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Selective ring *N*-protection of aminopyrazoles

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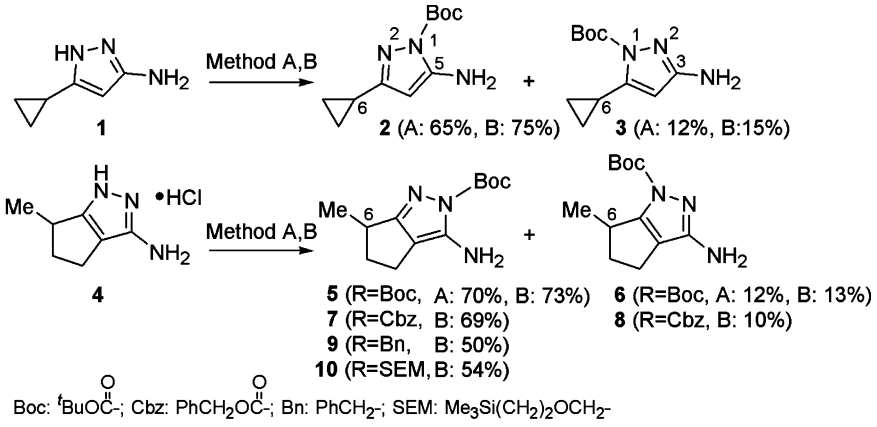
Dedicated to Professor Rudolf Wiechert on the occasion of his 75th birthday

Abstract—Two simple procedures for the selective protection of the ring *N* of aminopyrazoles as *tert*-butoxycarbamate (Boc) in high yields are reported; several other protecting groups (Cbz, Bn, SEM) can be introduced using the one-pot procedure (method B). The *N*-Boc protected aminopyrazoles are acylated at the exocyclic NH_2 group and subsequently deprotected to give the corresponding 3-acylaminopyrazoles in high yields. This procedure is applicable for the rapid parallel synthesis of 3-acylaminopyrazoles.

Aminopyrazoles are tautomerizable *C*-amino azoles with an amidrazon structure.[1] They are of considerable interest in the pharmaceutical and agrochemical industry for the discovery and development of new drugs[2a] and agrochemicals[2b] based on single and parallel synthesis approaches. Aminopyrazoles are also convenient starting materials for the synthesis of pyrazolopyrimidines[3] or reactive dienophiles in [4+2] cycloaddition reactions.[4]

In connection with a recent medicinal chemistry program we required a route to 3-acylaminopyrazoles. The selective acylation at the exocyclic NH_2 group has been reported;[5] however, in our hands, these and many other conditions gave mixtures of different amides which proved difficult to separate and purify; the desired 3-acylaminopyrazoles were isolated in low yields (<10%). The treatment of aminopyrazoles with 2 equiv. of the acylating agent followed by the selective saponification[6] of the acyl group attached to the ring nitrogen gave improved yields (20–60%), however isolation and purification of the reaction products often required preparative HPLC. Additionally, certain diacylated aminopyrazoles, in particular those possessing



Scheme 1. *Reagents and conditions*: Method A: (i) $(Me_3Si)_2NH$, Me_3SiCl; (ii) Boc_2O, MeCN. Method B: CH_2Cl_2/aq. KOH, Boc_2O.

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electron poor acyl groups were easily hydrolyzed completely under a variety of different saponification conditions. Summarized, the conditions tried proved unsatisfactory and unacceptable for parallel synthesis.

We now describe two convenient procedures to protect the ring *N* of aminopyrazoles with the Boc or Cbz group; selective carbamoylation of the ring *N* of aminopyrazoles has to our knowledge not been described. Treatment of the aminopyrazole **1**[7] either with $(Me_3Si)_2NH$ in the presence of Me_3SiCl followed by the addition of Boc_2O in MeCN (Method A) or directly with Boc_2O in a biphasic mixture of aq. KOH in CH_2Cl_2 (method B) gave the Boc-protected 5-aminopyrazole **2** in 65 and 75% yield respectively, together with 12 and 15% of the 3-aminopyrazole **3** after separation by chromatography on silica gel (Scheme 1).

Method A—general procedure: A mixture of the aminopyrazole (10 mmol) in $(Me_3Si)_2NH$ (30 ml) was treated dropwise at 23°C with Me_3SiCl (100 mmol) and refluxed for 5 h at 130°C. The resulting solution was concentrated and the residue distilled (Kugelrohr) to give a colorless oil. The crude silyl amine was dissolved in dry MeCN (50 ml), treated portionwise with Boc_2O (10 mmol), stirred for 10 h at 23°C and for 2 h at 50°C and concentrated. The residue was redissolved in AcOEt (50 ml), washed with satd aq. NH_4Cl soln and brine, dried (Na_2SO_4), filtered, evaporated and purified by chromatography on silica gel (gradient CH_2Cl_2→ CH_2Cl_2:MeOH) to give the *N*-1 Boc-protected aminopyrazoles.

Method B—general procedure: To a vigorously stirred solution of the aminopyrazole (10 mmol) in CH_2Cl_2 (80 ml) was added 4.5 N aq. KOH soln (80 mmol), followed by a soln of Boc_2O (10.5 mmol) in CH_2Cl_2 (10 ml). After 1.5 h the phases were separated and the organic phase washed with water and brine, dried (Na_2SO_4), filtered, evaporated and purified by chromatography on silica gel (gradient CH_2Cl_2→ CH_2Cl_2:MeOH) to give the *N*-1 Boc-protected aminopyrazoles.

Similar results to **1** were obtained with the bicyclic aminopyrazole **4**[8] (Scheme 1). The Boc-protection yielded derivatives **5** (Method A: 70%, Method B: 73%) along with the isomer **6** (Method A: 12%, Method B: 13%) in good overall yields. The treatment of **4** with benzylcarbamoylchloride (CbzCl) following Method B gave 69% of the Cbz-protected 5-aminopyrazoles **7** and 10% of the 3-aminopyrazole **8**. Additionally, using Method B in the presence of reactive alkylating agents, e.g. benzyl bromide or 2-(trimethylsilyl)ethoxymethylchloride (SEMCl), led to protected 5-aminopyrazoles **9** (50%) and **10** (54%).

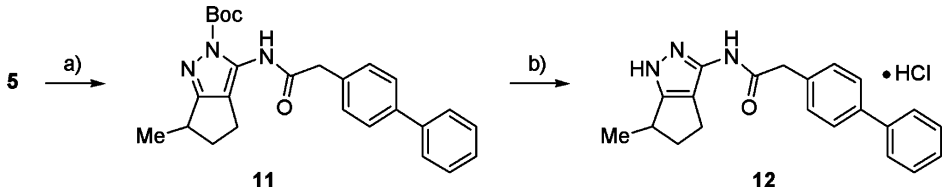
The endocyclic N–H of **1** has a calculated[10] pK_a value of 15.8 (±0.1)—thus acidic enough for an alkylation under Mitsunobu–Tsunoda–Ito conditions;[11] however, exploratory experiments with 4-methoxybenzyl alcohol in the presence of *N*,*N*,*N*′,*N*′-tetramethylazodicarboxamide (TMAD) and Bu_3P in CH_2Cl_2 proved low yielding (data not shown).

The structures of the *N*-Boc/Cbz protected aminopyrazoles[9] were determined by ^1H NMR ($CDCl_3$); most significant is the difference in chemical shift for the exocyclic NH_2 group. The NH_2 resonance of the 3-aminopyrazoles appear at $\delta = 2.9$–3.3 ppm and that of the 5-aminopyrazoles at much lower field ($\delta =$ 5.1–5.3 ppm) suggesting an intramolecular N–H···O=C H-bond. These values are in accordance with the chemical shifts reported by Ege et al.[12] for the reaction products obtained from the selective acylation of the ring *N*-1 of aminopyrazoles with isocyanates. Equally characteristic is the significant downfield shift (ca. 0.3–0.4 ppm) of the H-C(6) in **3** and **6** due to the magnetic anisotropy of the C=O bond of the neighboring *N*-Boc group.

The Boc-protected aminopyrazoles **2** and **5** were acylated with numerous acid chlorides (1.1–1.3 equiv.) in the presence of $^i Pr_2NEt$ (2 equiv.) in CH_2Cl_2 using parallel synthesis[13] in high yields (e.g. **11**, Scheme 2). Subsequent cleavage of the Boc group was conveniently achieved with a solution of 4 M HCl in dioxane to give the 3-acylaminopyrazoles (e.g. **12**, Scheme 2) as crystalline hydrochlorides in good to excellent overall yields (80–95%); similiar results were obtained either with the 3-isomer alone (e.g. **6**) or with mixtures of both isomers (e.g. **5**/**6** ca. 6:1).

Typical procedure for the Boc cleavage: A soln of **11** (432 mg, 1 mmol) in dioxane (3 ml) was treated with a soln of 4N HCl in dioxane (0.5 ml, 2 mmol), stirred for 5 h at 23°C and stored overnight at +4°C. The precipitate was filtered off, washed with cold diethylether and dried to give **12** (349 mg, 95%) as a white solid.

The single-crystal X-ray analysis of **11** (Fig. 1) revealed the arrangement of both carbonyl groups in the π-plane of the pyrazole ring and confirmed the ^1H NMR assignment of **11** and of the precursor **5**. An intramolecular H-bond exists between the exocyclic N–H and the carbonyl oxygen of the Boc group (*d*(N–O): 2.68 Å).



Scheme 2. *Reagents and conditions*: (a) *p*-Biphenylacetic acid chloride, $^i Pr_2NEt$, CH_2Cl_2, 90%; (b) 4 M HCl in dioxane, 95%.

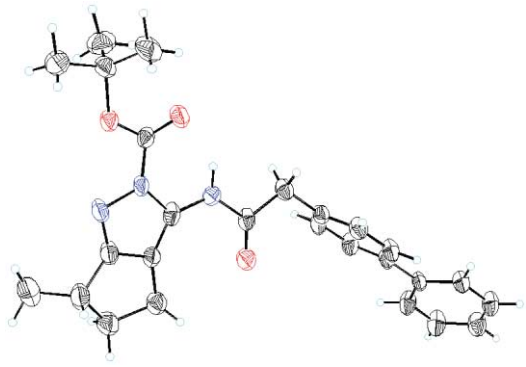


Figure 1. X-Ray structure analysis[14] of **11**: ORTEP[15] presentation (ellipsoids enclose 50% of the electron density).

Acknowledgements

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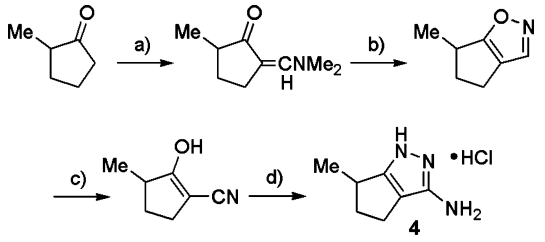
7. Aminopyrazole **1** has been reported without experimental details in Krasovsky, A. L.; Hartulyari, A. S.; Nenajdenko, V. G.; Balenkova, E. S. *Synthesis* **2002**, *1*, 133. We have prepared **1** according to WO 0,112,189 in 60% overall yield. ^{1}H NMR (300 MHz, $CDCl_3$, 298 K) of **1**: δ (ppm) = 5.60 (br.s, 3H), 5.29 (s, 1H, H-C(4)), 4.9 Hz, 1H, H-C(6), 0.93–0.87 (m, 2H), 0.69–0.64 (m, 2H).
8. Prepared from 2-methylcyclopentanone according to the following sequence:



Reagents and conditions: (a) $HC(OMe)_2NMe_2$, 110°C, 70%; (b) $H_2NOH{\cdot}HCl$, MeOH, 50°C, 98%; (c) NaOMe, MeOH, 23°C, 77%; (d) H_2NNH_2, EtOH, 23°C, 4 M HCl in dioxane, 70%. ^{1}H NMR (300 MHz, DMSO-d_6, 298 K) of **4**: δ (ppm) = 13.60 (br.s, NH), 6.91 (br.s, NH_2), 3.10 (sext. $J \approx 7.0$, 1H), 2.71–2.30 (m, 3H), 2.02–1.91 (m, 1H), 1.18 (d, $J = 6.7$, Me).

9. All new compounds were characterised by ^{1}H/^{13}C NMR, MS, TLC and—if crystalline—melting point ^{1}H NMR data (300 MHz, 298 K) of selected compounds: **2** ($CDCl_3$): δ (ppm) = 5.26 (br.s, NH), 1.90 (tt, $J = 8.4$, 5.0 Hz, 1H, H-C(6)), 1.64 (s, 9H, *tert*-Bu), 0.92–0.87 (m, 2H), 0.68–62 (m, 2H). **3** ($CDCl_3$): δ (ppm) = 3.25 (br.s, NH_2), 5.33 (s, 1H, H-(4)), 2.33 (tt, $J = 8.5$, 5.2 Hz, 1H, H-C(6)), 1.62 (s, 9H, *tert*-Bu), 0.99–0.93 (m, 2H), 0.66–0.61 (m, 2H). **5** ($CDCl_3$): δ (ppm) = 5.29 (br.s, NH_2), 3.05 (sext., $J \approx 7.0$, 1H, H-C(6)), 2.55–2.30 (m, 3H), 1.88 (m, 1H), 1.63 (s, 9H *tert*-Bu), 1.27 (d, $J = 7.1$, Me). **6** ($CDCl_3$): δ (ppm) = 3.30 (sext., $J \approx 7.0$, 1H, H-C(6)), 2.92 (br. s, NH_2), 2.75 (m, 1H), 2.60 (m, 1H), 2.1 (m, 1H), 1.60 (s, 9H, *tert*-Bu), 1.22 (d, $J = 7.1$, Me). **7** ($CDCl_3$): δ (ppm) = 7.50–7.30 (m, 5H), 5.42 (d, $J = 12.2$, PhC*H*), 5.38 (d, $J = 12.2$, PhC*H*), 5.00 (br.s, NH_2), 3.01 (sext. $J \approx 7.1$, H-C(6)), 2.58–2.31 (m, 3H), 1.96–1.82 (m, 1H), 1.26 (d, $J = 7.1$, Me). **9** ($CDCl_3$): δ (ppm) = 7.36–7.12 (m, 5H), 5.20 (d, $J = 12.1$, 1H, PhC*H*), 5.16 (d, $J = 12.1$, 1H, PhC*H*), 3.26 (br.s, NH_2), 3.01 (sext. $J \approx 7.0$, 1H, H-C(6)), 2.61–2.36 (m, 3H), 1.99–1.82 (m, 1H), 1.27 (d, $J = 7.1$, Me). **10** ($CDCl_3$): δ (ppm) = 5.11 (s, 2H, PhCH_2), 3.58 (t, $J \approx 7.6$, 1H, OC*H*CH_2), 3.55 (t, $J \approx 7.6$, 1H, OC*H*CH_2), 3.32 (br.s, NH_2), 3.11 (sext. $J \approx 7.0$, 1H, H-C(6)), 2.78–2.66 (m, 1H), 2.54–2.35 (m, 2H), 2.12–2.01 (m, 1H), 1.24 (d, $J = 7.1$, Me), 0.91 (t, $J \approx 7.8$, 1H, CH_2CHSiMe$_3$), 0.90 (dd, $J = 8.2$, 6.3, 1H, CH_2CHSiMe$_3$), −0.02 (s, SiMe$_3$). **11** ($CDCl_3$): δ (ppm) = 10.35 (br.s, NH), 7.61–7.53 (m, 4H), 7.46–7.32 (m, 5H), 3.76 (s, 2H, PhCH_2), 3.09–2.95 (m, 2H), 2.91–2.80 (m, 1H), 2.52–2.41 (m, 1H), 1.91–1.79 (m, 1H), 1.59 (s, 9H, *tert*-Bu), 1.27 (d, $J = 7.1$, Me). **12** (DMSO-d_6): δ (ppm) = 11.91 (br.s, NH), 10.30 (br.s, NH), 7.66–7.59 (m, 4H), 7.48–7.33 (m, 5H), 3.61 (s, 2H, PhCH_2), 3.10 (br.s, 1H, H-C(6)), 2.63–2.48 (m, 3H), 1.90–1.82 (m, 1H), 1.15 (d, $J = 6.9$, Me).
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14. Crystallographic data (excluding structure factors) for **11** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 205961. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44-1223-336-033 or e-mail: deposit@ccdc.cam.ac.uk).
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