Nef–Perkow Access to Indolizine Derivatives

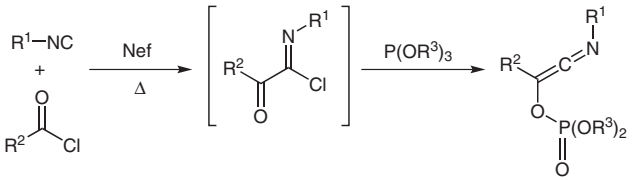
Didier Coffinier,* Laurent El Kaim,* Laurence Grimaud*

Laboratoire Chimie et Procédés, Ecole Nationale Supérieure de Techniques Avancées, 32 Bd Victor, 75739 Paris Cedex 15, France
Fax +33(1)45525587; E-mail: didier.coffinier@laposte.net; E-mail: laurent.elkaim@ensta.fr; E-mail: laurence.grimaud@ensta.fr
Received 2 August 2010

Abstract: We present herein a new access to indolizine derivatives involving 1,3-dipolar cycloaddition of pyridinium ylides with phosphorylated hydroxyketenimines. These ketenimines are easily formed via a Nef–Perkow cascade involving isocyanides as starting material.

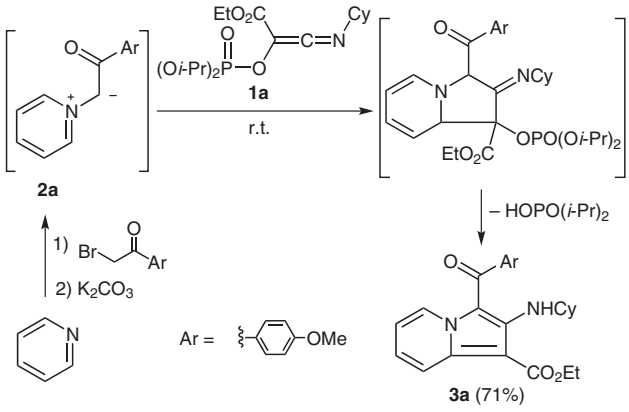
Key words: Nef reaction, isocyanide, indolizine, pyridinium ylide, cycloaddition

Best known for his discovery of the conversion of a nitro to ketone functionality, Nef also disclosed an interesting formation of imidoyl chlorides from the α-addition of acyl chlorides onto isocyanides.[1] In comparison with the more recent Ugi and Passerini reactions,[2] this reaction covers an aspect of isocyanide reactivity that has remained largely unexplored.[3] Following our interest in isocyanide-based multicomponent reactions, we recently revisited this reaction with the idea of transforming it into a three-component process by the final addition of various nontrivial nucleophiles. Eventually, this process led us to disclose a new solvent-free preparation of ketenimines by a two-step procedure involving a Nef reaction followed by the trapping of the resulting imidoyl chloride by a phosphite in a Perkow-type reaction (Scheme 1).[4] These ketenimines were fairly stable and could be separated on silica gel without extensive hydrolysis.



Scheme 1 Ketenimine formation

Ketenimines are known as reactive intermediates that can be trapped by various nucleophiles or involved in different cycloadditions.[5] An interesting feature of the cycloadditions with these species is their ability to interact either by their alkene or imine moiety.[6] We previously reported a 1,2,3-triazole formation through the reaction of phosphorylated hydroxyketenimines **1** with silyldiazomethane.[4] We were interested to explore further the influence of the phosphorylated group on cycloadditions with other 1,3-dipoles, such as the one derived from pyridines. Pyridinium ylides have been widely used in dipolar cycloadditions with unsaturated compounds.[7] These dipolar species are easily prepared through the alkylation of pyridine followed by a basic treatment of the resulting pyridinium salt. The ylide **2a** was prepared in acetonitrile from pyridine and *p*-methoxybromoacetophenone. To this in situ prepared ylide was directly added the ketenimine **1a**. The resulting mixture was left overnight at room temperature. After the usual treatment, the indolizine **3a** was obtained in a 71% isolated yield. This indolizine formation may be explained by a 1,3-dipolar cycloaddition involving the alkene moiety of the ketenimine **1a**, followed by an aromatization of the fused-ring system through the elimination of the phosphate (Scheme 2).



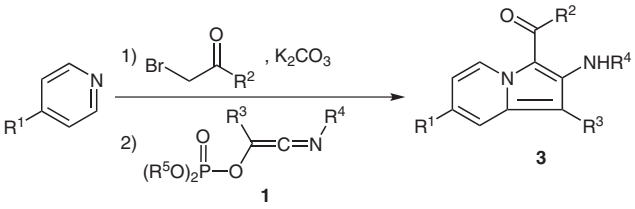
Scheme 2 Indolizine **3a** formation from **1a**

As shown by the various examples reported in Table 1, phosphorylated hydroxyketenimines **1** behave similarly with various pyridinium ylides to form indolizine derivatives **3** in good to moderate yields.

When dealing with ketenimines **1**, the best yields were obtained with carboethoxy-substituted derivatives **1a** and **1b**. This is probably associated with a more efficient control of the cycloaddition by a $HOMO_{(dipole)}$–$LUMO_{(ketenimine)}$ interaction; the ketenimine reacting as an electrophile with the initial bonding at the imine carbone of **1**. This is consistent with a weak coupling of **1a** with the electron-deficient ylide formed from bromopyruvic acid derivatives (entry 9) as well as with the lack of reactivity of **1f**. The latter may be explained by the reduced efficiency of nucleophilic additions onto the sterically hindered *N-tert*-butylketenimine.

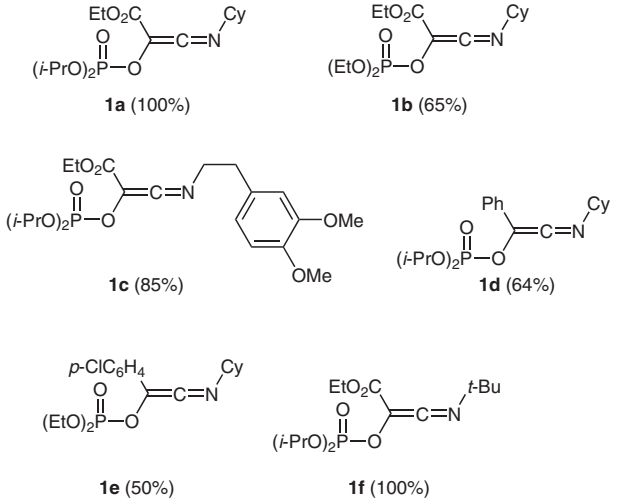
SYNLETT 2010, No. 16, pp 2474–2476
Advanced online publication: 14.09.2010
DOI: 10.1055/s-0030-1258569; Art ID: D20810ST

Table 1 Synthesis of Indolizine Derivatives **3**



Entry	R^1	R^2	**1**[a]	Product, yield (%)
1	H	4-$MeOC_6H_4$	**1b**	**3a** 63
2	H	4-BrC_6H_4	**1a**	**3b** 51
3	4-$O_2NCH_2C_6H_4$	4-$MeOC_6H_4$	**1a**	**3c** 36
4	H	4-$MeOC_6H_4$	**1c**	**3d** 61
5	H	4-$MeOC_6H_4$	**1d**	**3e** 31
6	H	4-$MeOC_6H_4$	**1e**	**3f** 37
7	H	MeO	**1a**	**3g** 74
8	H	MeO	**1d**	**3h** 23
9	H	MeO_2C	**1a**	–
10	H	4-$MeOC_6H_4$	**1f**	–

[a] For the different ketenimines **1** involved and the yields obtained for their preparation from the corresponding isocyanide, acylchloride and phosphite, see ref. 4.



In all these reactions, we could not isolate any product resulting from a cycloaddition onto the carbon–nitrogen moiety of the ketenimine, as opposed to the results observed with diazo compounds.[4] Reasonable yields are obtained mostly with carboethoxy-substituted ketenimine derivatives. Their very efficient synthesis from isocyanides and oxalyl chloride monoester make it possible to use them in the subsequent cycloaddition without any intermediate purification.

In conclusion, we have disclosed a new indolizine preparation from isocyanides. This synthesis features a new cyclization mode for phosphorylated hydroxy ketenimines **1**. Beside its mechanistic interest, this study brings a new access to scaffolds with significant biological interest. Indeed, indolizines have found applications as phospholipase A2 inhibitors,[8] channel calcium antagonists,[9] selective estrogen receptors modulators,[10] or melatonin receptors inhibitors.[11] We are currently exploring further the reactivity and synthetic potential of phosphorylated hydroxy ketenimines **1**.

Typical Procedure for the Preparation of Compound 3a

Pyridine (1 mmol) and bromoacetophenone (1 mmol) were heated in MeCN (0.3 M) at 60 °C for 30 min. Potassium carbonate (2 mmol) and a solution of **1a** (1 mmol) in MeCN (1 mL) were then added. The resulting mixture was left at r.t. overnight. Hydrolysis followed by an extraction with CH_2Cl_2 and a flash chromatography (EtOAc–PE) afforded **3a** as a pale yellow solid (mp 136–138 °C, 299 mg, 71%).

Spectroscopic Data for Indolizine 3a

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.58 (d, *J* = 7.1 Hz, 1 H), 8.07 (d, *J* = 8.6 Hz, 1 H), 7.81 (d, *J* = 8.8 Hz, 2 H), 7.32 (t, *J* = 8.1 Hz, 1 H), 6.96 (d, *J* = 8.8 Hz, 2 H), 6.85 (t, *J* = 7.1 Hz, 1 H), 6.56 (d, *J* = 10.4 Hz, 1 H), 4.43 (q, *J* = 7.3 Hz, 2 H), 3.89 (s, 3 H), 2.56 (br s, 1 H), 1.55–1.36 (m, 5 H), 1.48 (t, *J* = 7.3 Hz, 3 H), 1.10–0.98 (m, 1 H), 0.98–0.84 (m, 4 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 185.6, 166.7, 163.1, 150.5, 138.8, 133.4, 131.6, 128.2, 127.9, 118.2, 114.1, 113.7, 112.3, 93.9, 60.1, 58.5, 55.9, 33.8, 26.0, 25.3, 15.0. IR (thin film): 2360, 1664, 1591, 1508, 1423, 1313, 1218, 1173 cm^{-1}. HRMS: *m/z* calcd for $C_{25}H_{28}N_2O_4$: 420.2049; found: 420.2062.

Acknowledgment

Financial support was provided by GlaxoSmithKline, the CNRS and ENSTA ParisTech.

References

(1) Nef, J. U. *Justus Liebigs Ann. Chem.* **1892**, *270*, 267.
(2) For general reviews on Ugi- and Passerini-based multicomponent reactions, see: (a) Banfi, L.; Riva, R. *Org. React.* **2005**, *65*, 1. (b) Zhu, J. *Eur. J. Org. Chem.* **2003**, 1133. (c) Ugi, I.; Werner, B.; Dömling, A. *Molecules* **2003**, *8*, 53. (d) Hulme, C.; Gore, V. *Curr. Med. Chem.* **2003**, *10*, 51. (e) Bienaymé, H.; Hulme, C.; Oddon, G.; Schmitt, P. *Chem. Eur. J.* **2000**, *6*, 3321. (f) Dömling, A.; Ugi, I. *Angew. Chem. Int. Ed.* **2000**, *39*, 3168. (g) Dömling, A. *Chem. Rev.* **2006**, *106*, 17.
(3) (a) Ugi, I.; Fetzer, U. *Chem. Ber.* **1961**, *94*, 1116. (b) Adlington, R. M.; Barrett, A. G. M. *Tetrahedron* **1981**, *37*, 3935. (c) Westling, M.; Smith, R.; Livinghouse, T. *J. Org. Chem.* **1986**, *51*, 1159. (d) Van Wangenen, B. C.; Cardellina, J. H. *Tetrahedron Lett.* **1989**, *30*, 3605. (e) El Kaim, L.; Pinot-Périgord, E. *Tetrahedron* **1998**, *54*, 3799. (f) Livinghouse, T. *Tetrahedron* **1999**, *55*, 9947; and references cited therein. (g) Chen, J. J.; Deshpande, S. V. *Tetrahedron Lett.* **2003**, *44*, 8873. (h) El Kaim, L.; Gaultier, L.; Grimaud, L.; Vieu, E. *Tetrahedron Lett.* **2004**, *45*, 8047.
(4) Coffinier, D.; El Kaim, L.; Grimaud, L. *Org. Lett.* **2009**, *11*, 1825.

(5) (a) Sung, K.; Wu, S. H.; Wu, R. R.; Sun, S. Y. *J. Org. Chem.* **2002**, *67*, 4298. (b) Cheng, Y.; Ma, Y. G.; Wang, X. R.; Mo, J. M. *J. Org. Chem.* **2009**, *74*, 850. (c) Giera, H.; Huisgen, R.; Polborn, K. *Eur. J. Org. Chem.* **2005**, 3781. (d) Alajarin, M.; Vidal, A.; Tovar, F.; Ramirez de Arellano, M. C. *Tetrahedron: Asymmetry* **2004**, *15*, 489. (e) Ruiz, J.; Marquinez, F.; Riera, V.; Vivanco, M.; Garcia-Granda, S.; Diaz, M. R. *Angew. Chem. Int. Ed.* **2000**, *39*, 1821. (f) Sonveaux, E.; Ghosez, L. *J. Am. Chem. Soc.* **1973**, *95*, 5417. (g) Lu, P.; Wang, Y. *Synlett* **2010**, 165.

(6) Fabian, W. M. F.; Janoschek, R. *J. Org. Chem.* **1997**, *119*, 4253.

(7) (a) Bayazit, M. K.; Coleman, K. S. *J. Am. Chem. Soc.* **2009**, *131*, 10670. (b) Padwa, A.; Austin, D. J.; Precedo, L.; Zhi, L. *J. Org. Chem.* **1993**, *58*, 1144. (c) Tsuge, O.; Kanemasa, S.; Takenaka, S. *J. Org. Chem.* **1986**, *51*, 1853. (d) El Kaim, L.; Gizolme, M.; Grimaud, L. *Synlett* **2007**, 227. (e) Coldham, I.; Hufton, R. *Chem. Rev.* **2005**, *105*, 2765. (f) Kianmehr, E.; Ghanbari, M.; Niri, M. N.; Faramarzi, R. *J. Comb. Chem.* **2010**, *12*, 41.

(8) (a) Hagishita, S.; Yamada, M.; Shirahase, K.; Okada, T.; Murakami, Y.; Ito, Y.; Matsuura, T.; Wada, M.; Kato, T.; Ueno, M.; Chikazawa, Y.; Yamada, K.; Ono, T.; Teshirogi, I.; Ohtani, M. *J. Med. Chem.* **1996**, *39*, 3636. (b) Oslund, R. C.; Cermak, N.; Gelb, M. H. *J. Med. Chem.* **2008**, *51*, 4708.

(9) Gubin, J.; de Voglaer, H.; Inion, H.; Houben, C.; Lucchetti, J.; Mahaux, J.; Rosseels, G.; Peiren, M.; Clinet, M.; Polster, P.; Chatelain, P. *J. Med. Chem.* **1993**, *36*, 1425.

(10) Jorgensen, A. S.; Jacobsen, P.; Christiansen, L. B.; Bury, P. S.; Kanstrup, A.; Thorpe, S. M.; Naerum, L.; Wassermann, K. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2383.

(11) Poël, H. V.; Guillaumet, G.; Viaud-Massuard, M.-C. *Tetrahedron Lett.* **2002**, *43*, 1205.