Tetrahedron Letters, Vol.31, No.26, pp 3793-3796, 1990
Printed in Great Britain

0040-4039/90 $3.00 + .00
Pergamon Press plc

SYNTHESIS OF 4(1*H*)-PYRIDONES BY CARBONYLATION OF 2-AZA-1,3-DIENES.

José Barluenga, Raquel Pérez Carlón, Francisco J. González, and Santos Fustero
Departamento de Química Organometálica, Facultad de Química, Universidad de Oviedo, 33071-Oviedo, Spain

Summary: The synthesis of 4(1*H*)-pyridones 5 from electronically neutral 2-azadienes 1 and the system *N,N'*-carbonyldiimidazole/BF_3OEt_2 is described. The participation of *N,N'*-carbonyldiimidazole in two carbon-carbon bonds formation reaction is reported for the first time.

The pharmacological properties of functionalized pyridines makes of great interest the development of new synthetic routes for the preparation of these systems. Specifically, the 4(1*H*)-pyridones are interesting by their utility in the preparation of different types of β-lactamic antibiotics.[1]

Some of the methods developed for the synthesis of these systems imply pyrolytic reactions involving enamines,[2] [3+3]-fragment additions of ketimines to deficient acetylenes,[3] [4+2]-atoms fragments nucleophilic additions of dianions to lactim esters or nitriles,[4] or, more usually, modification of previously prepared heterocycles.[5] In contrast, very few examples of a [5+1]-heterocyclization reactions have been reported [6a] and most of them proceed through the formation of two C-N bonds, normally by nucleophilic addition of amines or ammonia to several substrates. [6b]

Here we wish to report a new and very simple synthesis of 4(1*H*)-pyridones through a [5+1]-reaction of electronically neutral 2-azadienes **1** and *N,N'*-carbonyldiimidazole **2**.

The reactivity and synthetic utility of this type of systems **1** have been studied in our Department for several years.[7] We have indicated that these systems are able to undergo [4+2]-cycloaddition reactions with electron-poor dienophiles.[8]

Likewise, in some occasions they are suitable to experiment [5+1]-heterocyclization reactions (Fig. 1); thus, for example, compounds **1** react with imines to give pentasubstituted pyridines.[9] In the same way, the reaction of **1** and halogenophosphines lead to 1,4-azaphosphinine derivatives through a cyclocondensation process.[10]

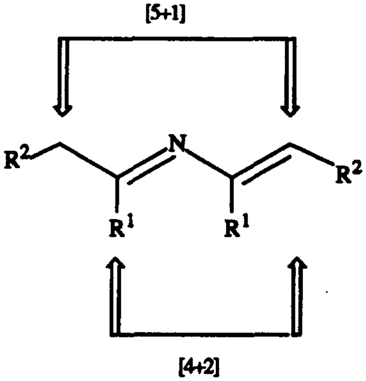
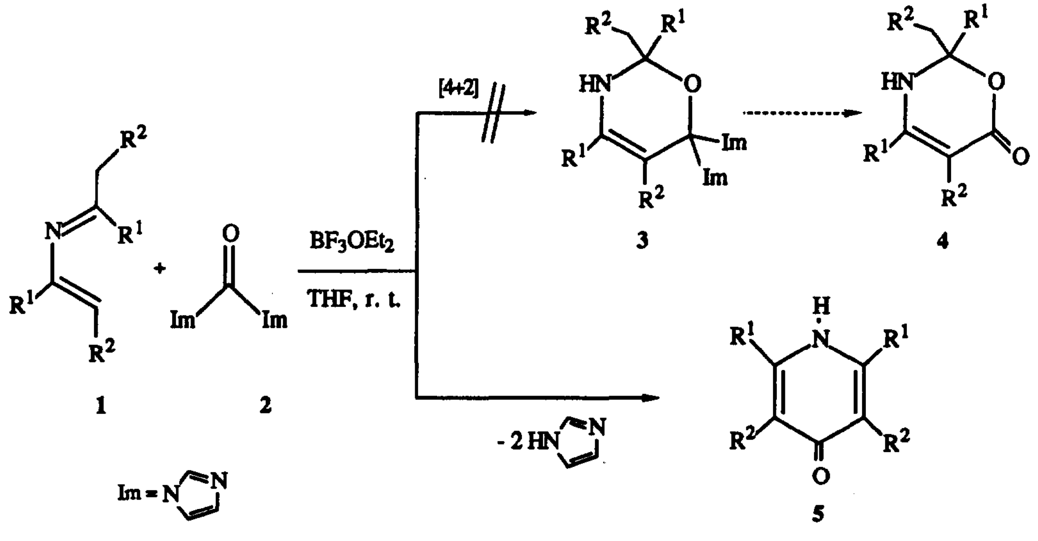


Fig. 1

In the course of our studies about the [4+2]-cycloaddition reactions of 2-azadienes **1** with heterocumulenes and carbonyl compounds, we tried *N,N'*-carbonyldiimidazole **2** because this reagent could behave as a carbon dioxide equivalent (see Scheme 1).[11] However, we found that the reaction of **1** with **2**, led to the 4(1*H*)-pyridones **5** (see Scheme 1, Table 1), instead of corresponding [4+2]-cycloadduct **3** or its derivative **4**.



Scheme 1

The reaction takes place in the presence of 1 eq. of BF_3OEt_2 (ratio **1**:**2**: BF_3OEt_2 = 1:1.2:1.2), proceed in smooth conditions, THF as solvent and room temperature for several hours, and give rise with high yields (see Table 1) to compounds **5** isolated as white crystalline solids.[12]

The 4(1*H*)-pyridones **5** were fully characterized on the basis of their spectroscopic data and mass-spectrometry.[13]

The course of this reaction is strongly influenced by the Lewis acid. Thus, when the reaction was carried out in absence of BF_3OEt_2 as catalyst, the starting materials were completely recovered.

The formation of these compounds implies a [5+1]-cyclocondensation process with the formation of two carbon-carbon bonds. In this context, it is worth nothing that the *N,N'*-carbonyldiimidazole has been extensively used as a "carbonyl transfer reagent" for carbon-heteroatom bond forming reactions [14] but its use in the formation of carbon-carbon bonds does not appear to be well precedented in the literature.

As far as we are aware, only one example of the participation of *N,N'*-carbonyldiimidazole in reactions of one carbon-carbon bond formation have been reported in the literature, in the critical step of total synthesis of (+)-Actinobolin.[15]

Table 1. 4(1*H*)-pyridones **5**.

Compd.	R^1	R^2	yield (%)[a]	m.p. (ºC)
5a	Ph	Me	80	260-2 (d)
5b	*p*-MeC_6H_4	Me	83	342-4 (d)
5c	Ph	Et	90	260-2 (d)
5d	Ph	*n*-Pr	85	234-6 (d)
5e	*c*-C_6H_{11}	Me	75	270-2 (d)

[a] Referred to 2-azadiene **1**.

Finally, when the *N,N'*-thiocarbonyldiimidazole was used in the reaction with **1** in the same conditions as above, the starting materials were recovered, due, probably, to the lower reactivity of double bond carbon-sulphur in relation with the oxygenated homologue.

In conclusion, we report in this communication a new and very simple synthesis of 4(1*H*)-pyridones **5** from 2-azadienes **1**, by reaction with the system *N,N'*-carbonyldiimidazole/BF_3OEt_2.

Acknowledgements. We thank the financial support received from the Comisión Asesora de Investigación Científica y Técnica (CAICYT). One of us (R. P. C.), thanks the Ministerio de Educación y Ciencia for a predoctoral scholarship.

References.

1. The presence of pyridone derivatives in the side chain of various penicillin and cephalosporin nuclei conferred a broad spectrum of activity to these compounds; see, for example: D. DeJohn, J.M. Domagala, J.S. Kaltenbronn, and U. Krolls, *J. Heterocyclic Chem.*, **1983**, *20*, 1295; J.M. Domagala, *J. Org. Chem.*, **1984**, *49*, 126.
2. F. Arya, J. Bouquant, J. Chuche, *Synthesis*, **1983**, 946.
3. J. Barluenga, F. López Ortiz, F. Palacios, and V. Gotor. *Synthetic Communications*, **1983**, *13(5)*, 411.
4. J.B. Jiang and M.J. Urbansky, *Tetrahedron Letters*, **1985**, 259.
5. M. Mitelbach, *Synthesis*, **1988**, 479.
6. a) D.M. Smith, in *Comprehensive Organic Chemistry*, P.G. Sammes, Ed. Pergamon Press, Oxford, **1979**, Vol. 4, p. 64-65; b) G. Jones, in *Comprehensive Heterocyclic Chemistry*, A.J. Boulton and A. Mckillop, Ed. Pergamon Press, Oxford, **1984**, Vol. 2, p. 436-437.
7. J. Barluenga, J. Joglar, F.J. González, and S. Fustero, *Synlett*, **1990**, *3*, 129.
8. J. Barluenga, F.J. González, S. Fustero, and V. Gotor, *J. Chem. Soc. Chem. Commun.*, **1986**, 1180; J. Barluenga, F.J. González, and S. Fustero, *Tetrahedron Letters*, **1989**, 2685.
9. J. Barluenga, J. Joglar, F.J. González, V. Gotor, and S. Fustero, *J. Org. Chem.*, **1988**, *53*, 5960.
10. J. Barluenga, F. Palacios, F.J. González, and S. Fustero, *J. Chem. Soc. Chem. Commun.*, **1988**, 1596.
11. For a related reaction with *N,N'*-thiocarbonyldiimidazole, see: D.L. Boger and S.N. Weinreb, *Hetero Diels-Alder Methodology in Organic Synthesis*, Academic Press, **1987**, p. 133-134.
12. **Typical Procedure:** A mixture of 2-azadiene **1** (5 mmol), *N,N'*-carbonyldiimidazole (6 mmol), boron trifluoride-etherate (6 mmol), and dry THF (5 ml) was stirred at room temperature for 2-8 h. Then, the reaction mixture was hydrolyzed with ice-cooled 3N NaOH, and extracted with a mixture of THF-ether (2/5). The organic layer was dried (Na_2SO_4), filtered, and evaporated under reduced pressure, to afford a solid residue, which by washing with ether, yields the 4(1*H*)-pyridones **5** as white solids. Recrystallization from hot hexane-chloroform (6:1) produces pure 4(1*H*)-pyridones **5** as crystalline white solids.
13. Satisfactory ^{1}H, ^{13}C NMR, Mass Spectra and Microanalyses were obtained for all 4(1*H*)-pyridones **5**. For example: (**5a**) ^{1}HNMR ($CDCl_3$, TMS, 300 MHz) δ 2.0 (s, 6H), 7.5 (br. s, 11H); ^{13}CNMR ($CDCl_3$, TMS, 75 MHz) δ 178.8 (C=O), 144.6 (C), 134.8 (C) (C), 129.0 (CH), 128.6 (CH), 128.4 (CH), 120.7 (C), 12.4 (CH_3); MS, *m/e*, 275 (M^+).
    (**5e**) ^{1}HNMR ($CDCl_3$, TMS, 300 MHz) δ 1.1-1.5 (m, 9H), 1.8-2.1 (m, 11H), 2.0 (s, 6H), 2.8 (m, 2H), 7.8 (br. s, 1H, exchangeable with D_2O); ^{13}CNMR ($CDCl_3$, TMS, 75 MHz) δ 178.9 (C=O), 147.0 (C), 118.6 (C), 39.3 (CH), 31.0 (CH_2), 26.2 (CH_2), 25.6 (CH_2), 10.1 (CH_3); MS, *m/e*, 287 (M^+)
14. M. Ogata, H. Matsumoto, S. Kida, and S. Shimizu, *Tetrahedron Letters*, **1979**, 5011 and references cited therein.
15. R.S. Garigipati, D.M. Tschaen, and S.M. Weinreb, *J. Am. Chem. Soc.*, **1985**, *107*, 7790.

(Received in UK 15 May 1990)