A münchnonimine-based method for the synthesis of 3,6-diaryl-2(*1H*)-pyridones

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A new and convenient procedure for the preparation of 3,6-diaryl-2(1*H*)-pyridones via 1,3-dipolar cycloaddition of münchnonimines to acrylic esters is described.

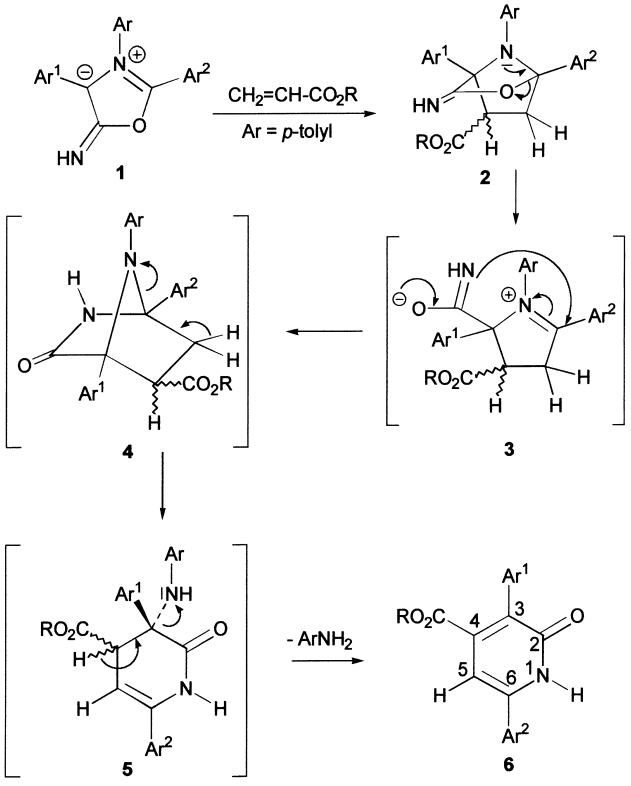
Keywords: mesoionic compounds, münchnonimines, cycloaddition, 2-pyridones

The 2-*1H*-pyridone ring is an important moiety of biologically active compounds and structurally interesting molecules.[1–9] Therefore there are numerous known methods for their synthesis[10–11] and new procedures are continually being developed.[12–17]

Our previous studies[29,30] on the reactivity of an open-chain analogue of Reissert compound hydrofluoroborate salt **1aA** ($Ar^1 = Ar^2 = Ph$) with ethyl acrylate have led us to the synthesis of ethyl 3,6-diphenyl-2-*1H*-pyridone-4-carboxylate **6aA*E*** ($Ar^1 = Ar^2 = Ph$, R = Et) (Scheme 1). The structural advantage and the convenient synthetic method of this compound led us to look for the generalisation of this procedure and we report here a more complete study of the scope of the process.

The cornerstone of our synthetic plan is the [3+2] cycloaddition of a münchnonimine intermediate (Scheme 1).

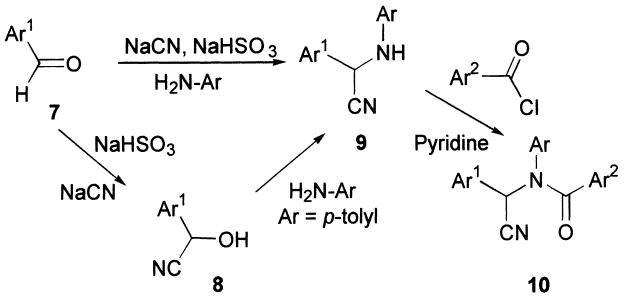
The mesoionic species **1** undergoes 1,3-dipolar cycloaddition with an acrylate ester to give the [3+2] cycloadduct **2**. The HN=C–O– bridge next opens, being assisted by the nitrogen electron pair of the pyrrolidine moiety, giving the transient species **3**. This last rearranges to the bicyclic intermediate **4**, opening of which gives the 3,4-dihydro-2(1*H*)-pyridone **5**, precursor of the final 2(1*H*)-pyridone **6**, formed by elimination of a molecule of *p*-toluidine.



Scheme 1 Mechanism of formation of the pyridones (6).

Moreover, since the heterocyclic ring bears two aryl groups *para*-disposed at positions 3 and 6, it seemed of particular interest to introduce an electron-donating group (EDG) on one aryl moiety and an electron-withdrawing group (EWG) on the other. Our goal was based on the insertion of a 2(1*H*)-pyridone ring as transmitting (central) ring in order to build an active Non Linear Optics push-pull molecule.

The general procedure for the preparation of the open-chain analogues (**10**) of Reissert compounds involved first the synthesis of an aminonitrile (**9**) by condensation of a primary amine with a cyanohydrin (**8**). The preparation of these aminonitriles was accomplished by two methods (Scheme 2).[43–45]



Scheme 2 Synthesis of 2-(N-aroyl-N-p-tolylamino) arylacetonitriles (10).

The aminonitrile **9** was then treated with an acid chloride to form the α-acylaminonitrile (a Reissert analogue) **10** (Scheme 2). Each Reissert salt analogue (1) was prepared (Scheme 3) by dissolving the corresponding Reissert analogue, a 2-(*N*-aroyl-p-tolylamino)arylacetonitrile 10, in dry ether and adding a 54 % etheral solution of fluoroboric acid.

The first step of our strategy cannot be extended to arylaldehydes bearing an electron-withdrawing substituent, because under these conditions they reacted in only a very poor yield. So, we started only with benzaldehyde and arylaldehydes bearing electron-donor substituents to obtain the best results. The succeeding steps, the preparation of the open-chain analogues of Reissert compounds and of their tetrafluoroborate salts, afforded good yields. The last reaction, the 1,3-dipolar cycloaddition and rearrangement, gave pyridones (**6**) in yields of between 36 and 85 %.

We have shown that a range of highly substituted 2(1*H*)-pyridones can be assembled using the [3+2] cycloaddition of 2-(*N*-aroyl-*p*-tolylamino)arylacetonitrile tetrafluoroborate

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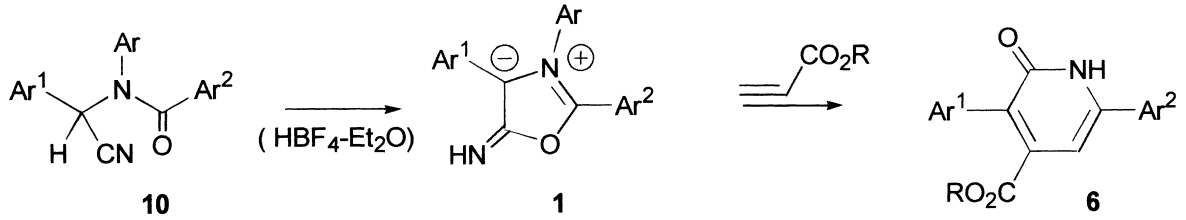

Scheme 3 Synthesis of 2-pyridones (**6**) via münchnonimines (**1**).

Table 1 Pyridones (**6**) synthesised via münchnonimines (**1**)

Ar^1	Ar^2	CO_2R	Pyridone
Phenyl **a**	Phenyl **A**	Ethyl ***E***	**6aA*E*** [29,30]
p-Anisyl **b**	Phenyl **A**	Ethyl ***E***	**6bA*E***
m-Anisyl **c**	Phenyl **A**	Ethyl ***E***	**6cA*E***
p-Chlorophenyl **d**	Phenyl **A**	Ethyl ***E***	**6dA*E***
Phenyl **a**	*p*-Anisyl **B**	Ethyl ***E***	**6aB*E***
p-Anisyl **b**	*p*-Anisyl **B**	Ethyl ***E***	**6bB*E***
m-Anisyl **c**	*p*-Anisyl **B**	Ethyl ***E***	**6cB*E***
Phenyl **a**	*p*-Tolyl **C**	Ethyl ***E***	**6aC*E***
p-Anisyl **b**	*p*-Tolyl **C**	Ethyl ***E***	**6bC*E***
m-Anisyl **c**	*p*-Tolyl **C**	Ethyl ***E***	**6cC*E***
m-Tolyl **e**	*p*-Tolyl **C**	Ethyl ***E***	**6eC*E***
Phenyl **a**	*p*-Nitrophenyl **D**	Ethyl ***E***	**6aD*E***
p-Anisyl **b**	*p*-Nitrophenyl **D**	Ethyl ***E***	**6bD*E***
m-Anisyl **c**	*p*-Nitrophenyl **D**	Ethyl ***E***	**6cD*E***
p-Chlorophenyl **d**	*p*-Nitrophenyl **D**	Ethyl ***E***	**6dD*E***
m-Tolyl **e**	*p*-Nitrophenyl **D**	Ethyl ***E***	**6eD*E***
2-Thienyl **f**	*p*-Nitrophenyl **D**	Hexyl ***H***	**6fD*H***
p-Dimethylaminophenyl **g**	*p*-Nitrophenyl **D**	Hexyl ***H***	**6gD*H***
p-n-Propyloxyphenyl **h**	*p*-Nitrophenyl **D**	Ethyl ***E***	**6hD*E***
p-n-Propyloxyphenyl **h**	*p*-Nitrophenyl **D**	Hexyl ***H***	**6hD*H***
p-Methylthiophenyl **i**	*p*-Nitrophenyl **D**	Hexyl ***H***	**6iD*H***
p-n-Hexyloxy **k**	*p*-Nitrophenyl **D**	Hexyl ***H***	**6kD*H***
p-Ethoxyphenyl **l**	*p*-Nitrophenyl **D**	Ethyl ***E***	**6lD*E***
2-Thienyl **f**	*p*-Cyanophenyl **E**	Hexyl ***H***	**6fE*H***
p-n-Propyloxyphenyl **h**	*p*-Cyanophenyl **E**	Hexyl ***H***	**6hE*H***
p-Methylthiophenyl **i**	*p*-Cyanophenyl **E**	Allyl ***A***	**6iE*A***
p-Methylthiophenyl **i**	*p*-Cyanophenyl **E**	Ethyl ***E***	**6iE*H***
p-Allyloxyphenyl **j**	*p*-Cyanophenyl **E**	Ethyl ***E***	**6jE*H***
p-Ethoxyphenyl **l**	*p*-Cyanophenyl **E**	Hexyl ***H***	**6lE*H***

salts (münchnonimine hydrofluoroborates – open-chain Reissert salt analogues). This efficient chemical pathway allows versatile functionalisation with a large choice of substituents and the possibility to develop polymers and sol-gel process. The polymerisation procedure and the sol-gel strategy are under current investigation.

Techniques used: IR, 1H NMR

References: 51

Schemes: 3

Table: 1

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References cited in this synopsis

1 K. Konno, K. Hashimoto, Y. Ohfune, H. Shimara, and T. Matsumoto, *J. Am. Chem. Soc*., 1988, **110**, 4807.
2 T.R. Kelly, S. Bell, N. Ohashi, and J. Armstrong-Chong, *J. Am. Chem. Soc*., 1988, **110**, 6471.
3 G. Pattenden and G.F. Smith, *Tetrahedron Lett*., 1990, **31**, 6557.
4 D.P. Curran and H. Liu, *J. Am. Chem. Soc*., 1992, **114**, 5863.
5 C.A. Veale, P.R. Bernstein, C. Bryant, C. Ceccarelli, J.R. Damewood Jr., R. Early, S. W. Feeney, B. Gomes, B.J. Kosmider, G.B. Steelman, R.M. Thomas, E.P. Vacek, J.C. Williams, D.J. Wolanin, and S. Woolson, *J. Med. Chem*., 1995, **38**, 98.
6 A.P. Kozikowski, G. Campiani, L-Q. Sun, S. Wang, A. Saxena, and B. P. Doctor, *J. Am. Chem. Soc*., 1996, **118**, 11357.
7 D.R. Williams, P.D. Lowder, and Y-G. Gu, *Tetrahedron Lett*., 1997, **38**, 327.
8 S.J. Brickner, *Chem. Ind*. (London), 1997, 131.
9 M. Rubiralta, E. Giralt, and A. Diez, *Piperidine: Structure, Preparation, Reactivity, and Synthetic Applications of Piperidine and its Derivatives,* Elsevier, Amsterdam, 1991.
10 H. Meislich, *in Pyridine and its Derivatives*, ed. E. Klingsberg, Interscience, New York, 1962. Vol. 3, pp. 509-890.
11 G. Jones, *in Comprehensive Heterocyclic Chemistry II*, eds A. R. Katritzky, C.W. Rees, and E.F.V. Scriven, Pergamon Press, Oxford, 1996. Vol.5.
12 R. Jain, F. Roshangar, and M.A. Ciufolini, *Tetrahedron Lett*., 1995, **36**, 3307.
13 Y. Tohda, T. Yanagidani, S.-i. Hiramatsu, N. Nishiwaki, K. Tani, and M. Ariga, *Bull. Chem. Soc. Japan*, 1997, **70**, 2781.
14 I. Collins and J.L. Castro, *Tetrahedron Lett*., 1999, **40**, 4069.
15 S.M. Sheehan and A. Padwa, *J. Org. Chem*., 1997, **62**, 438.
16 A. Padwa, S.M. Sheehan, and C. S. Straub, *J. Org. Chem*., 1999, **64**, 8648.
17 E.M. Brun, S. Gil, R. Mestres, and M. Parra, *Synthesis*, 2000, 273.
29 S. Perrin, K. Monnier, B. Laude, M.M. Kubicki, and O. Blacque, *Tetrahedron Lett*., 1998, **39**, 1753.
30 S. Perrin, K. Monnier, B. Laude, M.M. Kubicki, and O. Blacque, *Eur. J. Org. Chem*., 1999, 297.