Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters 49 (2008) 2996–2998
Tetrahedron Letters

A practical, two-step synthesis of 1-alkyl-4-aminopyrazoles

Anna A. Zabierek, Kaleen M. Konrad, Andrew M. Haidle *

Department of Drug Design and Optimization, Merck Research Laboratories, 33 Avenue Louis Pasteur, Boston, MA 02115, USA

Received 31 January 2008; accepted 29 February 2008
Available online 4 March 2008

Abstract

A novel synthesis of N1 alkyl-substituted pyrazoles with a free amino group at the C4 position is described. Commercially available 4-nitropyrazole was found to readily undergo Mitsunobu reactions with primary and secondary alcohols. Subsequent reduction of the nitro group via hydrogenation affords 1-alkyl-4-aminopyrazoles, which are valuable intermediates in the synthesis of pharmaceutically active compounds.

Keywords: 1-Alkyl-4-aminopyrazoles; Mitsunobu reaction

During the course of a medicinal chemistry lead optimization program, we wanted to replace an aniline that was appended to our core. We were looking for isosteric groups that would not only improve potency but also reduce lipophilicity, and we found that incorporation of 1-methyl-4-aminopyrazole accomplished both of these goals ($\log D$ with aniline fragment = 4.47; $\log D$ with 1-methyl-4-aminopyrazole fragment = 2.51). Additionally, pyrazole rings are less likely to undergo oxidative metabolism than other 5-membered aromatic heterocycles, so we were interested in exploring this new lead[1] (Fig. 1).

When we sought to expand the structure–activity relationship (SAR) around the methyl group, we were surprised to find a scarcity of commercially available 1-alkyl-4-aminopyrazoles. Additionally, the number of published routes to these compounds is fairly limited. The literature methods use two types of building blocks as the source of the 1-alkyl group, alkyl hydrazines and alkyl halides. Hydrazines have been condensed with sodium nitromalonaldehyde,[2] β-nitroenamines,[3] 2-(phenylacetamido)malonaldehyde,[4] and most recently vinamidinium salts.[5] With a focus on generating SAR information, the main problem

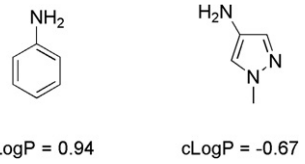


Fig. 1. Comparison of *c*Log*P* values for aniline and 1-methyl-4-aminopyrazole.

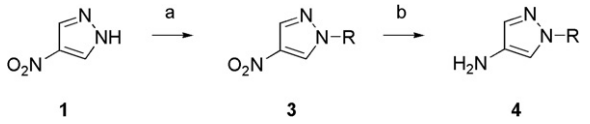
with all of these methods is the lack of a large diversity of commercially available hydrazines.

The other option from the literature reports to produce these intermediates involves alkylating a pyrazole nitrogen followed by introduction of the 4-amino group. 4-Nitropyrazole has been utilized in this fashion in the patent literature, and subsequent reduction afforded the desired 1-alkyl-4-amino pyrazole.[6] A recent report from workers at AstraZeneca highlights the alkylation of 4-bromopyrazole followed by Buchwald–Hartwig coupling with benzophenone imine, acidic deprotection, and free basing of the resulting HCl salt.[5] Again, the main limitation of these methods from our perspective was the dearth of commercially available alkyl halides of interest to us for our SAR exploration.

As an alternative to the published methods, we were intrigued by the possibility of using Mitsunobu chemistry

* Corresponding author. Tel.: +1 617 992 2389; fax: +1 617 992 2406.
E-mail address: andrew_haidle@merck.com (A. M. Haidle).

0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.02.169



Scheme 1. Reagents and conditions: (a) alcohol (**2**), PPh_3, DBAD, THF, 20 °C; (b) H_2, Pd/C, MeOH, 20 °C.

to append functionalized side chains at the pyrazole's 1-position (Scheme 1). This would allow us to use the large commercial pool of functionalized alcohols as our diversity source and to do so under mild reaction conditions that would be compatible with the desired functionality. The published[7] pK_a for 4-nitropyrazole is 9.64, so we reasoned that it would behave as a competent nucleophile under standard Mitsunobu conditions.[8] Indeed, we found an isolated literature example demonstrating the desired reactivity with a primary alcohol en route to synthesizing acyclic nitropyrazole nucleosides.[9] With this knowledge, we explored the scope of our proposed two-step 1-alkyl-4-amino pyrazole synthesis.

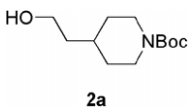
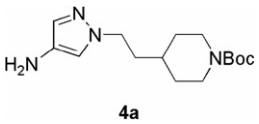
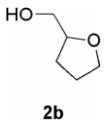
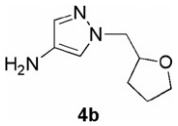
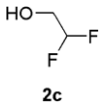
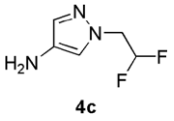
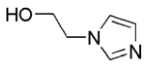
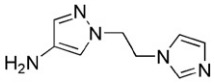
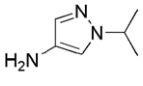
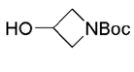
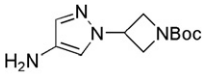
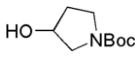
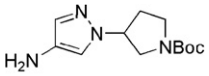
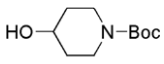
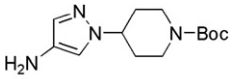
As the results shown in Table 1 indicate, primary alcohols, acyclic secondary alcohols, and cyclic secondary alcohols are good substrates for the initial Mitsunobu reaction. Most alcohols react rapidly under the standard conditions, with typical reactions reaching completion in under 30 min (although often the reactions were left stirring overnight). The crude reaction mixture was directly purified via silica gel chromatography to give the 1-alkyl-4-nitropyrazole intermediate, which was reduced via hydrogenation under standard conditions to afford the desired 1-alkyl-4-amino-pyrazoles without further purification.

From a medicinal chemistry standpoint, the pyrazoles containing branched alkyl groups off the N1 position are especially interesting. Compounds containing simple N-primary alkyl groups (e.g., methyl and ethyl) are often N-dealkylated through metabolic activation of the carbon attached to the pyrazole nitrogen.[1] We have found that compounds containing pyrazoles with N-branched alkyl substituents (e.g., the des-Boc version of **4h** attached to our core) are stable upon incubation with liver microsomes (unpublished results).

In summary, we have developed a practical and efficient two-step route to 1-alkyl-4-aminopyrazoles utilizing primary or secondary alcohols as the source of the alkyl group. The large number of commercially available alcohols coupled with the mild reaction conditions described herein allows ready access to diverse pyrazole building blocks that should find use in medicinal chemistry lead optimization programs.

Typical experimental procedure: To a solution of 4-nitropyrazole (**1**) (150 mg, 1.33 mmol, 1.0 equiv), *tert*-butyl 3-hydroxypyrrolidine-1-carboxylate (**2g**) (248 mg, 1.33 mmol, 1.0 equiv), and triphenylphosphine (418 mg, 1.59 mmol, 1.2 equiv) in tetrahydrofuran (6.6 mL) under argon at 20 °C was added di-*tert*-butyl azodicarboxylate (397 mg, 1.725 mmol, 1.3 equiv) over 1 min. After the reaction was

Table 1
1-Alkyl-4-aminopyrazoles produced via Scheme 1

Entry	Alcohol starting material	4-Aminopyrazole product	Two-step yield (%)
1	 **2a**	 **4a**	85
2	 **2b**	 **4b**	80
3	 **2c**	 **4c**	59
4	 **2d**	 **4d**	84
5	 **2e**	 **4e**	82
6	 **2f**	 **4f**	78
7	 **2g**	 **4g**	84
8	 **2h**	 **4h**	91

judged complete according to LC/MS analysis, the reaction mixture was concentrated and purified by silica gel flash chromatography (1:9 ethyl acetate–hexanes, grading to 1:1 ethyl acetate–hexanes) to afford alcohol **3g** (326.2 mg, 87%). ^{1}H NMR (1.4:1 rotamer ratio, * denotes peak due to the minor rotamer, 500 MHz, DMSO-d_6) δ: 8.95 (s, 1H), 8.95* (s, 1H), 8.30 (s, 1H), 8.30* (s, 1H), 5.03 (m, 1H), 5.03* (m, 1H), 3.71 (m, 1H), 3.71* (m, 1H), 3.59 (d, 1H, $J = 3.9$ Hz), 3.56* (d, 1H, $J = 4.1$ Hz), 3.43 (m, 2H), 3.38* (m, 2H), 2.34* (m, 2H), 2.30 (m, 2H), 1.38* (s, 9H), 1.36 (s, 9H). LRMS (EI): Calculated for $C_{12}H_{18}N_4O_4$ [M−*t*-Bu+H]$^+$: 227.1, found 227.1.

A suspension of **3g** (326.2 mg, 1.16 mmol, 1.0 equiv) and 10% palladium on carbon (123 mg, 0.116, 0.1 equiv) in methanol (7 mL) was placed under a hydrogen atmosphere by briefly evacuating the flask, then flushing with pure hydrogen from a balloon. The black suspension was stirred for 1 h at 20 °C before being filtered through a pad of

diatomaceous earth and washing with additional methanol. Concentration of the filtrate yielded 4-aminopyrazole **4g** (280.2 mg, 1.11 mmol, 96%, 84% over two steps). ^{1}H NMR (1.3:1 rotamer ratio, * denotes peak due to the minor rotamer, 500 MHz, DMSO-d_6) δ: 7.04 (s, 1H), 7.04* (s, 1H), 6.82 (s, 1H), 6.82* (s, 1H), 4.71 (m, 1H), 4.71* (m, 1H), 3.87 (br s, 2H), 3.87* (br s, 2H), 3.59 (m, 1H), 3.59* (m, 1H), 3.44 (m, 1H), 3.42* (m, 1H), 3.36 (m, 2H), 3.32* (m, 2H), 2.18 (m, 2H), 2.18* (m, 2H), 1.39* (s, 9H), 1.37 (s, 9H). LRMS (EI): Calculated for $C_{12}H_{20}N_4O_2$ [M−*t*-Bu+H]$^+$: 197.1, found 197.1.

Acknowledgments

The authors would like to thank Dr. Dapeng Chen and Ms. Andrea Mislak for performing the in vitro microsomal stability experiments, as well as Dr. Matthew Stanton for helpful discussions and proofreading the manuscript.

References and notes

1. Dalvie, D. K.; Kalgutkar, A. S.; Khojasteh-Bakht, S. C.; Obach, R. S.; O'Donnell, J. P. *Chem. Res. Toxicol.* **2002**, *15*, 269–299.
2. Alberti, C.; Tironi, C. *Farmaco, Ed. Sci.* **1964**, *19*, 618–637.
3. Nishiwaki, N.; Ogihara, T.; Takami, T.; Tamura, M.; Ariga, M. *J. Org. Chem.* **2004**, *69*, 8382–8386.
4. Alberti, C.; Tironi, C.; Bainotti, F.; Deleide, G. *Farmaco, Ed. Sci.* **1977**, *32*, 92–105.
5. Hill, G. B.; Mortlock, A. A. *Synthesis* **2007**, 1697–1701.
6. Jung, F. H.; Ple, P. WO Patent 2007099317, 2007.
7. Austin, M. W.; Blackborow, J. R.; Ridd, J. H.; Smith, B. V. *J. Chem. Soc.* **1965**, 1051–1057.
8. Mitsunobu, O. *Synthesis* **1981**, 1–28.
9. Walczak, K.; Wamberg, M.; Pedersen, E. B. *Helv. Chim. Acta* **2004**, *87*, 469–478.