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3-Acylaminopyrazole derivatives via a regioselectively *N*-protected 3-nitropyrazole

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Abstract—A simple procedure for the selective protection of the endocyclic 1-*N* of 3-aminopyrazoles as *tert*-butoxycarbamate (Boc) in good yield is described. A 3-nitropyrazole derivative represents the key intermediate with the nitro substituent determining the regiochemistry of the obtained protected compound. Subsequent acylation at the exocyclic amino group gave rise, after Boc removal, to a series of 3-acylaminopyrazoles in high yields and purities.

Cdks/Cyclins, a series of binary protein complexes altered in several major tumour types, are rate-limiting kinase enzymes in cell cycle progression and represent excellent molecular targets for therapeutic intervention.[1] Within a study aimed at finding a new Cdk2/Cyclin A inhibitor we had to devise an efficient synthesis of 5-cyclopropyl 3-pyrazolamides.[2]

It is well known that the 3-aminopyrazole system exists in several different tautomeric forms[3] and its reactivity towards acylating agents is a complex issue.[4] Attempts to directly introduce an acyl moiety on the exocyclic amino group generally affords complex reaction mixtures, including regioisomeric mono- and bi-acylated derivatives. The alternative approach of double acylation of the scaffold either with acyl chloride or activated carboxylic acids[5] and subsequent selective hydrolysis of the more labile endocyclic residue is not an optimal choice in terms of atom economy and moreover results in unsatisfactory yields. In our hands these approaches turned out to be of not general applicability and afforded mixtures of products that were often difficult to purify. Our goal was then to obtain an N-ring selectively protected scaffold endowed with a good reactivity towards the majority of commercially available acylating agents.

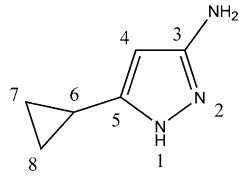

Figure 1.

Although it is possible to introduce a protective group such as Boc or Cbz at the endocyclic nitrogen in the α-position with respect to the exocyclic amino group,[6] the reactivity of these intermediates was revealed to be not sufficiently broad for our purpose. This can be explained either in terms of steric hindrance or a nucleophilicity decrease due to the hydrogen bond formation between N–H of the 3-amino group and C=O of the protecting group. In order to obtain a more reactive substrate we focused our efforts on the synthesis of 5-cyclopropyl-3-amino pyrazole protected at position 1 (Fig. 1).

Our strategy comprised the masking of the exocyclic amino group via an oxidation–reduction sequence and employing Boc, chosen on the basis of its facile removal, as the endocyclic protecting group. We actually found that a 3-nitro substituent can act at the same time as a protecting and directing group both for steric and electronic reasons (Scheme 1).

5-Cyclopropyl-3-aminopyrazole **1** was prepared in multi-grams scale in 58% overall yield starting from

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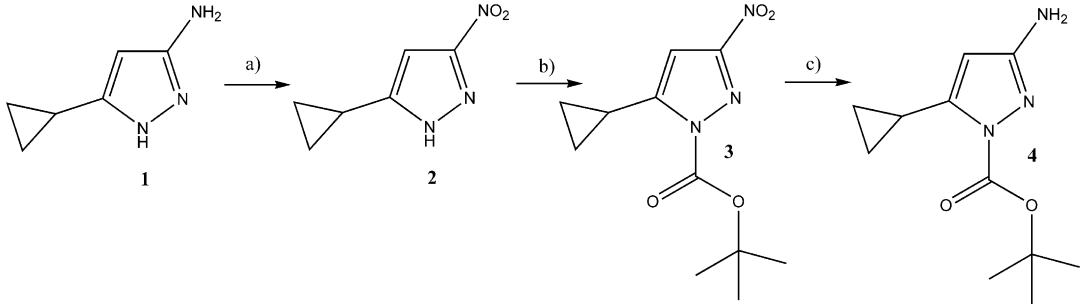
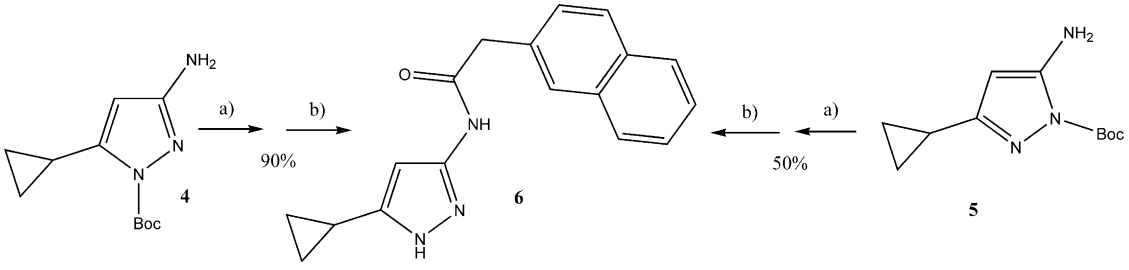


Scheme 1. Reagents and conditions: (a) Oxone®, NaOH, $NaHCO_3$, water, acetone, 0 °C, 56%; (b) $(Boc)_2O$, CH_2Cl_2/aq $NaHCO_3$, 95%; (c) H_2/Pd–C 10% 50 psi, EtOH, 95%.

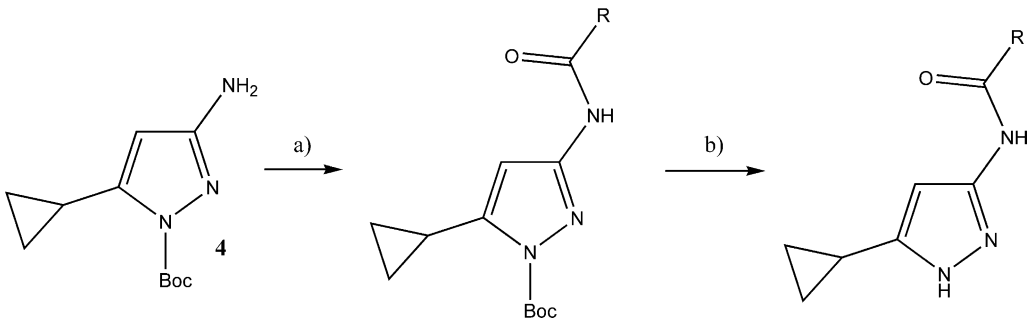
commercially available ethyl cyclopropanecarboxylate.[7] The conversion of the amino into nitro group was achieved by employing Oxone©/acetone system[8] providing the nitro-derivative **2** in 56% yield.[9] Subsequent treatment with Boc_2O in a biphasic mixture of aq $NaHCO_3$ and DCM afforded with high regioselectivity 1-*N*-Boc-protected 3-nitropyrazole **3** in 95% yield[10] after column chromatography. Compound **3** was then reduced in high yield to the desired compound **4** by catalytic hydrogenation.[11] The yield in the oxidation step was not considered an issue due to the high purity of crude **2** and the possibility to work on large scale for the preparation of **4**. The structure of **4** was unambiguously assigned by comparison of the ^1H NMR chemical shifts of the 2-*N*-Boc regioisomer **5** reported in the literature.[6a,12,13] In compound **5** an intramolecular hydrogen bond between the 3-NH_2 and the 2-CO_2t-Bu accounts for the downfield shift of the amino group ($\delta = 5.22$ ppm vs $\delta = 3.82$ ppm). Another remarkable difference in the ^1H NMR spectrum of the two regioisomers is the downfield shift (~0.4 ppm) of the cyclopropyl-CH signal of **4** versus **5** due to the magnetic anisotropy induced by the carbonyl group.

The different reactivity of **4** in comparison with **5** towards acylating agents was assessed by employing 2-naphthylacetic acid as model reactant (Scheme 2). Under the same experimental conditions (a—EDCI/DIPEA in CH_2Cl_2, b—TFA/CH_2Cl_2), **4** and **5** afforded the amide **6**[14] in 90% and 50% yield, respectively, thus confirming the convenience of our approach.

This strategy was pursued to explore the SAR around the amide portion of this class of compounds[2] in order to find a potential ATP-competitive inhibitor of the Cdk2/Cyclin A complex. We set up a two step parallel synthesis of 30 pyrazolyl amide derivatives by using **4** as starting material and carboxylic acids as acylating agents, for their superior stability and wider commercial availability as compared to acyl chlorides (Scheme 3).



Scheme 2. Reagents and conditions: (a) EDCI, DIPEA, 2-naphthylacetic acid, rt; (b) CH_2Cl_2–TFA 9:1, rt.



Scheme 3. Reagents and conditions: (a) polymer supported-DCC, RCO_2H, CH_2Cl_2, rt; (b) CH_2Cl_2–TFA 9:1, rt.

The optimized protocol involved the use of 4 equiv mol of polymer supported DCC, 3 equiv mol of carboxylic acid and 1 equiv mol of **4** for 96 h at room temperature on Quest 210 equipment[15] and subsequent removal of protecting group (TFA/CH_2Cl_2 1:9). All compounds, manually triturated with diethyl ether without any further purification, were obtained in good to high yields (65–90% overall) and high purities (85–100%). Characterization by ^{1}H NMR and LC–MS furnished data according to those already published.[2,7]

In conclusion, an efficient route to regioselectively protected 5-cyclopropyl-3-amino pyrazole **4**, via an oxidation/reduction sequence, was established. This valuable intermediate was successfully converted into 5-cyclopropyl-3-acylamino pyrazoles under mild conditions in high yields. The reaction conditions and the easy availability of carboxylic acids make this an attractive approach for a wide exploration of this class of compounds.

References and notes

1. Sherr, C. J. *Science* **1996**, *274*, 1672–1677.
2. Pevarello, P.; Brasca, M. G.; Amici, R.; Orsini, P.; Traquandi, G.; Corti, L.; Piutti, C.; Sansonna, P.; Villa, M.; Pierce, B. S.; Pulici, M.; Giordano, P.; Martina, K.; Fritzen, E. L.; Nugent, R. A.; Casale, E.; Cameron, A.; Ciomei, M.; Roletto, F.; Isacchi, A.; Fogliatto, G.; Pesenti, E.; Pastori, W.; Marsiglio, A.; Leach, K. L.; Clare, P. M.; Fiorentini, F.; Varasi, M.; Vulpetti, A.; Warpehoski, M. A. *J. Med. Chem.* **2004**, *47*(13), 3367–3380.
3. Puello, J. Q.; Obando, B. I.; Foces-Foces, C.; Infantes, L.; Claramunt, R. M.; Cabildo, P.; Jiménez, J. A.; Elguero, J. *Tetrahedron* **1997**, *53*(31), 10783–10802.
4. Elnagdi, M. H.; Abdel-Galil, F. M.; Riad, B. Y.; Elgemeie, G. E. H. *Heterocycles* **1983**, *20*(12), 2437–2470.
5. Brinkmeyer, R. S.; Terando, N. H. *J. Heterocycl. Chem.* **1989**, *26*, 1713–1717.
6. (a) Seelen, W.; Schäfer, M.; Ernst, A. *Tetrahedron Lett.* **2003**, *44*, 4491–4493; (b) Pevarello, P.; Amici, R.; Brasca, M. G.; Longo, A.; Piutti, C.; Orsini, P.; Traquandi, G.; Villa, M.; Varasi, M. International Patent WO 2002/048114 (Pharmacia Italia S.p.A., Italy).
7. Pevarello, P.; Orsini, P.; Traquandi, G.; Varasi, M.; Fritzen, E. L.; Warpehoski, M.; Pierce, B. S.; Brasca, M. G. International Patent WO 2001/012189 (Pharmacia and Upjohn S.p.A., Italy).
8. (a) Zabrowski, D. L.; Moormann, A. E.; Beck, K. R., Jr. *Tetrahedron Lett.* **1988**, *29*(36), 4501–4504; (b) Webb, K. S.; Seneviratne, V. *Tetrahedron Lett.* **1995**, *36*(14), 2377–2378.
9. Experimental procedure: A solution of acetone (340 mL) in water (220 mL) and a solution of Oxone® (130 g, 0.21 mol) in water (580 mL) were simultaneously added dropwise to a solution of NaOH (2.7 g, 0.0675 mol), $NaHCO_3$ (46.5 g, 0.553 mol) and 3-cyclopropyl-5-amino-1*H*-pyrazole **1** (7.1 g, 0.058 mol) in water (450 mL) under vigorous stirring at 0 °C. After stirring 4 h, the reaction mixture was quenched with a saturated solution of sodium sulfite and thoroughly extracted with ethyl acetate. The organic phase was washed with brine, dried over anhydrous Na_2SO_4 and evaporated to dryness to afford **2** (4.9 g, 56% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 0.79 (m, 2H, cyclopropyl C*H*H + CH*H*); 1.10 (m, 2H, cyclopropyl CH*H* + C*H*H); 2.01 (dddd, 1H, J = 5.1. 5.1, 8.2, 8.2, cyclopropyl C*H*); 6.51 (s, 1H, pyrazole C*H*). EI-MS: *m*/*z* 153 (100, M^+); 136 (60, $M-OH^\cdot$). Anal. Calcd for $C_6H_7N_3O_2$: C, 47.06; H, 4.61; N, 27.44. Found: C, 47.52; H, 4.71; N, 27.01.
10. Experimental procedure: Boc_2O (35 g, 0.16 mol) was added portionwise to a stirred solution of 3-cyclopropyl-5-nitro-1*H*-pyrazole **2** (4.9 g, 0.032 mol) in DCM (200 mL) and a saturated solution of $NaHCO_3$ (200 mL) at room temperature. After 24 h of stirring, the organic phase was separated and dried over Na_2SO_4. After removal of the solvent, the residue was chromatographed on silica gel by eluting with cyclohexane–EtOAc 6/4 to provide **3** (7.7 g, 95% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 0.78 (m, 2H, cyclopropyl C*H*H + CH*H*); 1.13 (m, 2H, CH*H* + C*H*H); 1.68 (s, 9H, $(CH_3)_3$–); 2.48 (dddd, 1H, J = 5.3, 5.3, 8.5, 8.5, cyclopropyl C*H*); 6.49 (s, 1H, pyrazole C*H*). ESI (+) MS: *m*/*z* 276 (100, MNa^+); 220 [60, $(MNa-C_4H_8)^+$]. Anal. Calcd for $C_{11}H_{15}N_3O_4$: C, 52.17; H, 5.97; N, 16.59. Found: C, 52.55; H, 6.05; N, 16.36.
11. Experimental procedure: *tert*-Butyl 3-nitro-5-cyclopropyl-1*H*-pyrazole-1-carboxylate **3** (1.2 g, 4.74 mmol) dissolved in ethanol (20 mL) was hydrogenated in the presence of 200 mg of Pd/C 10% at 50 psi and room temperature to give almost pure **4** (0.96 g, 95% yield). ^{1}H NMR (400 MHz, $CDCl_3$) ppm: 0.64 (m, 2H, cyclopropyl C*H*H + CH*H*); 0.97 (m, 2H, cyclopropyl CH*H* + C*H*H); 1.63 (s, 9H, $(CH_3)_3$–); 2.34 (dddd, 1H, J = 5.2, 5.2, 8.4, 8.4, cyclopropyl C*H*); 3.82 (br s, 2H, NH_2); 5.39 (s, 1H, pyrazole C*H*). ESI (+) MS: *m*/*z* 246 (20, MNa^+); 168 [100, $(MH-C_4H_8)^+$]; 124 [90, $(MH-C_5H_8O_2)^+$]. Anal. Calcd for $C_{11}H_{17}N_3O_2$: C, 59.17; H, 7.67; N, 18.82. Found: C, 59.27; H, 7.67; N, 18.92.
12. *tert*-Butyl 5-amino-3-cyclopropyl-1*H*-pyrazole-1-carboxylate (**5**). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 0.65 (m, 2H, cyclopropyl C*H*H + CH*H*); 0.93 (m, 2H, cyclopropyl CH*H* + C*H*H); 1.65 (s, 9H, $(CH_3)_3$–); 1.90 (m, 1H, cyclopropyl C*H*); 4.95 (s, 1H, pyrazole C*H*); 5.22 (br s, 2H, NH_2). ESI (+) MS: *m*/*z* 224 (100, MH^+). Anal. Calcd for $C_{11}H_{17}N_3O_2$: C, 59.17; H, 7.67; N, 18.82. Found: C, 59.14; H, 7.70; N, 18.69.
13. Ege, G.; Gilbert, K.; Maurer, K. *Chem. Ber.* **1987**, *120*, 1375–1395.
14. *N*-(5-Cyclopropyl-1*H*-pyrazol-3-yl)-2-(2-naphthyl)acetamide (**6**). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 0.63 (m, 2H, cyclopropyl C*H*H + CH*H*); 0.92 (m, 2H, cyclopropyl CH*H* + C*H*H); 1.80 (tt, 1H, J = 8.5, 5.0 Hz, cyclopropyl C*H*); 3.73 (s, 2H, CH_2-naphthyl); 6.13 (s, 1H, pyrazole C*H*); 7.52 (m, 3H, naphthyl); 7.91 (m, 4H, naphthyl); 10.53 (br s, 1H, CON*H*); 12.04 (br s, 1H, pyrazole N*H*). ESI (+) MS: *m*/*z* 292 (100, MH^+). HRMS (FAB) calcd for $C_{18}H_{17}N_3O$ + H1 292.1444, found 292.1452. Anal. Calcd for $C_{18}H_{17}N_3O$: C, 74.21; H, 5.88; N, 14.42. Found: C, 74.38; H, 5.85; N, 14.31.
15. Organic Synthesizer Quest™ 210, Argonaut Technologies.