (17). *Anal.* Calcd for $C_{18}H_{11}N_2O_2ClS \cdot 0.33\ H_2O$: C, 59.92; H, 3.26; N, 7.76. Found: C, 60.09; H, 2.95; N, 7.40.

**(3-Chloro-1-benzothien-2-yl)[5-hydroxy-1-(4-methoxybenzyl)-1*H*-pyrazol-4-yl]methanone (11c)**

Starting from pyrazolone (**1c**) (1.02 g, 5 mmol) and 3-chloro-1-benzothiophene-2-carbonyl chloride (**5**) (1.16 g, 5 mmol) 1.10 g (55%) of compound (**11c**) were obtained as dark yellow–brownish powder. Mp 123–124°C (1-propanol). $^1$H-NMR (500 MHz, DMSO-$d_6$): δ (ppm) 8.13 (m, 1H, benzothiophene H-7), 7.93 (m, 1H, benzothiophene H-4), 7.76 (s, 1H, H-3), 7.19 (m, 2H, Ph H-2,6), 7.61 (m, 1H, benzothiophene H-6), 7.60 (m, benzothiophene H-5), 6.90 (m, 2H, Ph H-3,5), 5.5 (br s, 1H, OH), 5.06 (s, 2H, $CH_2$), 3.70 (s, 3H, OMe); $^{13}$C-NMR (125 MHz, DMSO-$d_6$): δ (ppm) 178.8 (CO), 158.8 (Ph C-4), 155.0 (C-5), 140.3 (C-3), 137.1 (benzothiophene C-7a), 136.0 (benzothiophene C-3a), 134.7 (benzothiophene C-2), 129.1 (Ph C-2,6), 128.4 (Ph C-1), 127.7 (benzothiophene C-6), 126.1 (benzothiophene C-5), 123.5 (benzothiophene C-7), 122.8 (benzothiophene C-4),120.4 (benzothiophene C-3), 114.0 (Ph C-3,5), 104.8 (C-4), 55.1 (OMe), 48.8 ($CH_2$); $^{15}$N-NMR (50 MHz, DMSO-$d_6$): δ (ppm) –184.5 (N-1), N-2 not found; IR (KBr): ν ($cm^{-1}$) 1614; MS (*m/z*, %): 400 ($M^+$, 1), 398 ($M^+$, 4), 364 (13), 363 (53), 121 (100). *Anal.* Calcd for $C_{20}H_{15}N_2O_3ClS$: C, 60.23; H, 3.79; N, 7.02. Found: C, 60.02; H, 4.00; N, 6.92.

**Cyclizations of 4-Aroylpyrazolones (6a–c), (8a–c), (9a–c), and (11a–c): General Procedure for the Synthesis of 7a–c, 10a–c, and 12a–c.**

Under anhydrous conditions, the appropriate 4-aroylpyrazol-5-ol (**6a**–**c**), (**8a**–**c**), (**9a**–**c**), or (**11a**–**c**) was dissolved in dry DMF (3–5 mL per mmol) and added to a suspension of NaH (60% in mineral oil; 1 equiv) in dry DMF (3 mL per mmol). The reaction mixture was heated at reflux overnight and then the solvent was removed under reduced pressure. $H_2O$ (3–5 mL per mmol) was added to the residue and stirring was continued for further 1 h. The formed precipitate was filtered off, washed with water and light petroleum, and recrystallized.

**3-Methyl-1-phenylchromeno[2,3-*c*]pyrazol-4(1*H*)-one (7a)**

Starting from 4-(*o*-fluorobenzoyl)pyrazolone (**6a**) (296 mg, 1 mmol) 205 mg (74%) of compound (**7a**) were obtained as almost colourless needles. Alternatively, starting from 4-(*o*-chlorobenzoyl)pyrazolone (**8a**) (938 mg, 3 mmol) 473 mg (57%) of compound (**7a**) were obtained as colourless needles. Mp 168–170 °C (aqueous EtOH), (lit.,[2a] mp 172–173 °C). IR (KBr): ν ($cm^{-1}$) 1666; MS (*m/z*, %): 277 ($M^+$ + 1, 20), 276 ($M^+$, 100), 275 ($M^+$ – 1, 75), 77 (40).

**1-Phenylchromeno[2,3-*c*]pyrazol-4(1*H*)-one (7b)**[23,24]

Starting from 4-(*o*-fluorobenzoyl)pyrazolone (**6b**) (565 mg, 2 mmol) 385 mg (73%) of compound (**7b**) were obtained. Alternatively, starting from 4-(*o*-chlorobenzoyl)pyrazolone (**8b**) (597 mg, 2 mmol) 322

mg (61%) of compound (**7b**) were obtained. Mp 171–173 °C (aqueous EtOH), (lit.,[24] mp 170–172 °C). IR (KBr): ν ($cm^{-1}$) 1666; MS (*m/z*, %): 263 ($M^+$ + 1, 20), 262 ($M^+$, 100), 121 (55), 77 (17). *Anal.* Calcd for $C_{16}H_{10}N_2O_2$: C, 73.27; H, 3.84; N, 10.68. Found: C, 73.20; H, 4.12; N, 10.65.

**1-(4-Methoxybenzyl)chromeno[2,3-*c*]pyrazol-4(1*H*)-one (7c)**

Starting from 4-(*o*-fluorobenzoyl)pyrazolone (**6c**) (653 mg, 2 mmol) 294 mg (48%) of compound (**7c**) were obtained. Alternatively, starting from 4-(*o*-chlorobenzoyl)pyrazolone (**8c**) (686 mg, 2 mmol) 118 mg (19%) of compound (**7c**) were obtained. Mp 151–153 °C (aqueous EtOH). IR (KBr): ν ($cm^{-1}$) 1671; MS (*m/z*, %): 306 ($M^+$, 19), 121 (100). *Anal.* Calcd for $C_{18}H_{14}N_2O_3$: C, 70.58; H, 4.61; N, 9.15. Found: C, 70.28; H, 4.54; N, 8.97.

**3-Methyl-1-phenylthieno[2',3':5,6]pyrano[2,3-*c*]pyrazol-4(1*H*)-one (10a)**

Starting from 4-(thienoyl)pyrazolone (**9a**) (478 mg, 1.5 mmol) 241 mg (57%) of compound (**10a**) were obtained. Mp 135–137 °C (aqueous EtOH). IR (KBr): ν ($cm^{-1}$) 1644; MS (*m/z*, %): 283 ($M^+$ + 1, 25), 282 ($M^+$, 100), 281 ($M^+$ – 1, 75), 77 (58). *Anal.* Calcd for $C_{15}H_{10}N_2O_2S$: C, 63.81; H, 3.57; N, 9.92. Found: C, 63.51; H, 3.59; N, 9.72.

**1-Phenylthieno[2',3':5,6]pyrano[2,3-*c*]pyrazol-4(1*H*)-one (10b)**

Starting from 4-(thienoyl)pyrazolone (**9b**) (457 mg, 1.5 mmol) 193 mg (48%) of compound (**10b**) were obtained. Mp 173–174 °C (aqueous EtOH). IR (KBr): ν ($cm^{-1}$) 1647; MS (*m/z*, %): 269 ($M^+$ + 1, 18), 268 ($M^+$, 100), 142 (33), 127 (49), 77 (40). *Anal.* Calcd for $C_{14}H_8N_2O_2S$: C, 62.67; H, 3.01; N, 10.44. Found: C, 62.44; H, 3.19; N, 10.21. HRMS Calcd for $C_{14}H_8N_2O_2S$: 268.0307. Found: 268.0314.

**1-(4-Methoxybenzyl)thieno[2',3':5,6]pyrano[2,3-*c*]pyrazol-4(1*H*)-one (10c)**

Starting from 4-(thienoyl)pyrazolone (**9c**) (523 mg, 1.5 mmol) 309 mg (66%) of compound (**10c**) were obtained. Mp 159–161 °C (aqueous EtOH). IR (KBr): ν ($cm^{-1}$) 1637; MS (*m/z*, %): 312 ($M^+$, 16), 121 (100). *Anal.* Calcd for $C_{16}H_{12}N_2O_3S$: C, 61.53; H, 3.87; N, 8.97. Found: C, 61.47; H, 3.66; N, 8.97.

**3-Methyl-1-phenyl[1]benzothieno[2',3':5,6]pyrano[2,3-*c*]pyrazol-4(1*H*)-one (12a)**

Starting from 4-([1]benzothienoyl)pyrazolone (**11a**) (738 mg, 2 mmol) 419 mg (63%) of compound (**10a**) were obtained. Mp 180–182 °C (toluene-hexanes). IR (KBr): ν ($cm^{-1}$) 1649; MS (*m/z*, %): 333 ($M^+$ + 1, 24), 332 ($M^+$, 100), 331 ($M^+$ – 1, 41), 77 (37). *Anal.* Calcd for $C_{19}H_{12}N_2O_2S \cdot 0.33\ H_2O$: C, 67.44; H, 3.77; N, 8.28. Found: C, 67.37; H, 3.78; N, 8.22.

**1-Phenyl[1]benzothieno[2',3':5,6]pyrano[2,3-*c*]pyrazol-4(1*H*)-one (12b)**

Starting from 4-([1]benzothienoyl)pyrazolone (**11b**) (710 mg, 2 mmol) 465 mg (73%) of compound (**10b**) were obtained. Mp 232–234 °C (toluene-hexanes). IR (KBr): ν ($cm^{-1}$) 1640; MS (*m/z*, %): 319 ($M^+$ +1, 21), 318 ($M^+$, 100), 176 (28), 77 (23). *Anal.* Calcd for $C_{18}H_{10}N_2O_2S$: C, 67.91; H, 3.17; N, 8.80. Found: C, 67.79; H, 3.39; N, 8.70.

**1-(4-Methoxybenzyl)[1]benzothieno[2',3':5,6]pyrano[2,3-*c*]pyrazol-4(1*H*)-one (12c)**

Starting from 4-([1]benzothienoyl)pyrazolone (**11c**) (798 mg, 2 mmol) 536 mg (74%) of compound (**10c**) were obtained. Mp 225–227 °C (1-propanol). IR (KBr): ν ($cm^{-1}$) 1645; MS (*m/z*, %): 362 ($M^+$, 27), 121 (100). *Anal.* Calcd for $C_{20}H_{14}N_2O_3S$: C, 66.28; H, 3.89; N, 7.73. Found: C, 66.12; H, 3.96; N, 7.65.

**General Procedure for the Synthesis of Compounds (7d), (10d), and (12d).**

Under anhydrous conditions, a solution of the PMB-substituted congener of type (**c**) and trifluoroacetic acid (TFA, 3–5 mL per mmol) was stirred overnight at 70 °C. After removal of excess TFA under reduced pressure the residue was stored over solid KOH for 1 h. Then ice-cold diethyl ether–acetone (2:1, 3–5 mL per mmol) was added, the resulting suspension was filtered off and washed with cold diethyl ether to give the unsubstituted parent compound of type (**d**) as beige powder.

**Chromeno[2,3-*c*]pyrazol-4(1*H*)-one (7d)**

Starting from the PMB-protected congener (**7c**) (153 mg, 0.5 mmol) 47 mg (51%) of compound (**10c**) were obtained. Mp 240–242 °C, (lit.,[25] mp 243 °C). IR (KBr): ν ($cm^{-1}$) 1660; MS (*m/z*, %): 186 ($M^+$, 100). HRMS Calcd for $C_{10}H_6N_2O_2$: 186.0429. Found: 186.0423.

**Thieno[2',3':5,6]pyrano[2,3-*c*]pyrazol-4(1*H*)-one (10d)**

Starting from the PMB-protected congener (**10c**) (156 mg, 0.5 mmol) 42 mg (44%) of compound (**10c**) were obtained. Mp 240–242°C (EtOH–DMF). IR (KBr): ν ($cm^{-1}$) 1639; MS (*m/z*, %): 192 ($M^+$, 100). HRMS Calcd for $C_8H_4N_2O_2S$: 191.9993. Found: 191.9989.

**Benzothieno[2',3':5,6]pyrano[2,3-*c*]pyrazol-4(1*H*)-one (12d)**

Starting from the PMB-protected congener (**12c**) (181 mg, 0.5 mmol) 98 mg (81%) of compound (**10c**) were obtained. Mp 263–265 °C. IR (KBr): ν ($cm^{-1}$) 1634; MS (*m/z*, %): 242 ($M^+$, 100). HRMS Calcd for $C_{12}H_6N_2O_2S$: 242.0150. Found: 242.0153.

**ACKNOWLEDGEMENTS**

We are grateful to Dr. L. Jirovetz for recording the MS spectra.

## REFERENCES AND NOTES


1. (a) J. Fotie and D. S. Bohle, *Anti-Infect. Agents Med. Chem.*, 2006, **5**, 15 (*Chem. Abstr.*, 2006, **144**, 120767). (b) M. M. M. Pinto, M. E. Sousa, and M. S. J. Nascimento, *Curr. Med. Chem.,* 2005, **12**, 2517.
2. (a) A. S. Sarenko, I. Ya. Kvitko, and L. S. Éfros, *Khim. Geterotsikl. Soedin.*, 1972, 799; *Chem. Heterocycl. Compd. (Engl. Transl., NY)*, 1972, **8**, 722. (b) D. R. Buckle and C. J. M. Rockell, *J. Chem. Soc., Perkin Trans. 1,* 1982, 627. (c) A. Alberola, R. Álvaro, A. González Ortega, and C. Sañudo, *Tetrahedron*, 1997, **53**, 16185. (d) F. J. Villani, T. A. Mann, E. A. Wefer, J. Hannon, L. L. Larca, M. J. Landon, W. Spivak, D. Vashi, S. Tozzi, G. Danko, M. del Prado, and R. Lutz, *J. Med. Chem.*, 1975, **18**, 1. (e) A. Turck, L. Mojovic, and G. Quéguiner, *Synthesis*, 1988, 881. (f) F. Trécourt and G. Quéguiner, *J. Chem. Res., Synop.*, 1982, 76 (*Chem. Abstr.*, 1982, **97**, 38865).
3. (a) A. Kleemann, J. Engel, B. Kutscher, and D. Reichert, 'Pharmaceutical Substances: Syntheses, Patents, Applications', 4th ed., Thieme, Stuttgart, 2001, p. 99. (b) J. Bell, *Clin. Drug Invest.*, 2005, **25**, 555.
4. V. Colotta, L. Cecchi, D. Catarzi, F. Melani, G. Filacchioni, C. Martini, P. Tacchi, and A. Lucacchini, *Pharm. Pharmacol. Lett.*, 1992, **2**, 74 (*Chem. Abstr.*, 1993, **118**, 32807).
5. G. A. Eller, V. Wimmer, A. W. Haring, and W. Holzer, *Synthesis*, 2006, 4219.
6. V. I. Minkin, A. D. Garnovskii, J. Elguero, A. R. Katritzky, and O. V. Denisko, *Adv. Heterocycl. Chem*., 2000, **76**, 157 (*Chem. Abstr.*, 2000, **133**, 309576).
7. B. S. Jensen, *Acta Chem. Scand.*, 1959, **13**, 1668 (*Chem. Abstr.*, 1962, **56**, 66890).
8. P. J. Kocieński, 'Protecting Groups', 3rd ed., Thieme, Stuttgart, 2003, pp. 257–268.
9. (a) C. Subramanyam, *Synth. Commun.*, 1995, **25**, 761. (b) J. Eskildsen, J. Kristensen, P. Vedsø, and M. Begtrup, *J. Org. Chem.*, 2001, **66**, 8654.
10. G. A. Eller and W. Holzer, *Heterocycles*, 2004, **63**, 2537.
11. W. Becker, G. A. Eller, and W. Holzer, *Synthesis*, 2005, 2583.
12. S. Braun, H.-O. Kalinowski, and S. Berger, '150 and More Basic NMR Experiments: A Practical Course – Second Expanded Edition', Wiley-VCH, Weinheim, 1998, pp. 596 (*Chem. Abstr.*, 1999, **131**, 184497).
13. D. G. Davis and A. Bax, *J. Am. Chem. Soc.*, 1985, **107**, 7197.
14. S. K. Sarkar and A. Bax, *J. Magn. Reson.*, 1985, **62**, 109.
15. (a) A. Bax, *J. Magn. Reson.*, 1984, **57**, 314. (b) T. Jippo, O. Kamo, and N. Nagayama, *J. Magn. Reson.*, 1986, **66**, 344.
16. W. Willker, D. Leibfritz, R. Kerssebaum, and W. Bermel, *Magn. Reson. Chem.*, 1993, **31**, 287.
17. A. Michaelis, *Justus Liebigs Ann. Chem.*, 1911, **385**, 1.

18. C. Corral, A. Lasso, J. Lissavetzky, A. Sánchez Alvarez-Insúa, and. A. M. Valdeolmillos, *Heterocycles*, 1985, **23**, 1431.
19. F. J. Ehrgott, G. R. Schulte, and C. G. Goddard, EP 393936, 1990 (*Chem. Abstr.*, 1991, **115**, 71386).
20. J. D. McKenney, Jr and R. N. Castle, *J. Heterocycl. Chem.*, 1987, **24**, 1525.
21. $^{19}F,^{1}H$ through-space coupling.
22. $^{19}F,^{13}C$ through-space coupling.
23. (a) G. Singh, L. Singh, and M. P. S. Ishar, *Tetrahedron*, 2002, **58**, 7883. (b) Singh et al. reported the synthesis of a mixture of **7b** and its corresponding *N*2-phenyl isomer. According to our detailed spectroscopic analysis, it seems to be obvious that they have misread and mixed up both the isomeric ratio and the NMR chemical shift assignments.
24. R. Kobayashi, M. Hosoya, and Y. Naka, JP 5003220, 1975 (*Chem. Abstr.* 1975, **83**, 206254).
25. F. Eiden and G. Rademacher, *Arch. Pharm. (Weinheim, Ger.)*, 1983, **316**, 34 (*Chem. Abstr.*, 1983, **98**, 125915).