Tetrahedron Letters 51 (2010) 6186–6188

Contents lists available at ScienceDirect

Tetrahedron Letters

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

# A new pyridine synthesis from azoenamines

Didier Coffinier, Laurent El Kaim *, Laurence Grimaud, Simon Hadrot

*Laboratoire Chimie et Procédés, DCSO, UMR 7652, Ecole Nationale Supérieure de Techniques Avancées, 32 Bd Victor, Paris 75015, France*

ARTICLE INFO

*Article history:*
Received 16 June 2010
Revised 26 August 2010
Accepted 20 September 2010
Available online 25 September 2010

*Keywords:*
Hydrazones
Pyridines
Enamine
Azoenamine

ABSTRACT

Azoenamines are formed during the interaction of α-ketohydrazones with secondary amines. These compounds can be converted into pyridines when treated with acetylenedicarboxylates under basic conditions.



Hydrazones have a rich history with known reactions associated to the early development of organic synthesis at the end of the 19th century.[1] More recently, a renewal of studies devoted to these compounds can be observed in association with organometallic chemistry and the subsequent development of enantioselective processes.[2] Interested by new applications of hydrazones in heterocyclic synthesis, we disclosed a few years ago, a Mannich coupling of α-ketohydrazones[3] and applied it to trap various azoalkenes to form heterocycles.[4] In all these reactions, the α-ketone function appeared unreactive, presenting just an electron-withdrawing effect associated with an easier deprotonation of the hydrazone (Scheme 1). However, when working with pyrrolidine and ketohydrazone **1a**, we were surprised to observe the formation of an azoenamine side product **2a** resulting from the condensation of pyrrolidine with **1a** (Scheme 1).

The azoenamine **2a** could be obtained in quantitative yields by simply heating **1a** with 1 equiv of pyrrolidine in toluene. The particular reactivity of pyrrolidine was confirmed when the same reaction was attempted with morpholine. Indeed, after three hours at reflux, the ketohydrazone was recovered unreacted. The azoenamine **2a** proved to be rather stable, as it can be purified by fast silica gel chromatography without observing hydrolysis to give back the starting **1a**. Very few azoenamines have been reported in the literature and little is known about their chemistry.[5] We envisioned that these species could easily be deprotonated to form a stabilised anion which could then behave as an electron-rich heterodiene in various cycloadditions (Scheme 2).[6]

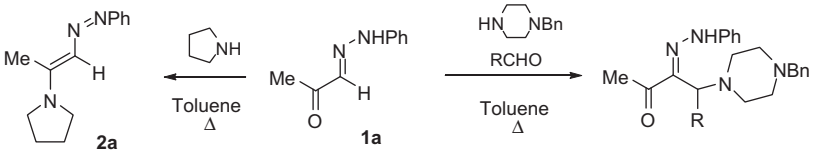
Consequently, **2a** was treated with a catalytic amount of DBU in the presence of an excess of diethyl acetylenedicarboxylate (DEAD) in hot toluene. Under these conditions, we were pleased to observe formation of the pyridine **3a** in a moderate 40% isolated yield. The yield could be raised to 50% by replacing DBU with diisopropylethylamine (DIPEA). This new pyridine synthesis probably involves a formal cycloaddition of deprotonated hydrazone A followed by elimination of aniline to form the aromatic system (Scheme 3). Deprotonation of the hydrazone leading to enhanced nucleophilic behavior is supported by the absence of reactivity of diphenyl acetylene in this reaction (with or without base).

Substitution of the phenyl moiety of **1a** by an electron-withdrawing *p*-nitrophenyl group did not improve the reaction as **3a** was obtained in a reduced 21% isolated yield. As the enamine **2a** was formed quantitatively with equimolar amounts of the reactants in toluene, a simplified procedure was performed from the starting hydrazone. Under such conditions, pyridines could be obtained from one-pot couplings of alkyl acetylenedicarboxylate, substituted α-ketohydrazones and pyrrolidines (Scheme 4).

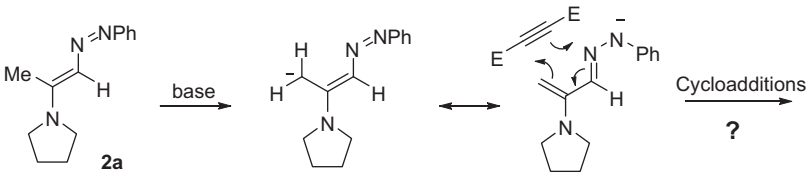
We wished to broaden the scope of this strategy to prepare pyridines substituted with different amino moieties. When working with morpholine, we were unable to obtain any efficient coupling with **1a** in refluxing toluene, even with a large excess of morpholine. A conversion of 25% (determined by NMR) was the best we observed with a two-molar excess of morpholine. In spite of these difficulties, the use of trimethylaluminum allowed us to induce the coupling giving, after work-up, a quantitative formation of the expected enamine **2c**. Enamines **2d** and **2e** could be similarly obtained from **1a** and the corresponding secondary amines (Scheme 5). These enamines are much more sensitive to hydrolysis than **2a** and attempted purification on silica gel usually led to their complete hydrolysis. Therefore, they were used directly after rapid hydrolysis and an extraction. With these crude enamines in hand, we tested the corresponding pyridine formation with either

* Corresponding author. Tel.: +33 145525537; fax: +33 145528322.
*E-mail address:* laurent.elkaim@ensta.fr (L. El Kaim).

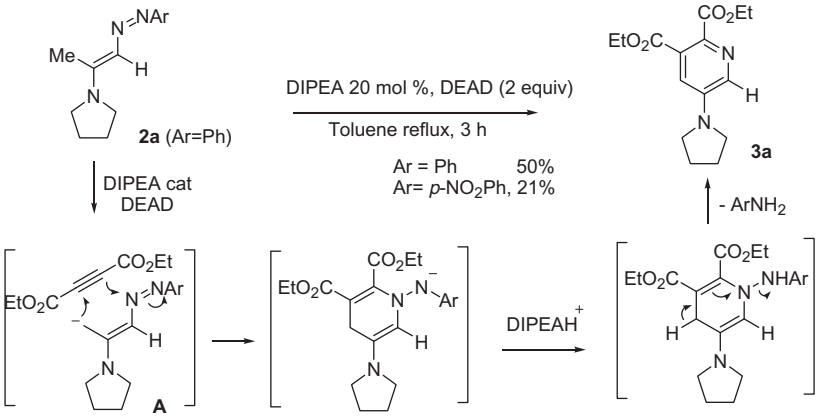
0040-4039/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2010.09.098



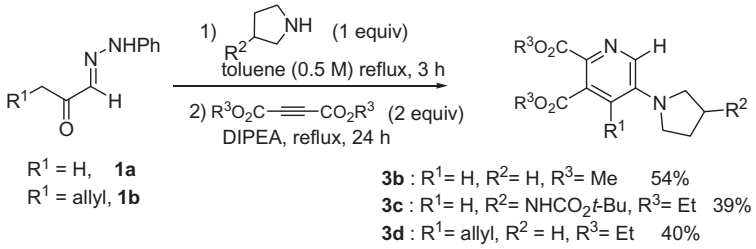

**Scheme 1.** Mannich reaction of α-ketohydrazone **1a**.



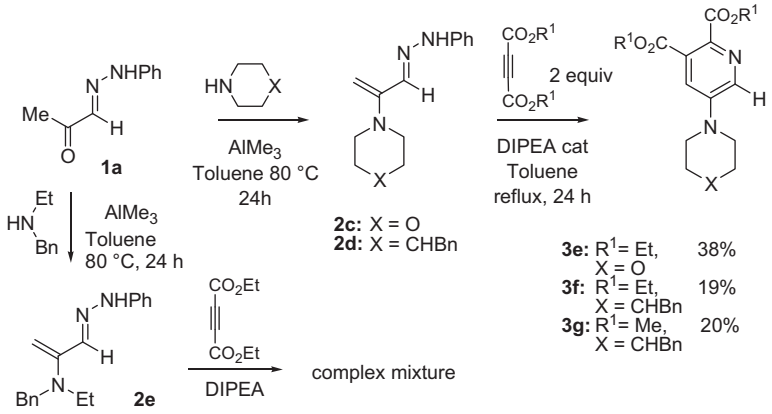

**Scheme 2.** Mannich reaction of α-ketohydrazone **1a**.




**Scheme 3.** Pyridine formation from enamine **1a**.




**Scheme 4.** Pyridine formation from α-ketohydrazone **1a**.




**Scheme 5.** Pyridine formation from six-membered cyclic amines.

dimethyl or diethyl acetylenedicarboxylate. The yields were lower than those obtained with pyrrolidines. The reaction seems to be limited to the use of cyclic amines as shown by the behavior of **2e** which gave a complex mixture when treated with the alkyne.

In conclusion, we have developed a new pyridine synthesis from α-ketohydrazones.[7] Improved access to this heterocyclic family is important as pyridines display important biological activities.[8] This reaction involves the formation of intermediate azoenamines whose reactivity has been poorly studied. Even if the final yields are moderate, this synthesis is of interest as the procedure is very simple and the starting hydrazones are readily prepared using the Japp–Klingemann reaction between β-keto acids and diazonium salts.[9]

## Acknowledgements

D.C. thanks GlaxoSmithKline and the Centre National pour la Recherche Scientifique for a fellowship. The financial support was provided by ENSTA.

## References and notes

1. Kitaev, Y. P.; Buzykin, B. I. *Russ. Chem. Rev.* **1972**, *41*, 495–515; Robinson, B. *The Fischer Indole Synthesis*; John Wiley & Sons: Chichester, 1982; Patai, S.. In *Hydrazo, Azo and Azoxy Groups*; John Wiley & Sons: Chichester, 1975; Vols. 1 and 2.
2. Burk, M. J. *J. Am. Chem. Soc.* **1991**, *113*, 8518; Enders, D.; Reinhold, U. *Tetrahedron: Asymmetry* **1997**, *8*, 1895; Manabe, K.; Oyamada, H.; Sugita, K.; Kobayashi, S. *J. Org. Chem.* **1999**, *64*, 8054–8057; Friestad, G. K.; Ding, H. *Angew. Chem., Int. Ed.* **2001**, *40*, 4491; Herrera, R. P.; Monge, D.; Martin-Zamora, E.; Fernandez, R.; Lassaleta, J. M. *Org. Lett.* **2007**, *9*, 3303–3306.
3. Atlan, V.; Bienaymé, H.; El Kaim, L.; Majee, A. *Chem. Commun.* **2000**, 1585–1586; El Kaim, L.; Gaultier, L.; Grimaud, L.; Harwood, L. M.; Michaut, V. *Green Chem.* **2003**, *5*, 477–479.
4. Atlan, V.; El Kaim, L.; Grimaud, L.; Jana, N. K. *Synlett* **2002**, 352–354; Baillez, V.; El Kaim, L.; Michaut, V. *Synth. Commun.* **2004**, *34*, 109–118.
5. McNab, H.; Murray, E. A. *J. Chem. Soc., Chem. Commun.* **1981**, 722; McNab, H.; Murray, E. A. *J. Chem. Soc., Perkin Trans. 1* **1989**, 583; Machaeek, V.; Eegan, A.; Halama, A.; Rozoavska, O.; Sirba, V. *Collect. Czech. Chem. Commun.* **1995**, *60*, 1367.
6. For a related access to pyridines by a [4+2] cycloaddition of α,β-unsaturated hydrazones see: Dolle, R. E.; Armstrong, W. P.; Shaw, A. N.; Novelli, R. *Tetrahedron Lett.* **1988**, *29*, 6349–6352.
7. *Typical procedure for* **3d**: To a solution of 100 mg of hydrazone **1b** (0.5 mmol) in 1 mL of dry toluene was added 40 μl of pyrrolidine (0.5 mmol, 1.0 equiv) and the mixture was stirred at 100 °C for 2 h. Then, 160 μl of diethyl acetylenedicarboxylate (1 mmol, 2.0 equiv) and 18 μl of *N*-ethyldiisopropylamine (0.1 mmol, 0.2 equiv) were added, and the mixture was further heated at 100 °C for 24 h. Flash chromatography on silica gel ($Et_2O$/petroleum ether, 50:50) gave the desired product **3d** as a yellow oil (66 mg, 40%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.22 (s, 1H), 6.00 (tdd, $J$ = 6.6, 10.1, 16.7 Hz, 1H), 5.12–5.04 (m, 2H), 4.39–4.28 (m, 4H), 3.58 (d, $J$ = 6.6, 4H), 2.00–1.95 (m, 4H), 1.38 (t, $J$ = 7.1 Hz, 3H), 1.37 (t, $J$ = 7.1 Hz, 3H). $^{13}$C NMR (100.6 MHz, $CDCl_3$) $\delta$ 168.1, 167.9, 143.7, 139.8, 138.2, 136.3, 127.0, 122.8, 116.5, 62.4, 62.2, 50.2, 40.1, 26.2, 14.5, 14.4. IR (thin film) 2985, 1729, 1569, 1472, 1464, 1410, 1376, 1275 cm$^{-1}$. HRMS calcd for $C_{18}H_{24}N_2O_4$: 332.1736, found: 332.1737. Typical procedure for **3e**: To a solution of 320 mg of hydrazone **1a** (2 mmol) in 2 mL of dry toluene at 0 °C were added $AlMe_3$ (1 ml, 2 mmol, 1 equiv as a 2 M solution in toluene) then morpholine (190 μl, 2.2 mmol, 1.1 equiv). The mixture was heated at 100 °C under an argon atmosphere for 24 h. The addition at room temperature of a saturated solution of sodium tartrate, followed by stirring for 15 min afforded, after extraction ($CH_2Cl_2$), crude **2c** which was further reacted with diethylacetylene dicarboxylate as for **3b**. Flash chromatography on silica gel ($Et_2O$/petroleum ether, 60:40) afforded the desired product **3e** as a yellow oil (230 mg, 38%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 9.01 (s, 1H), 8.67 (s, 1H), 4.47 (q, 7.1 Hz, 2H), 4.41 (q, $J$ = 7.1 Hz, 2H), 3.85–3.80 (m, 4H), 3.13–3.10 (m, 4H), 1.44 (t, $J$ = 7.1 Hz, 3H), 1.41 (t, $J$ = 7.1 Hz, 3H). $^{13}$C NMR (100.6 MHz, $CDCl_3$) $\delta$ 167.0, 164.5, 148.2, 147.3, 145.4, 140.3, 123.5, 67.6, 62.4, 62.3, 53.5, 14.6, 14.5. IR (thin film) 2985, 1726, 1595, 1577, 1472, 1452, 1419, 1368, 1275 cm$^{-1}$. HRMS calcd for $C_{15}H_{20}N_2O_5$: 308.1372, found: 308.1370.
8. Chu, G.-H.; Saeui, C. T.; Worm, K.; Weaver, D. G.; Goodman, A. J.; Broadrup, R. L.; Cassel, J. A.; DeHaven, R. N.; Labuda, C. J.; Koblish, M.; Brogdon, B.; Smith, S.; Le Bourdonnec, B.; Dolle, R. E. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 5931–5935; Wilson, K. J.; Van Niel, M. B.; Cooper, L.; Bloomfield, D.; O'Connor, D.; Fish, L. R.; MacLeod, A. M. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2643–2648; Saitton, S.; Del Tredici, A. L.; Mohell, N.; Vollinga, R. C.; Boström, D.; Kihlberg, J.; Luthman, K. *J. Med. Chem.* **2004**, *47*, 6595–6602; Reddy, T. R. K.; Mutter, R.; Heal, W.; Guo, K.; Gillet, V. J.; Pratt, S.; Chen, B. *J. Med. Chem.* **2006**, *49*, 607–615.
9. Japp, F. R.; Klingemann, F. *Chem. Ber.* **1887**, *20*, 2492.