Tetrahedron Letters 51 (2010) 6799–6801

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Syntheses of 1-substituted-3-aminopyrazoles

Nan Ji *, Erik Meredith, Donglei Liu, Christopher M. Adams, Gerald D. Artman III, Keith C. Jendza, Fupeng Ma, Nello Mainolfi, James J. Powers, Chun Zhang

Global Discovery Chemistry, Novartis Institutes for BioMedical Research, 250 Massachusetts Avenue, Cambridge, MA 02139, USA

ARTICLE INFO

Article history:
Received 15 September 2010
Revised 7 October 2010
Accepted 12 October 2010
Available online 23 October 2010

ABSTRACT

A series of 1-substituted-3-aminopyrazoles were prepared via Chan–Lam coupling reactions, alkylation, and pyrazole ring formation.

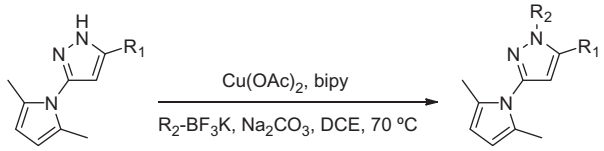
© 2010 Elsevier Ltd. All rights reserved.

3-Aminopyrazoles have served as important building blocks for drug development.[1] Although isolated syntheses of 1-substituted-3-aminopyrazoles have been reported,[2] these methods have relied on non-regioselective alkylation of 1*H*-3-aminopyrazole or 1*H*-3-nitropyrazole and were limited in substrate scope and/or by the availability of the corresponding starting material. Here, we report our approach to provide alternative, practical solutions to address this synthetic challenge.

1*H*-3-Aminopyrazoles are relatively inexpensive and commercially-available building blocks. They can be easily protected to form the corresponding pyrrolopyrazoles (**1**).[3] We have found that such compounds can be functionalized directly at the 1-position via Chan–Lam coupling reactions.[4] For example, compound **1a** reacted smoothly with the commercially available potassium cyclopropyltrifluoroborate in the presence of $Cu(OAc)_2$, 2,2′-bipyridine, sodium carbonate in dichloroethane at elevated temperature to give the corresponding 1-cyclopropyl-3-aminopyrazole (**2a**) in 56% yield with >95:5 regioselectivity.[5,6] Interestingly, when the corresponding boronic acid was used, the reaction did not proceed to full conversion and gave lower yield. The protective group within **2a** was easily removed under the conditions developed by Chenard[7] to provide the corresponding 3-amino-1-cyclopropylpyrazole in 79% yield (Scheme 1). This sequence proved effective for a variety of substrates (Table 1, **1b**–**g**). In all the substrates investigated, the regioselectivity remained high (>95:5) except for **1e**: this is likely a consequence of the relatively large dimethylpyrrole group, which favors reactivity at distal nitrogen atom. However, the regioselectivity remained excellent for larger substituents at R_1 (**1f**, **1g**), which indicates that the electronic nature of the ring is also playing a critical role in determining the more reactive nitrogen atom. More sterically hindered borates (entry **1e**) suffered from lower yields and poor regioselectivity (88:12 in favor of **2e**).

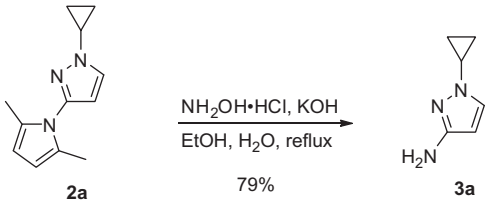
Although the method proved useful to install a variety of R_2 groups, efforts to install methyl group by using either methylboronic

Table 1
Chan–Lam couplings of pyrrolopyrazoles



1 **2**

Entry	R_1	R_2	Isolated yields (%)
a	H		56
b	H		65
c	CH_3		47
d	CH_3		35
e	CH_3		7
f			99
g			38
h	CH_3	CH_3	0



2a **3a**

Scheme 1. Removal of the pyrrolyl protecting group.

* Corresponding author.
E-mail address: nan.ji@novartis.com (N. Ji).

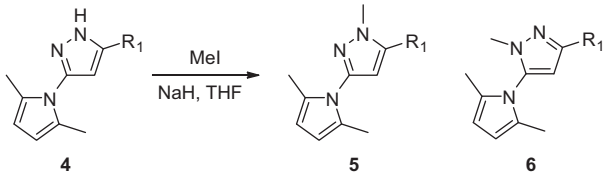
0040-4039/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2010.10.073

acid or the corresponding trifluoroborate salt were unsuccessful (entry **1h**). In order to address this problem, we decided to access these compounds via a more conventional approach. Pyrrolopyrazole (**4**) was first deprotonated with sodium hydride and the resulting mixture was treated with iodomethane (Table 2). This procedure generally provided 1:1 mixtures of both regioisomers, which could be separated by silica gel chromatography or HPLC. Interestingly, for a substrate containing the electron-withdrawing CF_3 group at R_1 (**4f**), the corresponding 1-methyl-5-aminopyrazole (**6f**) was the major product.

Despite our success at functionalizing at the N1 position of 1*H*-3-aminopyrazoles, the developed conditions could not be utilized to access the 1-*tert*-butyl analogs.

Fortunately, *tert*-butylhydrazine hydrochloride is readily available from commercial sources, and its reaction with 2-chloroacrylonitrile in aqueous media provided a simple and direct method to access 3-amino-1-*tert*-butylpyrazole (Table 3).[8] Interestingly, the regioselectivity of the cyclization process was influenced by the ratio of additives.[9] Under the optimal conditions (K_2CO_3/$NaHCO_3$ = 1:2), a 5.9:1 mixture of **9** and **10** was obtained (50% isolated yield for **9**). The improvement in regioselectivity proved significant because it not only led to higher yield of the desired isomer, but also made the separation of isomers with silica gel chromatography on larger scales more straightforward.

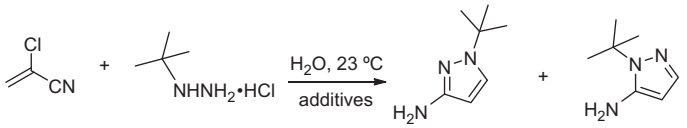
Table 2
N-Methylation of pyrrolylpyrazoles by alkyation



4 **5** **6**

Entry	R1	Ratio (**5**:**6**)	Combined yield (5)
a		1:1	85
b		2:1	92
c		1:1	80
d		1:1	66
e		1:1	84
f	CF_3	1:3.6	87

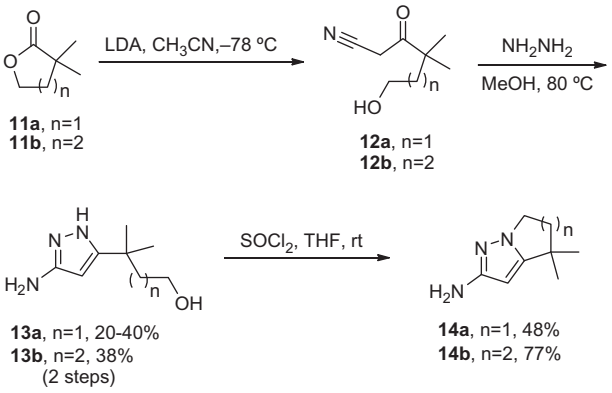
Table 3
Synthesis of 1-*tert*-butyl-3-aminopyrazole



7 **8** **9** **10**

Additives (K_2CO_3:$NaHCO_3$)	Ratio (**9**:**10**)
1:0	2.5:1
4:1	2.9:1
2:1	3.3:1
1:1	4.3:1
1:2	5.9:1
0:1	3.2:1
None	No reaction

Bicyclic compounds such as **14** (Scheme 2) represent another class of 1-substituted 3-aminopyrazoles. The synthesis of **14** started with the reaction of lactone **11** with acetonitrile under basic conditions at −78 °C to provide the β-ketonitrile **12**. The crude product (**12**) was heated in a solution of hydrazine in methanol at elevated temperature to produce the 1*H*-3-aminopyrazole **13**. This was then treated with thionyl chloride in tetrahydrofuran at room temperature to provide the bicyclic pyrazole **14** in decent to good yields.



Scheme 2. Syntheses of 1,5-disubstituted-3-aminopyrazoles.

In summary, we have developed efficient syntheses of 1-substituted 3-aminopyrazoles from readily available starting materials.[10] The variety of methods described here should provide for easier access to these useful building blocks.

References and notes

1. (a) Velcicky, J.; Feifel, R.; Hawtin, S. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 1293; (b) Yamada, H.; Kawanishi, H.; Ando, A. JP2003231633.; (c) Le-Brun, A.; Thompson, F.; Tiraboschi, G.; Mailliet, P.; Salvino, J. M.; WO 2004078732 A1.; (d) *Trends in Heterocyclic Chem.* **1991**, *2*, 97 and references therein.; (e) Artman III, G. D.; Elliott, J. M.; Ji, N.; Liu, D.; Ma, F.; Mainolfi, N.; Meredith, E.; Miranda, K.; Powers, J. J.; Rao, C. WO 2010066684 A2.
2. (a) Vasilevskii, S. F.; Shvartsberg, M. S. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1980**, *5*, 1071; (b) Torres, J.; Lavandera, J. L.; Cabildo, P.; Claramunt, R. M.; Elguero, J. *J. Heterocycl. Chem.* **1988**, *25*, 771; (c) Tironi, C.; Fruttero, R.; Garrone, A. *Farmaco* **1990**, *45*, 473; (d) Di Fabio, R.; St-Denis, Y.; Sabbatini, F. M.; Andreotti, D.; Arban, R.; Bernasconi, G.; Braggio, S.; Blaney, F. E.; Capelli, A. M.; Castiglioni, E.; Di Modugno, E.; Donati, D.; Fazzolari, E.; Ratti, E.; Feriani, A.; Contini, S.; Gentile, G.; Ghirlanda, D.; Provera, S.; Marchioro, C.; Roberts, K. L.; Mingardi, A.; Mattioli, M.; Nalin, A.; Pavone, F.; Spada, S.; Trist, D. G.; Worby, A. *J. Med. Chem.* **2008**, *51*, 7370; (e) Guillemont, J.; Benjahad, A.; Oumouch, S.; Decrane, L.; Palandjian, P.; Vernier, D.; Queguiner, L.; Andries, K.; de Bethune, M.-P.; Hertogs, K.; Grierson, D. S.; Nguyen, C. H. *J. Med. Chem.* **2009**, *52*, 7473.
3. Breukelman, S. P.; Meakins, G. D.; Tirel, M. D. *J. Chem. Soc., Chem. Commun.* **1982**, 800.
4. (a) Chan, D. M. T.; Monaco, K. L.; Wang, R.-P.; Winters, M. P. *Tetrahedron Lett.* **1998**, *39*, 2933–2936; (b) Lam, P. Y. S.; Clark, C. G.; Saubern, S.; Adams, J.; Winters, M. P.; Chan, D. M. T.; Combs, A. *Tetrahedron Lett.* **1998**, *39*, 2941–2949.
5. Bénard, S.; Neuville, L.; Zhu, J. *J. Org. Chem.* **2008**, *73*, 6441.
6. Molander, G. A.; Figueroa, R. *Aldrichim. Acta* **2005**, *38*, 49.
7. Chenard, B. L. *J. Org. Chem.* **1984**, *49*, 1224.
8. McKerrecher, D.; Pike, K. G.; Waring, M. J. WO07007041 A1.
9. The regioselectivity was determined ^{1}H NMR analysis: a sample of reaction mixture was concentrated and the residue was dissolved in $CDCl_3$. An NMR analysis of this solution was performed. Peaks from the regioisomers were identified and ratio of regioisomers was calculated based on integration values.
10. **Experimental procedure**:
Preparation of **2a**: A suspension of $Cu(OAc)_2$ (1.13 g, 6.20 mmol) and 2,2′-bipyridine (0.97 g, 6.20 mmol) in dichloroethane (20 mL) was heated at 70 °C for 15 min, then transferred to a suspension of potassium cyclopropyltrifluoroborate (1.84 g, 12.4 mmol), **1a** (1.00 g, 6.20 mmol), and Na_2CO_3 (1.32 g, 12.4 mmol) in dichloroethane (10 mL). The resulting dark-green mixture was stirred at 70 °C for 4 h, then partitioned between EtOAc and 1 N HCl. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel chromatography (0–100% EtOAc–heptane) to provide **2a**

(700 mg, 56%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.52 (d, J = 2.3 Hz, 1H), 6.16 (d, J = 2.3 Hz, 1H), 5.87 (s, 2H), 3.68–3.62 (m, 1H), 2.13 (s, 6H), 1.22–1.18 (m, 2H), 1.09–1.03 (m, 2H).

Preparation of **3a**: A solution of potassium hydroxide (4.06 g, 72.3 mmol) in water (35 mL) and EtOH (35 mL) was added to a slurry of hydroxylamine hydrochloride (10.1 g, 145 mmol) in EtOH (53 mL). Compound **2e** (5.24 g, 24.11 mmol) was added and the mixture was refluxed for 20 h. The volatiles were removed in vacuo and the residue was partitioned between EtOAc and water. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were dried (Na_2SO_4) and the dried solution was concentrated. The residue was purified by silica gel chromatography (0–3% MeOH–DCM) to provide **4e** (2.67 g, 79%). ^{1}H NMR (CDCl3) δ ppm 7.20 (d, J = 2.3 Hz, 1H), 5.58 (d, J = 2.3 Hz, 1H), 3.52 (br s, 2H), 3.46–3.40 (m, 1H), 1.07–1.00 (m, 2H), 0.99–0.94 (m, 2H).

Preparation of **5b**: NaH (2.27 g, 56.8 mmol) was added to a solution of **4b** (7.70 g, 37.9 mmol) in THF (400 ml) at 0 °C (gas evolution!). The resulting mixture was stirred for another 10 min at 0 °C, 10 min at room temperature. MeI (4.74 ml, 76.0 mmol) was added and the resulting mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with DCM, washed with saturated aqueous solution of ammonium chloride, and concentrated. The residue was purified by silica gel chromatography (0–30% EtOAc–heptane) to provide **5b** (5.24 g, 63%) and **6b** (2.40 g, 29%). Compound **5b**: ^{1}H NMR (DMSO-d_6) δ ppm 6.06 (s, 1H), 5.72 (s, 2H), 3.77 (s, 3H), 3.09–3.02 (m, 1H), 2.01 (s, 6H), 1.30–1.21 (m, 6H). Compound **6b**: ^{1}H NMR (DMSO-d_6) δ ppm 6.17 (s, 1H), 5.85 (s, 2H), 3.34 (s, 3H), 2.91–2.84 (m, 1H), 1.90 (s, 6H), 1.24–1.20 (m, 6H).

Preparation of **9**: A mixture of 2-chloroacrylonitrile (**7**) (13.7 mL, 0.171 mol), *tert*-butylhydrazine hydrochloride (21.4 g, 0.171 mol), potassium carbonate (23.7 g, 0.171 mol), and sodium bicarbonate (28.8 g, 0.343 mol) in water (300 mL) was stirred at room temperature over night. The resulting mixture was extracted with EtOAc (2×) and the combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel chromatography (15–80% EtOAc–heptane) to provide **9** (12.0 g, 50%). ^{1}H NMR (DMSO-d_6) δ ppm 7.34 (d, J = 2.3 Hz, 1H), 5.36 (d, J = 2.3 Hz, 1H), 4.47 (s, 2H), 1.40 (s, 9H).

Preparation of **14b**: A solution of *n*-butyllithium (53.6 mL, 86 mmol, 1.6 M in heptane) was added to a precooled (−78 °C) solution of diisopropylamine (12.8 mL, 90 mmol) and THF (150 mL). The solution was then removed from the cold bath for 20 min and then replaced in the bath at −78 °C. Then a solution of 3,3-dimethyltetrahydro-2*H*-pyran-2-one (5.00 g, 39.0 mmol), acetonitrile (4.1 mL, 78 mmol), and THF (50 mL) was added. After 15 min, the solution was removed from the cold bath and allowed to warm to room temperature. After an additional 2 h, the solution was diluted with saturated aqueous NH_4Cl and extracted with EtOAc (2×). The combined organic phases were dried (Na_2SO_4), filtered, and concentrated. The residue was used directly in the next step without further purification. A solution of crude 7-hydroxy-4,4-dimethyl-3-oxoheptanenitrile (**12b**) (3.00 g, 17.7 mmol), hydrazine (0.85 mL, 26.6 mmol) in MeOH (25 mL) was heated at 80 °C. After 16 h, another aliquot of hydrazine (0.85 mL, 26.6 mmol) was added and heating was continued for an additional 8 h. The solution was then concentrated and purified via flash column chromatography (10% MeOH–DCM) to provide **13b** (2.75 g, 38%, two-steps). To a solution of 4-(5-amino-2*H*-pyrazol-3-yl)-4-methyl-pentan-1-ol (5.00 g, 27.3 mmol) in THF (150 mL) at rt was added thionyl chloride (10.0 mL, 136 mmol). Stirring was continued for 2 h before the mixture was added slowly to a mixture of 28% aqueous NH_4OH (250 mL) and ice (100 g). The aqueous slurry was then extracted with DCM (2 × 200 mL) and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The residue was then purified by silica gel chromatography (1–10% MeOH–DCM) to provide **14b** (3.47 g, 77%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 5.37 (s, 1H), 3.88 (t, J = 6.2 Hz, 2H), 3.49 (br s, 2H), 2.05–1.95 (m, 2H), 1.66–1.58 (m, 2H), 1.24 (s, 6H).