Iminophosphoranes in Heterocyclic Chemistry. A Simple One-Pot Synthesis of Dihydropyrimidines and Pyrimidines

Elisabetta Rossi*, Giorgio Abbiati, Elena Pini

Istituto di Chimica Organica della Facoltà di Farmacia, Università degli Studi di Milano, Via Venezian, 21, I-20133 Milano, Italy
Fax 0039-02-70638473; E-mail: Elisabetta.Rossi@unimi.it

Received 26 April 1999

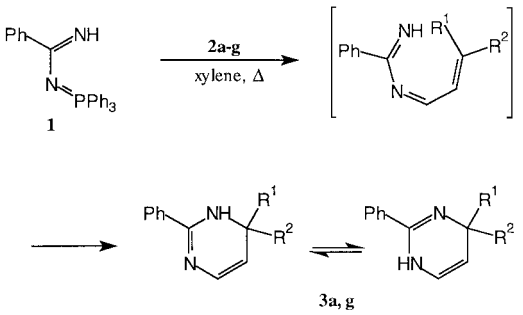
Abstract: The condensation of N-triphenylphosphoraniliden-benzamidine with acyclic α,β-unsaturated aldehydes produces dihydropyrimidines in good to high yields. The methodology has been extended to alicyclic and heterocyclic aldehydes.

Key words: amidines, nitrogen-ylids, condensation reactions, dihydropyrimidines, 8pyrimidines

The condensation of amidines with α,β-unsaturated aldehydes is an attractive [3+3]-fragment approach to dihydropyrimidines. However, until recently, only few works dealing with this reaction have appeared in the literature and the lack of growing up of this methodology was attributed to the instability of the dihydropyrimidine ring.[1] Some years ago Weis and co-workers successfully developed a new synthetic strategy for these condensation reactions, starting from the observation that the inaccessibility of these compounds was related to the synthetic approach used rather than to the intrinsic nature of the dihydropyrimidine ring.[2] The two key steps in the reaction mechanism were performed in separate stages: a preparation under mild conditions of hydroxytetrahydropyrimidine followed by thermal or catalysed dehydration to 1,4(1,6)-dihydropyrimidine.

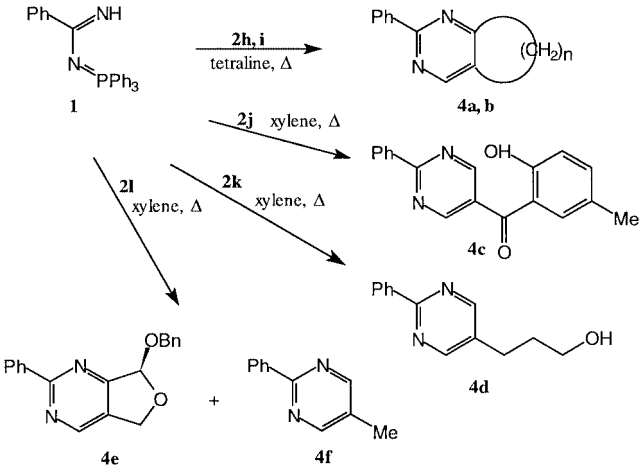
Following our studies directed towards the development of new synthetic methods of nitrogen heterocycles from amidine systems,[3] we thought that functionalized dihydropyrimidines could be easily prepared in a one-pot reaction between the iminophosphorane derived from benzamidine and α,β-unsaturated aldehydes. The use of iminophosphoranes has been emerging as a valuable tool for the construction of nitrogen-containing heterocycles.[4] We have previously published the synthesis of quinazoline and dihydroquinazoline ring starting from iminophosphoranes of N-aryl substituted benzamidines.[5] Based on these results, we now wish to report the preparation of dihydropyrimidines **3a–g** by the reaction of iminophosphorane **1**[6] with acyclic α,β-unsaturated aldehydes **2a–g** (Scheme 1).[7,8]

The reaction mechanism probably involves an aza-Wittig reaction followed by a 6e-π-electrocyclic ring closure of the azatriene intermediate to give dihydropyrimidines. We describe these latter compounds as a mixture of 1,6- and 1,4-dihydroisomers because combined X-ray, IR, UV and NMR data demonstrated that 1,6-dihydropyrimidines exist in solution and in the solid state in enamine-imine tautomeric equilibrium with the 1,4-isomers.[1]



Scheme 1

We also report the extension of this methodology to the cyclic α,β-unsaturated aldheydes **2h–l**. Alicyclic aldehydes **2h–i** are less reactive than acyclic aldehydes and the condensation was successfully attempted using tetraline at reflux. Under these conditions 4,5-tetra- and 4,5-pentamethylene fused pyrimidines **4a–b** were obtained in high yields. Further, 4,6-unsubstituted pyrimidines **4c–d** were isolated from the reactions between 3-formyl-6-methylchromone **2j** and 3-formyl-dihydropyrane **2k** with iminophosphorane **1** (Scheme 2). Finally, **1** reacts with *(R)*-2-(benzyloxy)-2,5-dihydrofuran-4-carboxaldehyde **2l**, with lower overall yields, giving rise to pyrimidines **4e** and **4f**, both arising from the initially formed dihydropyrimidine by loss of molecular hydrogen or benzylformate (Scheme 2).



Scheme 2

The obtained results are collected in the Table.

In conclusion, this synthesis, starting from the easily obtainable iminophosphorane **1** and acyclic α,β-unsaturated aldehydes **2a–g**, enables a general and easy access to 1,6(1,4)-dihydropyrimidines. Particularly noteworthy is the success of this one-pot protocol with α,β-unsaturated aldehydes ranging from unsubstituted to alkyl, aryl and substituted aryl aldehydes. Extension of this methodology to cyclic aldehydes **2h–l** allows the preparation of the fused pyrimidine **4a**[9], and of the new fused derivatives **4b** and **4e**. Finally, the presence of an oxygen atom in the γ position of the aldehyde moiety (**2j–k**) prevents the isolation of the expected tricyclic and bicyclic dihydropyrimidines which evolve to the corresponding pyrimidines by fission of the oxygenated ring.[10] Further work is in progress in order to evaluate the scope and limitations of these reactions and, in particular, with the aim to extend the synthetic procedure to the preparation of fused dihydropyrimidines and/or pyrimidines.

Acknowledgement

Financial support from CNR (Roma) is gratefully acknowledged.

References and Notes

(1) a) Weis, A. L. In *Advances in Heterocyclic Chemistry*, Katritzky, A. L., Ed., Academic, Orlando (FL), 1985; *38*, p 45. b) Weis, A. L., van der Plas, H. C. *Heterocycles* **1986**, 1433. c) Brown, D. J. In *The Chemistry of Heterocyclic Compounds*, Taylor, E. C., Weissberger, A., Eds., John Wiley, N. Y., 1994, *52*, p 817.

(2) a) Weis, A. L.; Frolow, F.; Zamir, D.; Bernstein, M. *Heterocycles* **1984**, *22*, 657. b) Weis, A. L. *Synthesis* **1985**, 528. c) Weis, A. L.; Zamir, D. *J. Org. Chem.* **1987**, *52*, 3421.

(3) a) Rossi, E.; Pini, E. *Tetrahedron* **1996**, *52*, 7939, and references cited therein. b) Rossi, E.; Abbiati, G.; Pini, E. *Tetrahedron* **1997**, *53*, 14107. c) Rossi, E.; Abbiati, G.; Pini, E. *Tetrahedron* **1999**, *55*, 6961.

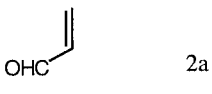
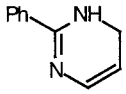
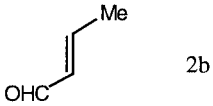
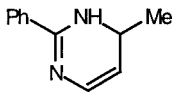
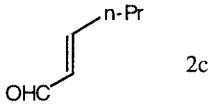
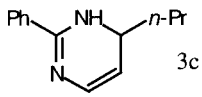
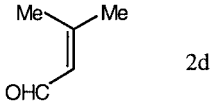
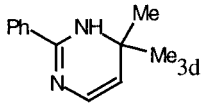
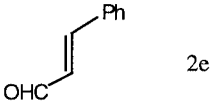
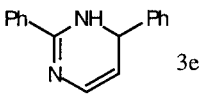
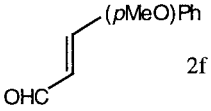
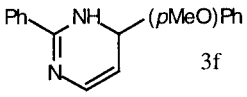
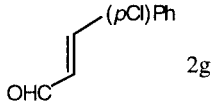
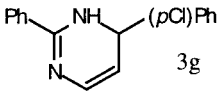
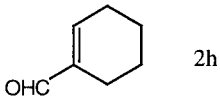
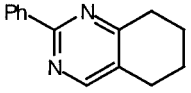
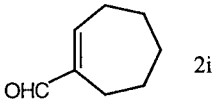
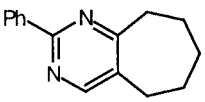
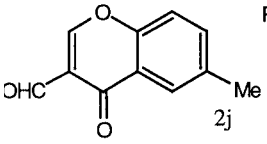
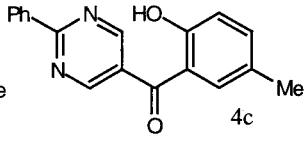
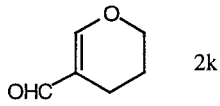
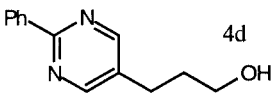
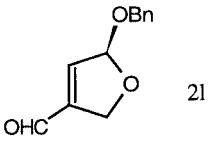
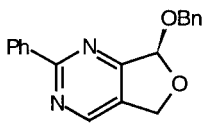
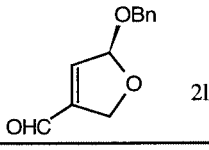
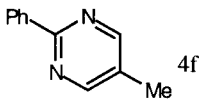
(4) For recent reviews on iminophosphoranes see: a) Gussar, N. I. *Russ. Chem. Rev.* **1991**, *60*, 146. b) Eguchi, S.; Matsushita, Y.; Yamashita, K. *Org. Prep. Proced. Int.* **1992**, *24*, 209. c) Molina, P.; Vilaplana, M. J. *Synthesis* **1994**, 1197. d) Wamhoff, H.; Richardt, G.; Stölben, S. In *Advances in Heterocyclic Chemistry*, Katritzky, A. L., Ed., Academic, Orlando (FL), 1995; *64*, p 159. For some of recent leading references see: a) Okawa, T.; Eguchi, S. *Tetrahedron* **1998**, *54*, 5853. b) Quintela, J. M.; Alvarez-Sarandés, R.; Peinador, C. *Tetrahedron* **1998**, *54*, 8107. c) Saito, T.; Ohkubo, T.; Kuboki, H.; Maeda, M.; Tsuda, K.; Karakasa, T.; Satsumabayashi, S. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3065. d) Takahashi, M.; Suga, D. *Synthesis* **1998**, 986. e) Okawa, T.; Toda, M.; Eguchi, S.; Kakehi, A. *Synthesis* **1998**, 1467. f) Okawa, T.; Kawase, M.; Eguchi, S. *Synthesis* **1998**, 1185.

(5) a) Rossi, E.; Celentano, G.; Stradi, R.; Strada, A. *Tetrahedron Lett.* **1990**, *31*, 903. b) Rossi, E.; Calabrese, D.; Farma, F. *Tetrahedron* **1991**, *47*, 5819.

(6) a) Derkach, G. I.; Kirsanov, A. V. *Zh. Obshch. Khim.*, **1962**, 2254; *Chem. Abstr.* **1963**, *58*, 9126b. b) Yoshida, H.; Ogata, T.; Inokawa, S. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1541.

(7) α,β-Unsaturated aldehydes **2a–e** and **2j** are commercially available, **2f–i** and **2k–l** were prepared according to the following references: **2f–g** : Babler, J. H. *Synth. Commun.* **1982**, *12*, 839; **2h**: Heilbron, I.; Jones, E. R. H.; Richardson,

Table Aldehydes **2**, Dihydropyrimidines **3** and Pyrimidines **4**.

2		3 or 4		Yield[a]
	2a		3a	78
	2b		3b	86
	2c		3c	82
	2d		3d	75
	2e		3e	90
	2f		3f	75
	2g		3g	80
	2h		4a	80
	2i		4b	85
	2j		4c	65
	2k		4d	80
	2l		4e	32
	2l		4f	25

Yields refer to single runs, are given for pure isolated products. All new products had satisfactory elemental analysis and spectral data were consistent with postulated structures.

R. W.; Sondheimer, F. *J. Chem. Soc.* **1949**, 737; **2i**: Braude, E. A.; Evans, E. A. *J. Chem. Soc.* **1955**, 3334; **2k**: Piancatelli, G.; D'Ottavi, G.; Scettri, A. *Ann. Chim.* **1972**, *62*, 394; **2l**: Sundin, A.; Frejd, T.; Magnusson, G. *J. Org. Chem.* **1986**, *51*, 3927.

(8) A typical procedure for dihydropyrimidines **3** is as follow: a solution of iminophosphorane **1**[6] (0.5 g, 1.31 mmol) and crotonaldehyde **2b** (0.12 g, 1.71 mmol) in dry xylene (15 mL) was heated under reflux for 2 h. The solvent was then removed under reduced pressure. The residue, purified by flash chromatography (silica gel, 8:2:2 v/v petroleum ether/ethyl acetate/triethylamine) afforded **3b** (0.194 g, 86 % yield). ^{1}H NMR and ^{13}C-NMR were recorded in commercial $CDCl_3$, under these conditions average spectra, between 1,4- and 1,6 dihydro forms, were obtained[1a]. ^{1}H-NMR δ 1.28 (d, 3H, J = 6.3); 4.30 (m, 1H); 4.82 (dd, 1H, J = 3.3, 7.4); 5.90 (bs, 1H); 6.30 (d, 1H, J = 7.4); 7.37 (m, 3H); 7.66 (m, 2H). ^{13}C-NMR δ 25.9, 47.7, 108.4, 127.1, 129.0, 130.1, 131.3, 134.7, 155.0.

(9) a) Baumgarten, H. E.; Creger, P. L.; Villars, C. E. *J. Am. Chem. Soc.* **1958**, *80*, 6609; b) Zumbrunn, A.; Lamberth, C.; Schaub, F. *Synth. Commun.* **1998**, *28*, 474.

(10) a) Löwe, W. *Synthesis* **1976**, 274; b) Löwe, W. *Liebigs Ann. Chem.* **1977**, 1050; c) Pene, C.; Hubert-Habart, M. *J. Heterocyc. Chem.* **1980**, *17*, 329.

Article Identifier:
1437-2096,E;1999,0,08,1265,1267,ftx,en;G12799ST.pdf