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Tetrahedron Letters 45 (2004) 2137–2139
Tetrahedron Letters

Convenient synthesis of 4-amino-3,5-disubstituted pyrazoles in one-step from the corresponding diketo oximes

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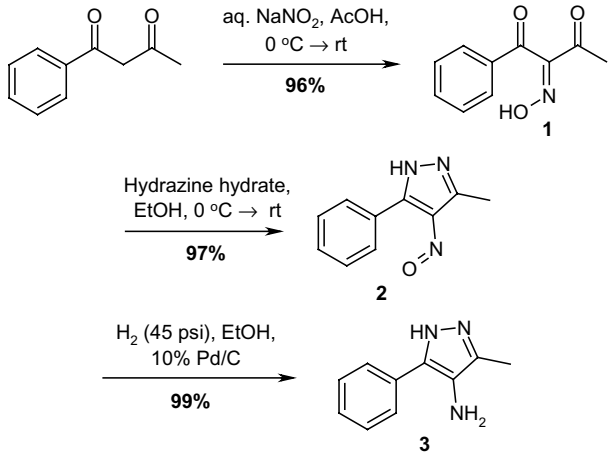
Received 7 November 2003; revised 3 December 2003; accepted 12 January 2004

Abstract—A convenient one-step protocol for the synthesis of 4-amino-3,5-disubstituted pyrazoles has been developed. This method employs readily available diketo oximes as starting materials, and employs hydrazine hydrate for the cyclization and subsequent reduction of the intermediate nitroso compound.

Diketo oximes, **1**, find great use in organic synthesis. These compounds are useful building blocks in five-membered heterocyclic chemistry. These oximes can be used for the synthesis of pyrroles,[1] thiazoles,[2] oxazoles,[3] and pyrazoles.[4] The pyrazole synthesis is of particular use because these compounds are themselves building blocks for larger pyrazole containing structures, such as pyrazoloisoquinolines,[5] pyrazolopyrimidines,[6] and pyrazolopyrazine[7] (which find wide use in the pharmaceutical industry). There are a number of synthetic approaches to substituted 4-amino pyrazoles. One such route uses oximes (such as **1**), which when treated with hydrazine hydrate yield the nitroso pyrazoles, which can be further reduced under a variety of conditions (H_2, Pd/C;[5,8] N_2H_4, Pd/C, or Raney Ni;[9] $Na_2S_2O_4$;[5] $SnCl_2$/HCl;[10] TiO_2, irradiation;[11] $LiAlH_4$).[12] Another approach is to use a 4-acyl azide pyrazole[6] and under Curtius conditions[13] one can obtain the desired 4-amino pyrazole. One last example is by nitration of an appropriately substituted pyrazole followed by reduction.[14]

As part of our continuing interest in the synthesis of novel heterocyclic compounds, we needed an efficient method for the synthesis of various 4-amino-3,5-disubstituted pyrazoles. Our first attempt to synthesize these compounds followed known literature procedures starting from the readily available β-diketones (Scheme 1).[15] The diketo oxime **1** was synthesized in excellent yield (96%) by addition of an aqueous solution of sodium nitrite[16] to a 0 °C solution of 1-benzoylacetone in AcOH. The diketo oxime was then treated with hydrazine hydrate in EtOH to yield the nitroso pyrazole **2**, which was isolated in excellent yield (97%) after concentration of the reaction mixture and subsequent precipitation from an ether/hexanes solution. Reduction via hydrogenation gave the amino pyrazole **3** (99%). The procedure worked well and was amenable to scale-up (10 g scale). However, we were concerned about the isolation of the nitroso compound **2** owing to the inherent toxicity of these types of compounds.[17] Thus, we were hoping to avoid an additional reduction step, thereby removing the need to handle the nitroso compound **2**.



Scheme 1.

Keywords: Pyrazole; Reduction; Hydrazine hydrate.
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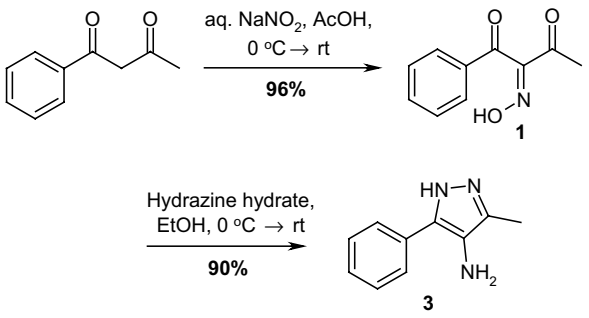
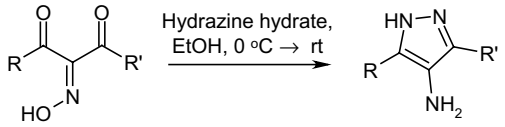
doi:10.1016/j.tetlet.2004.01.045



Scheme 2.

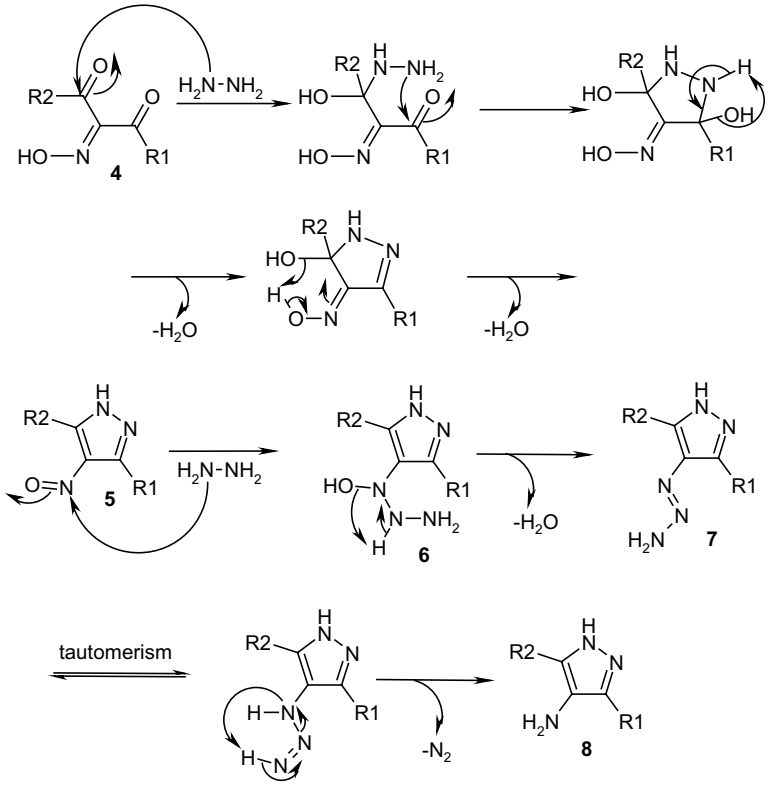
To this end, treatment of the diketo oxime **1** with excess hydrazine hydrate (10 equiv) in EtOH gave the desired 4-amino-3,5-disubstituted pyrazole **3** in excellent yield (Scheme 2). The reaction worked well with 1-phenylbutan-1,3-dione; however, we were interested in a variety of disubstituted amino pyrazoles and these results are summarized in Table 1. The examples show that the reaction is of general utility, and works equally well with electron-rich aryl groups (entries 1, 6, and 7) and electron-deficient groups (entries 2 and 5). The 4-$(CH_3)_2$NPh compound (entry 6) gave a lower overall yield than other compounds investigated due to problems in the isolation.[18] This reaction also allows for the use of heterocyclic aryl groups (entries 3 and 4) and alkyl substituents (entry 8). The amount of hydrazine hydrate needed for this transformation was next evaluated. The reaction can be carried out with only 3 equiv of hydrazine hydrate; however, the reaction time is lengthened to 40 h (entry 11).[19] The reaction time with 2 equiv of hydrazine hydrate could be shortened by heating (45 °C), but the yield is lower (entry 12). This cyclization/reduction reaction is also amenable to scale-up with this reaction routinely performed on multi-gram scale.

Table 1.



Entry	R	R′	Yield[a] (%)
1	4-MeOPh	CH_3	90
2	3-ClPh	CH_3	86
3	2-Furyl	CH_3	85
4	2-Thiophenyl	CH_3	89
5	4-BrPh	CH_3	95
6	4-$(CH_3)_2$NPh	CH_3	50[18]
7	3-$(CH_3)_2$NPh	CH_3	71
8	*tert*-Butyl	CH_3	85
9	Ph	CH_2CH_3	73
10	Ph	$CH(CH_3)_2$	78
11	3-OBnPh	CH_3	84[b]
12	Ph	CO_2Et	48[c]

[a] All reactions were run overnight.
[b] Reaction carried out with 3 equiv of hydrazine hydrate and run for a total of 40 h.
[c] Reaction carried out with 2 equiv of hydrazine hydrate and run for 2 h at 45 °C.



Scheme 3.

It appears that the reaction proceeds through the nitroso pyrazole **5** (by LCMS analysis[20]) with subsequent further reduction to the amino pyrazole **8**. The initial cyclization (**4** → **5**) usually occurs within 2 h and the reactions are allowed to proceed overnight to ensure complete conversion. The reaction is proposed to go through the mechanism in Scheme 3. After cyclization to **5** hydrazine addition to the aryl nitroso intermediate gives the hydroxy compound **6**. Loss of water and rearrangement gives the diazo compound **7**, which after loss of N_2, yields the amino pyrazole compound **8**.

Representative example: To a 0 °C solution of 1-(2-furyl)-butane-1,2,3-trione 2-oxime (4.70 g; 26.0 mmol) in EtOH (70.0 mL) was added dropwise hydrazine hydrate (12.0 mL; 6.60 g; 206 mmol). After addition, the reaction mixture was warmed to rt and allowed to stir for 16 h, at which point TLC and LCMS showed essentially complete conversion. The reaction mixture was concentrated, taken up in EtOAc and washed with 3 N HCl. The organic layer was discarded, and the aqueous portion basified with 10 N NaOH and then extracted with EtOAc. The organic extracts were dried (Na_2SO_4) and concentrated leaving 3.62 g (22.2 mmol; 85%) of 5-(2-furyl)-3-methyl-1*H*-pyrazol-4-ylamine as a tan solid. HPLC $R_T = 0.45$ MS (ESI) 164 (M+H) calculated for $C_8H_9N_3O$ (163.18); ^1H NMR δ 7.46 (d, 1H, $J = 1.2$ Hz), 6.56 (d, 1H, $J = 3.1$ Hz), 6.49 (dd, 1H, $J = 3.3$, 1.8 Hz), 2.23 (s, 3H).

In conclusion, we have developed a convenient synthesis of 4-amino-3,5-disubstituted pyrazoles in one-step from the corresponding diketo oximes. The reaction has been shown to work well with a number of substrates allowing for both aryl and alkyl groups.

Acknowledgements

The authors would like to thank Dr. Kent Neuenschwander and Mr. Anthony Scotese for their help in performing some of the experiments included in this manuscript.

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15. A number of β-diketones are commercially available. Those diketones that were not commercially available were synthesized following the procedure of Popic et al. Popic, V. V.; Korneev, S. M.; Nikolaev, V. A.; Korobitsyna, I. K. *Synthesis* **1991**, 195–198.
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18. There were numerous uncharacterized side products formed in the reaction. However, the overall yield of 50% was still an improvement over the two-step protocol for this compound (40%).
19. The nitroso pyrazole compound was formed after 1 h (TLC and LCMS analysis).
20. The LC retention time for the intermediate nitroso compound of the tandem reaction (**1** → **3**) was identical to **2**, which was characterized by LCMS. HPLC (Synergi 2U Hydro-RP 20 × 4.0 mm Col, water (0.1% trifluoroacetic acid)/acetonitrile (0.1% trifluoroacetic acid) = 10/90 → 90/10): $R_f = 2.51$ min. $C_{10}H_9N_3O$ (187.20) MS (ESI) 188 (M+H).