Pergamon

Tetrahedron Letters, Vol. 36, No. 51, pp. 9297-9300, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)02006-3

REACTION OF *IN SITU* GENERATED α,β–UNSATURATED IMINES WITH CH-NUCLEOPHILES: A NOVEL AND EFFICIENT SYNTHESIS OF PYRIDINES.*

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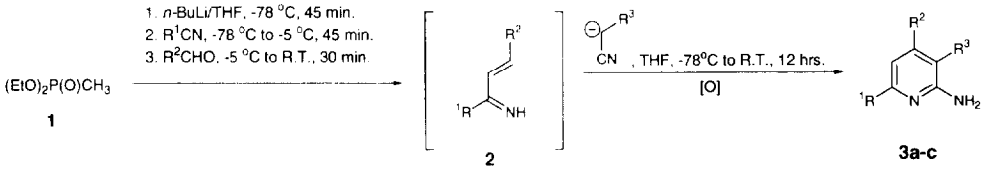
Abstract: A novel and highly efficient procedure for the synthesis of 2,4,6- trisubstituted and 2,3,4,6-tetrasubstituted pyridines has been developed. It is based on the one-pot reaction of *in situ* generated α,β–unsaturated imines with CH-nucleophiles.

The interest towards pyridine ring containing compounds is determined by their widespread occurence in nature as well as by remarkable versatility of pyridine derivatives in synthetic organic chemistry. The pyridine nucleus is a major component of a variety of natural products and drugs.[1,2] Numerous reports for the last two decades have described the application of pyridine derivatives as ligands for metal-cage complexes, in particular with lanthanides,[3] and ruthenium.[4,5] Recently, chiral metal catalysts with pyridine derivatives as ligands were shown to be enantioselective, and reactive catalysts for the synthesis of enantiopure organic compounds.[6]

A wide variety of synthetic approaches to the pyridine nucleus are available.[7,8,9] One of the most common syntheses involves the construction of the pyridine ring from [4+2] atom fragments.[10] However, there is no literature data to our best knowledge on the application of α,β–unsaturated imines as building blocks for similar reactions. Recent reports described an elegant preparation of these unstable compounds and their application for the synthesis of *E* -allylic amines,[11] and α,β–unsaturated ketones.[12] The generality of the procedure for the synthesis of α,β–unsaturated imines (**2**, Scheme 1), the mild conditions of the reaction, as well as ready availability of starting materials allowed us to conclude that **2** may be a versatile building block for construction of the pyridine ring. In order to explore this idea we studied reaction of *in situ* generated **2**[11] with anions of aryl substituted acetonitriles (Scheme 1).

Scheme 1.



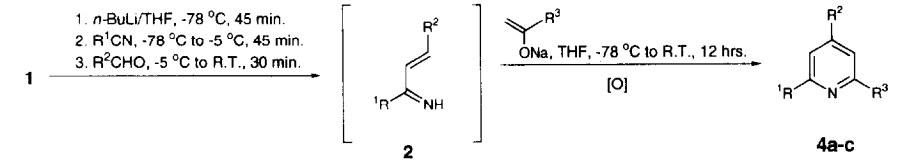
Pyridine	R^1	R^2	R^3	Yield, %[a]	M.p., °C
3a				72	154-155
3b				61	190-191
3c				68	208-209

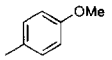
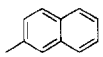
[a]Yield of isolated, analytically pure compound.[13]

In our attempt to optimize the reaction conditions, we found that the best yields of the target 2-aminopyridines **3a-c** were achieved in THF as the solvent.[14] Change of the base for the deprotonation of **1** from *n*-BuLi[11] to *sec*- or *tert*-BuLi did not affect the outcome of the reaction. Considerably better yields (by ca. 7-10%) of **3a-c** were achieved when freshly distilled components for the synthesis of **2**, namely, nitriles R_1CN, and aldehydes R^2CHO were used. Temperature was found to play a crucial role in the outcome of the reaction, probably due to the thermal instability of the imine **2**. If the reaction was allowed to stand for more than 30 min at room temperature on the stage of preparation of **2**, the yields of **3a-c** were 23-27%, and the formation of tarry materials was observed. The procedure is limited to nonenolizable nitriles and aldehydes. The application of sodium or potassium salts of acetonitriles furnished better yields of **4a-c** (by ca. 4-7%) than the corresponding lithium salts.[14] Reactions of **2** with anions of alkylnitriles, namely, acetonitrile, butyronitrile or allyl cyanide resulted in a complex mixture of products, none of them major. GC MS analysis of the reaction indicated the presence of the target aminopyridines, albeit in a low yield (11%, 7%, and 9% respectively). Attempts to isolate them by a variety of techniques were unsuccessful.

In the second series of experiments, we studied the reaction of **2** with sodium enolates of methyl aryl ketones. The results are summarized in Scheme 2.

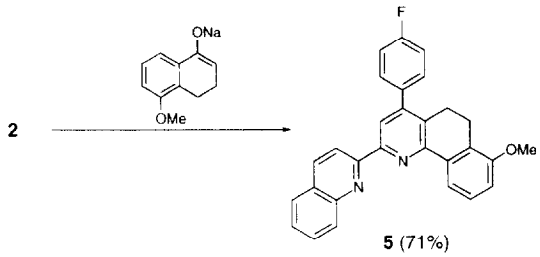
Scheme 2.



Pyridines	R^1	R^2	R^3	Yield, %[a]	M.p., °C
4a				67	136-137[15]
4b				63	163-164
4c				64	260-262

[a]Yield of isolated, analytically pure compound.[15]

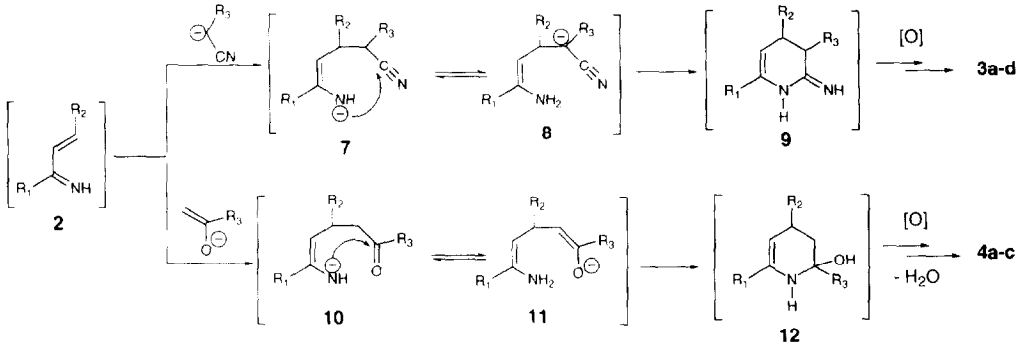
Reaction conditions were essentially similar to those reported for the reaction of **2** with anions of substituted acetonitriles[14]. Reaction of **2** and enolate of acetaldehyde[16] resulted in a complex mixture of products. No target pyridine has been detected by GC MS. Reaction of **2** with more sterically crowded sodium enolate of 5-methoxytetralone led to **5** in a good yield.



5 (71%)

It is likely that the mechanism of the reaction involves an initial attack of α,β–unsaturated imine by the CH-nucleophile (Scheme 3). The resulting intermediates **7** or **10** are in the equilibrium with stabilized anions **8** or **11**. Slow cyclization of **7** or **10** results in the formation of an intermediate tetrahydropyridine **9** or **12** followed by oxidation into **3a-d** or **4a-c**, respectively.

Scheme 3.



In summary, we have described an efficient procedure for the synthesis of 2,4,6-trisubstituted and 2,3,4,6-tetrasubstituted pyridines which is based on the reaction of anions generated from acetonitriles and alkylarylketones with *in situ* generated α,β–unsaturated imines. Further investigation on the scope, limitation, and mechanism of the reported reaction is in progress.

References and Notes.

***This paper is dedicated to my wife Natalie Ikizalp.**

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1. Coutts, R.T.; Casy, A.F. *"Pyridines and Reduced Pyridines of Pharmacological Interest"* in *"Pyridine and its Derivatives,"* Ed. by Abramovitch, R.A.; Wiley & Sons, New York, London, Sydney, Toronto; **1975**, Supplement part IV, p.445.
2. Boodman, N.S.; Hawthorne, J.O.; Masciantonio, P.X.; Simon, A.W. *Synthetic and Natural Sources of the Pyridine Ring"* in *"Pyridine and Its Derivatives."* Ed. by Abramovitch, R.A.; Wiley& Sons, New York, London, Sydney, Toronto; **1974**, Supplement part I, p. 183.
3. Alpha, B.; Lehn, J.M.; Perathoner, S.; Sabbatini, N. *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 1266.
4. Beler, P.; De Cola, L.; Von Zelewsky, A. *J. Chem. Soc.,Chem. Commun.* **1988**, 1057.
5. a) Ziessel, R.; Lehn, J.M. *Helv. Chim. Acta* **1990**, *73*, 1149; b) Balzani, V.; Bargmans, E.; Lehn, J.M.; Sabbatini, N.; Tetrorde, R.; Zeissel, R. *Helv. Chim. Acta* **1990**, *73*, 2083.
6. a) Macedo, E.; Moberg, C. *Tetrahedron: Asymmetry* **1995**, *6*, 549, and references cited therein; b) Chen, C.; Tagami, K.; Kishi, Y. *J. Org. Chem.* **1995**, *60*, 5386.
7. McKillop, A.; Boulton, A.J. *"Synthesis of Six-Membered Rings"* in *"Comprehensive Heterocyclic Chemistry,"* Ed. by Katritzky, A.R.; Rees, C.W.; Pergamon Press, Oxford, New York, Toronto, Sydney, Paris, Frankfurt, **1984**, Vol. 2, Part 2A. p.67.
8. Newkome, G.R.; Paudler, W.W. *"Contemporary Heterocyclic Chemistry,"* Wiley Interscience, New York, Chichester, Brisbane, Toronto, Singapore **1982**, pp. 177, 291.
9. a) Middeton, W.J.; Krespan, C.G.; *J. Org. Chem.* **1968**, *33*, 3625; b) Blaha, K.; Chervinka, O. *Adv. Heterocycl. Chem.* **1966**, *6*, 147.

10. Jones, G. *"Pyridines and their Benzo Derivatives: (v) Synthesis"* in *"Comprehensive Heterocyclic Chemistry,"* Ed. by Katritzky, A.R.; Rees, C.W.; Pergamon Press, Oxford, New York, Toronto, Sydney, Paris, Frankfurt, **1984**, Vol. 2, Part 2A, pp.395, 441.
11. Shin, W.S.S.; Lee, K.; Oh, D.Y. *Tetrahedron Lett.* **1995**, *36*, 281. For recent applications of β–enaminophosphonates in synthesis see also Palacios, F.; Garcia, J.; Ochoa de Retana, A.M.; Oyarzabal, J. *Heterocycles* **1995**, *41*, 1915, and references cited therein.
12. Lee, K.; Oh, D.Y. *Synthesis* **1991**, 213.

13. Selected physical data for compounds **3a-c**. All the NMR spectra were performed at 500 MHz in $CDCl_3$ with TMS as an internal standard. **3a**: ^{1}H NMR δ 4.58 (s, 2H, exch. D_2O), 6.92 (app t, J = 8.5 Hz, 2H), 7.09 (dd, J = 8.5 Hz, J ≈ 2.5 Hz, 2H), 7.12 (d, J = 8.5 Hz, 2H), 7.20 (s, 1H), 7.29 (d, J = 8.5 Hz), 7.41 (d, J = 7.5 Hz, 1H), 7.46 (app t, J = 7.5 Hz, 2H), 8.05 (d, J = 8.5 Hz, 2H). MS: m/z 375 (M^+, 100). Analysis, Calcd. for $C_{23}H_{16}ClFN_2$: C, 73.69; H, 4.30. Found: C, 73.43; H, 4.40. **3b**: ^{1}H NMR δ 3.85 (s, 3H), 4.54 (s, 2H, exch. D_2O), 6.92 (d, J = 8.5 Hz, 2H), 7.05 (app d, J = 8.5 Hz, 2H), 7.18 (d, J = 8.5 Hz, 2H), 7.23 (s, 1H), 7.29 -7.44 (m, 4H), 7.49 -7.54 (m, 4H), 7.73 (app d, J = 8.5 Hz, 2H). MS: m/z 402 (M^+, 100). HR MS, Exact mass calcd. for $C_{28}H_{22}N_2O$: 402.1732. Found: 402.1714. **3c**: ^{1}H NMR δ 3.88 (s, 3H), 4.59 (s, 2H, exch. D_2O), 6.91 (d, J = 8.5 Hz, 2H), 7.11 (d, J = 8.5 Hz, 2H), 7.16 (s, 1H), 7.18 (d, J = 8.5 Hz, 1H), 7.31 (d, J = 8.5 Hz, 2H), 7.53 (t, J = 7.5 Hz, 1H), 7.71 (t, J = 7.5 Hz, 1H), 7.84 (d, J = 7.5 Hz, 1H), 8.10 (s, 1H), 8.16 (d, J = 8.5 Hz, 1H), 8.26 (d, J = 8.5 Hz, 1H), 8.51 (d, J = 7.5 Hz, 1H). Analysis, Calcd. for $C_{27}H_{20}ClN_3O$: C, 74.05; H, 4.60. Found: C, 73.89; H, 4.71.

14. In a typical experimental procedure a solution of *n*-BuLi in hexanes (2.5M, 1mM) was added to a vigorously stirred solution of diethyl methylphosphonate (1 mM) in dry THF (5 mL) at -78°C under argon. A solution of freshly distilled nitrile (1mM) in 1 mL of THF was slowly added by syringe, and the resulting colorless to pale-yellow mixture was slowly warmed to -5°C for 45 min.[11] A solution of freshly distilled aldehyde (1mM) in 1 mL of THF was slowly added, and the resulting mixture was slowly warmed up to room temperature (30 min). A solution of sodium or potassium salt of substituted acetonitrile or alkyl aryl ketone (prepared by slow addition of the corresponding CH-acid (1.1 mM) to a solution of $Na^+(K^+)$ $^-N(SiMe_3)_2$ (2 mM) in THF) transfered by needle to the previously prepared solution of **2** at -78°C. The resulting dark yellow homogenious mixture was stirred at -78°C for an additional 15 min., slowly warmed to room temperature (1 hr), and stirred at room temperature for an additional 10-12 h until TLC (hexanes/ether, 1:1) and GC MS analyses indicated absence of starting substituted acetonitrile or alkyl aryl ketone. Stream of oxygen (5mL/min) was passed through the resulting mixture (15-20 min.), it was quenched with 0.1N HCl, extracted with 5X15 mL of EtOAc, organic extract was washed with 3X30 mL of brine, dried over Na_2SO_4, concentrated to 10 mL, cooled down in the freezer, triturated with dry cold ether, the resulting precipitate was collected, and washed with cold ether to give analytically pure pyridines **3-6** (45-55% yield). Additional 15-20% of the target compounds were isolated from the mother liquor by column chromatography (Silicagel, eluent: hexanes/EtOAc, 1:1).

15. Selected physical data for compounds **4a-c, 5. 4a**: m.p. 136-137°C (135-136°C, Reddelien, G. *Ber.* **1920,** *53B*, 334). **4b**: ^{1}H NMR δ 3.84 (s, 3H), 7.12 (app d, J = 8.5 Hz, 2H), 7.54 (m, 2H), 7.90-8.11 (m, 5H), 8.25-8.35 (m, 3H), 8.38 (app s, 1H), 8.47 (d, J = 8.5 Hz), 8.73 (app d, J = 4.5 Hz, 2H), 8.78 (app s, 1H). MS: m/z 388 (M^+, 100). HR MS: Exact mass calcd. for $C_{27}H_{20}N_2O$: 388.1576. Found: 388.1585. **4c:** m.p. 264-265°C (264-265°C, Anderson, H.L.; Anderson, S.; Sanders, J.K.M. *J. Chem. Soc., Perkin Trans.1* **1995**, 2231). **5:** M.p. 214-215°C. ^{1}H NMR δ 2.68 (m, 2H), 2.92 (m, 2H), 3.95 (s, 3H), 6.97 (d, J = 8.5 Hz, 1H), 7.21 (t, J = 8.5 Hz, 2H), 7.40-7.50 (m, 3H), 7.52 (t, J = 7.5 Hz, 1H), 7.72 (t, J = 7.5 Hz, 1H), 7.76 (d, J = 7.5 Hz, 1H), 8.24 (d, J = 7.5 Hz, 1H), 8.31 (d, J = 8.5 Hz, 2H), 8.51 (s, 1H), 8.86 (d, J = 7.5 Hz, 1H). MS: m/z 432 (M^+, 100). HR MS: Exact mass calcd for $C_{29}H_{21}FN_2O$: 432.1638. Found: 432.1635.

16. Fitzgerald, J.J.; Drysdale, N.E.; Olofson, R.A. *J. Org. Chem.* **1992**, *57*, 7122 and references cited therein.

(*Received in USA* 26 *September* 1995; *revised* 19 *October* 1995; *accepted* 20 *October* 1995)