Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 47 (2006) 5797–5799
Tetrahedron Letters

A general method for the preparation of 3-acyl-4-cyano-5-amino-pyrazoles

Min Ge,* Eric Cline and Lihu Yang

Merck & Co., Rahway, NJ 07065, USA

Received 24 February 2006; revised 24 May 2006; accepted 30 May 2006
Available online 27 June 2006

Abstract—This letter describes a general synthesis for N1-substituted 3-acyl-4-cyano-5-amino-pyrazoles.

Pyrazoles and their derivatives are widely used as pharmaceuticals and agrochemicals.[1] There is significant interest in the preparation of 5-amino-4-cyanopyrazoles, with a wide array of groups at N-1. This class of compounds has been reported to be selective Cox-2 inhibitors, cyclooxygenase inhibitors, pesticides, and antihypertensive agents.[2] Furthermore, they are also extensively used in the synthesis of fused heterocyclic systems, which are purine antagonists.[1a]

Recently we were interested in a series of 3-acyl-4-cyano-5-amino-pyrazoles. This type of pyrazoles is usually synthesized using the diazonium salt of aniline (Fig. 1, routes a and b).[3] Obviously, the success of both methods depends on the stability and reactivity of the diazonium salts. Because the diazonium salts of alkyl amines are often unstable, the N-1 substituents of the pyrazoles are limited to phenyl groups. For broader N-1 substituent changes, a general method is desired. In this sense, the third method (Fig. 1, route c) seems to be an attractive method because of many available substituted hydrazines.

While there are some reports on the synthesis of 3-acyl-4-*H*-5-amino-pyrazoles through hydrazines, this method has not been reported for 3-acyl-4-*cyano*-5-amino-pyrazoles.[1d,e] In fact, few such pyrazoles with non-aryl N-1 substitutions have been reported, highlighting the difficulties in the synthesis of this type of pyrazoles.

Indeed, it was found that the reaction of **1** with 4-chloroaniline did not give any desired product (Fig. 2). Careful analysis of the reaction mixture indicated that acyl hydrazine **2** was formed as the major side product, along with extensive decomposition of the starting material **1**. This suggests that hydrazone formation is disfavored during the condensation step, probably because malononitrile is an excellent leaving group (Fig. 2).

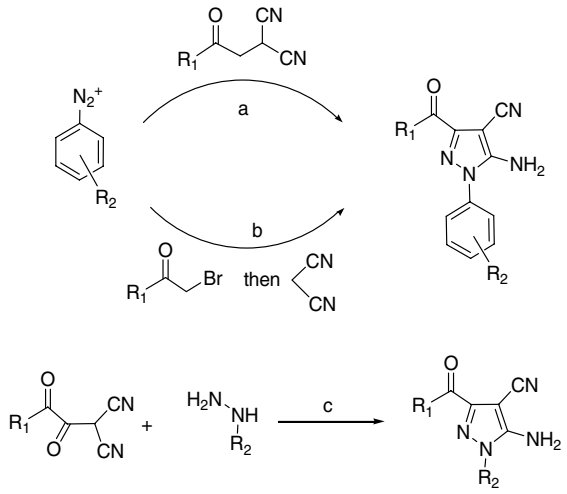


Figure 1. Methods for the synthesis of 3-acyl-5-amino-pyrazoles.

We thought that converting the hydroxyl group to a better leaving group should favor the formation of the desired hydrazone intermediate.[4] However, an intermediate such as **4** (Scheme 1) has not been reported before. Attempts to alkylate the enolate **1** under various conditions (NaH, MeI, or Me_2SO_4) failed to give the desired methyl enol ether, possibly due to the low reactivity of enolate **1**. After extensive experimentation, we found that treating **1** in refluxing $POCl_3$ for 1 h and then quenching the reaction mixture with methanol gave a

* Corresponding author. Tel.: +1 732 594 3587; fax: +1 732 594 3007; e-mail: min_ge@merck.com

0040-4039/$ - see front matter
doi:10.1016/j.tetlet.2006.05.173

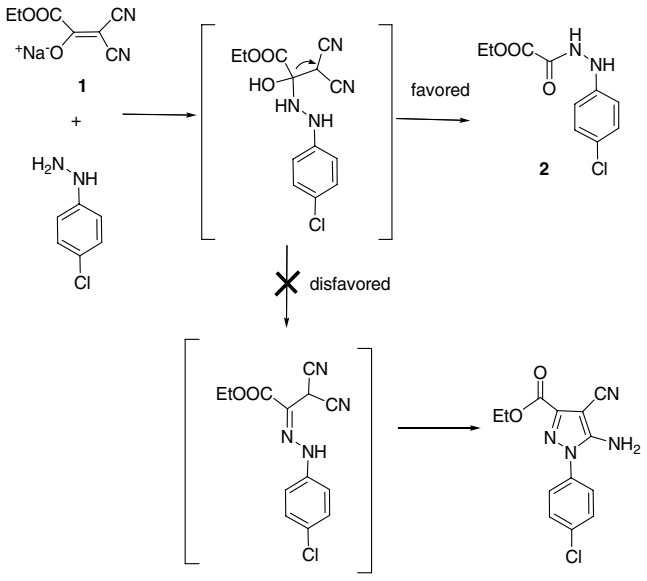
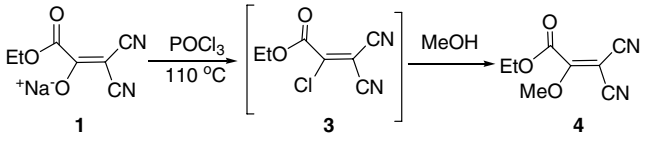


Figure 2. Proposed mechanism for the formation of side-product **2**.



Scheme 1. Synthesis of methyl vinyl enol ether **4**.

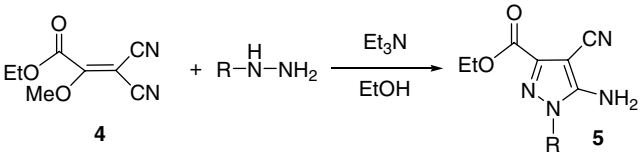
relatively stable product, which was identified to be the desired methyl enol ether **4** by ^{1}H and ^{13}C NMR (Scheme 1).[5–7]

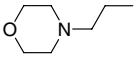
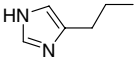
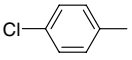
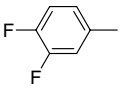
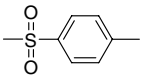
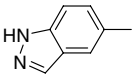
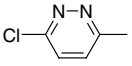
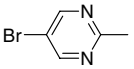
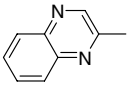
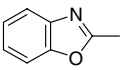
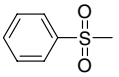
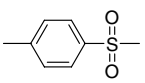
As we expected, the reactions between **4** and substituted hydrazines in ethanol provided the desired 5-amino-pyrazoles cleanly in good to modest yields.[8] A wide variety of substituents can be incorporated, including alkyl, aryl, sulfonyl, and heterocycles (Table 1). In most cases, the desired pyrazoles are precipitated out of the reaction solution and analytically pure products can be isolated by simple filtration.

These 5-amino-pyrazoles are very versatile intermediates for the synthesis of many biologically important scaffolds. For example, direct reaction of pyrazole **5c** with *N*-hydroxycarboximidamides can give the oxadiazole such as **8** (Scheme 2, route a). Or, after basic hydrolysis, pyrazole acid **6** can be coupled to various amines to give amides such as **9** (Scheme 2, route c). Acid **6** can also be converted to the Weinreb amide, followed by the treatment of Grignard reagents (or organolithium reagents) to provide pyrazoles with further variation at C-3 (such as **7**, Scheme 2). These pyrazoles can be further converted to fused heterocycles such as pyrazolopyrimidine, pyrazolopyrimidinones, and pyrazolopyridazines using known chemistry.[3a]

This method can also be used in the one-pot formation of 3-*aryl*/*alkyl*-4-cyano-5-amino-pyrazoles (Scheme 3). Thus, treatment of enolate **11** with $POCl_3$ in methylene chloride at *room temperature*, followed by methanol

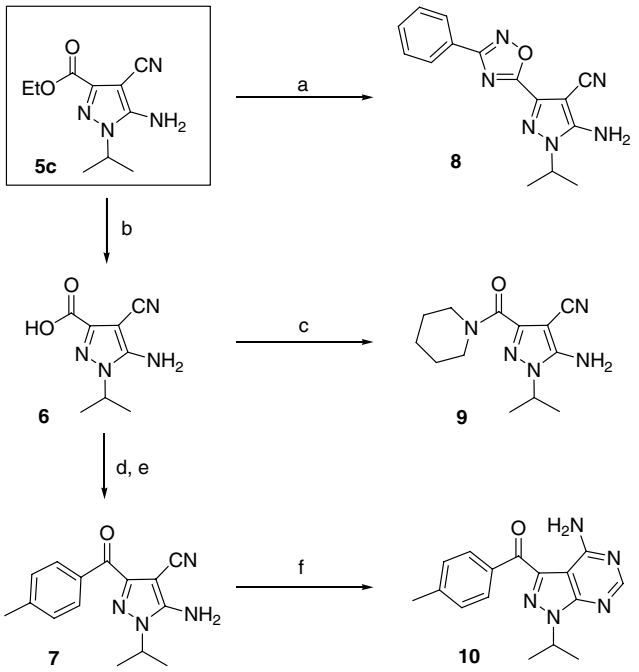
Table 1.



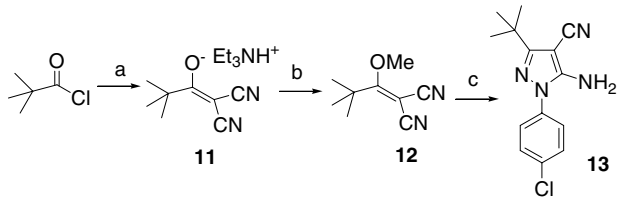
Entry	R–NHNH$_2$	Product (yield, %)[a,b]
1	H_3C–	**5a** (78)
2	Et–	**5b** (72)
3	*i*-Pr–	**5c** (78)
4	*t*-Bu–	**5d** (73)
5		**5e** (75)
6		**5f** (80)
7		**5g** (66)
8		**5h** (87)
9		**5i** (79)
10		**5j** (73)
11		**5k** (54)
12		**5l** (58)
13		**5m** (46)
14		**5n** (67)
15		**5o** (83)
16		**5p** (80)
17		**5q** (78)
18		**5r** (75)
19		**5s** (65)
20		**5t** (70)

[a] Isolated yield.

[b] The regiochemistry of the products was assigned by NMR analysis as well as comparison to the known compound **5h**.[3]



Scheme 2. Reagents and conditions: (a) NaH, *N*-hydroxyl benzamidine, 80 °C, 2 h, 65%; (b) LiOH, MeOH, 12 h, rt, 100%; (c) piperidine, EDC, CH_2Cl_2, 4 h, rt, 78%; (d) MeONHMe·HCl, EDC·HCl, CH_2Cl_2, NEt_3, 82%; (e) C_7H_7MgBr, THF, −78 to 0 °C, 2 h, 88%; (f) $HCONH_2$, HCOOH, DMF, reflux, 73%.



Scheme 3. Reagents and conditions: (a) malononitrile, Et_3N, EtOAc, 90%; (b) $POCl_3$, CH_2Cl_2, rt, 10 min, then MeOH; (c) 4-chlorophenylhydrazine·HCl, Et_3N, MeOH, 71%.

quenching, provided the corresponding methyl enol ether **12** as a methanolic solution, which can be used directly to yield the desired pyrazole **13** after the addition of triethylamine and corresponding hydrazine. This one-pot procedure complements the reported method using Me_2SO_4 as alkylating reagent,[4] and is especially suitable for sterically hindered or base sensitive substrates when alkylation becomes difficult.

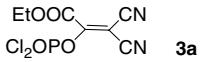
In summary, we have developed a general method for the synthesis of N-1 substituted 3-acyl-5-amino-pyrazoles. We envision that this method will be very useful in the construction of small molecule libraries with pyrazole core structures.

Acknowledgments

We would like to thank Drs. Songnian Lin and Christopher Thompson for critical reading and helpful discussions.

References and notes

1. (a) Cheng, C. C.; Robins, R. K. *J. Org. Chem.* **1956**, *21*, 1240–1256; (b) Hainzl, D.; Cole, L. M.; Casida, J. E. *Chem. Res. Toxicol.* **1998**, *11*, 1529–1535; (c) Zhang, J.; Didierlaurent, S.; Fortin, M.; Lefrancois, D.; Uridat, E.; Vevert, J. P. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2575–2578; (d) Vanotti, E.; Fiorentini, F.; Villa, M. *J. Heterocycl. Chem.* **1994**, *31*, 737–739; (e) Straub, A.; Stasch, J.; Alonso-Alija, C.; Benet-Buchholz, J.; Ducke, B.; Feurer, A.; Furstner, C. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 781–784.
2. (a) Minich, M. L.; Rast, B.; Sakya, S. M.; Sahvnya, A. WO 2003037874 A1, 2003; (b) Heil, M.; Erdelen, C. DE 19532066 A1, 1997; (c) Gustavsson, A.; Jendeberg, L.; Beierlein, K.; Lindqvist, B. WO 2003053976 A1, 2003.
3. (a) Abdelhamid, A. O.; Negm, A. M.; Abbsa, I. M. *J. Prakt. Chem.* **1989**, *1*, 31–36; (b) Shawali, A. S.; Abdelhamid, A. O. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 321–324.
4. This strategy has been used for the synthesis of 3-*aryl*-5-amino-pyrazoles, where pre-formed methyl enol ether led to the facile formation of the desired pyrazoles. See: Hanefeld, U.; Rees, C. W.; White, A. J. P.; Williams, D. J. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1545–1552.
5. We are not certain about the identity of the intermediate because both vinyl chloride **3** and compound **3a** can lead to the corresponding enol ether **4** after methanol treatment. This intermediate is too unstable to be isolated. However, there is one report supporting vinyl chloride as the intermediate. See: Friedrich, K.; Thieme, H. K. *Synthesis* **1973**, *5*, 111.



3a

6. The enol ether **4** is quite stable under acidic conditions but quickly decomposes under basic conditions.
7. Experimental for enol ether synthesis: To **1** (7.2 g, 38.3 mmol) was added $POCl_3$ (10.7 mL, 115 mmol) at room temperature. After stirring for 15 min, this dark solution was warmed up to 110 °C over 30 min and kept at 110 °C for another 30 min. The solution was then cooled to room temperature and concentrated to a solid at 10 Torr. With cooling in an ice bath, methanol (200 mL) was added to this solid slowly. After addition, the brown suspension was concentrated to an oil at 20 Torr. This oil was purified by flash chromatography (eluting with 50% EtOAc/hexanes) to give enol ether **4** (3.0 g, 44%) as a yellow liquid. Avoid excess transfer because the pure material is not very stable. $R_f = 0.6$ (50% EtOAc/hexanes); ^{1}H NMR (500 MHz, DMSO-d_6) δ 4.40 (q, $J = 7.1$ Hz, 2H), 4.24 (s, 3H), 1.31 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) 172.1, 158.2, 112.2, 111.8, 64.9, 63.8, 14.1.
8. To a suspension of *i*-propylhydrazine HCl salt (765 mg, 6.9 mmol) in ethanol (10 mL) was added triethylamine (7.6 mmol, 1.1 mL), followed by a solution of **4** (1.5 g, 8.3 mmol) in ethanol (1.5 mL) at room temperature. Reaction was completed within 15 min as indicated by LC–MS. The reaction was concentrated in vacuo. The resulted oil was purified by flash chromatography, eluting with a gradient from 0% to 20% EtOAc/CH_2Cl_2 to give the desired pyrazole **5c** (1.21 g, 78%) as a yellow solid. $R_f = 0.34$ (20% EtOAc/CH_2Cl_2); ^{1}H NMR (500 MHz, DMSO-d_6) δ 6.80 (s, 2H, NH_2), 4.50 (q, $J = 6.4$ Hz, 1H), 4.26 (q, $J = 7.1$ Hz, 2H), 1.29–1.25 (m, 9H). LC–MS (ES+) calcd for $C_{10}H_{15}N_4O_2$ [M+H$^+$] 223.1, found 223.1.