Pergamon

Tetrahedron Letters, Vol. 36, No. 17, pp. 2937-2940, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)00442-4

Trimethylorthoformate: A Mild and Effective Dehydrating Reagent for Solution and Solid Phase Imine Formation.

Gary C. Look,* Martin M. Murphy, David A. Campbell, and Mark A. Gallop

Affymax Research Institute, 4001 Miranda Avenue,
Palo Alto, California 94304

Abstract: Trimethylorthoformate has been found to be an effective dehydrating solvent for the formation of imines, both in the solid phase as well as solution phase.

A venerable and useful transformation in organic synthesis is the condensation of an amine with a ketone or aldehyde to form an imine.[1] The resultant product may be used as a versatile component in both nucleophilic[2] and cycloaddition reactions.[3] As a part of our work in the area of combinatorial organic synthesis, we required a general method for imine formation that was suitable for solid phase work. While the classical methods of azeotropic removal of water[4] and reaction in the presence of molecular sieves[5] were of some utility, we desired a technique that did not require elevated temperatures or an additional solid component that would have to be subsequently removed from the resin. We describe herein the use of trimethylorthoformate as a solvent with the dehydrating power to drive imine formation. This solvent is suitable for solid-supported as well as solution phase organic synthesis.[6]

In a survey of reagents and solvents used for imine formation, tetramethylorthosilicate was the most similar to the orthoformate for *in situ* dehydration.[7] However, this reagent requires acid catalysis and elevated temperature. Additionally, removal of the silicon containing byproducts can be problematic. Trimethylorthoformate has been used as an inexpensive, yet effective dehydrating agent for acetal formation.[8] Furthermore, the methanol and methylformate byproducts are easily removed after the reaction is complete. With this information, we sought to examine trimethylorthoformate for imine formation.

Table **1** and Figure **1** list a series of imines which were formed under solution phase conditions using trimethylorthoformate as the reaction solvent. For these studies, only amino acids were examined as the amine component although other amines have been used.[9] Electron poor as well as electron rich aldehydes have been successfully used for imine formation. However, electron rich aldehydes react somewhat more sluggishly than do other aldehydes. The imines are isolated after rinsing an ether solution of the crude reaction mixture with excess water followed by concentration of the organic solutions *in vacuo*. Although, aliphatic aldehydes and ketones usually gave nonisolable imines due to imine-enamine tautomerization, these imines are viable intermediates for *in situ* reduction and cycloaddition reactions.[10,11]

Table 1. Selected Characterization Data for Solution Phase Imines.

Compound	Yield (%)	^{1}H NMR chemical shift of imine C-H (ppm)[a]	^{13}C NMR chemical shift of C=N (ppm)[a]	IR absorption of imine C=N stretch (cm^{-1})
1	92	8.29	165.3	1648
2	96	8.27	165.0	1649
3	88	8.32	162.8	1643
4	98	8.30	162.2	1644
5	100	8.25	163.2	1642
6	89	8.24	162.6	1643
7	94	8.27	165.1	1652
8	>98	8.36	162.7	1701 (br)
9	>98	8.21	164.4	1644

[a]NMR spectra were obtained in $CDCl_3$.

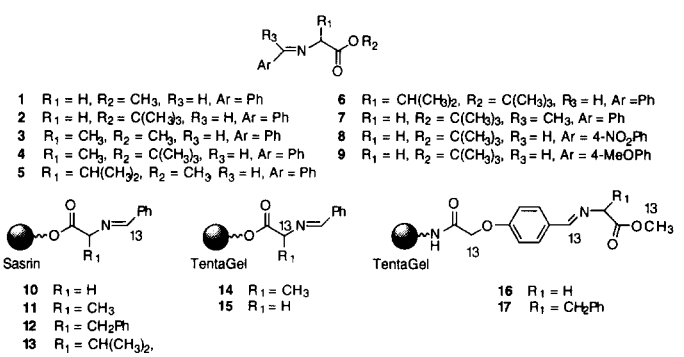

Figure 1. Solution and solid-supported imines formed by trimethylorthoformate-mediated condensation.

In comparison with the solution phase studies, imines **10-13** were prepared from the Sasrin-bound amino acids using ^{13}C labeled benzaldehyde and imines **14** and **15** from TentaGel AC-bound 2-^{13}C labeled amino acids (Table 2). Condensations of the aldehydes and amines are performed in trimethylorthoformate at room temperature using as little as two equivalents of aldehyde. In cases where the solubility of the amine component in neat TMOF is poor, co-solvents such as THF and CH_3CN have been used.[10] Although the reactions are typically run for one to two hours, most unhindered imines are formed in less than 10 minutes as evidenced by fast ^{13}C NMR monitoring of the reactions.[12] The formation of imine was indicated by resonances in the 160 ppm range for compounds derived from a labeled aldehyde and in the 65-68 ppm range for compounds labeled at the α-carbon of the amino acid. These spectal data correlated well with those of the solution phase imines formed previously.

Table 2. Diagnostic ^{13}C NMR chemical shifts for resin bound imines with enriched carbons.

Compound	C=N Chemical shift (ppm)[a]	C-N Chemical shift (ppm)[a]
10	165.5	-
11	163.0	-
12	163.9	-
13	163.5	-
14	-	68.8
15	-	62.7
16	164.5	-
17	163.7	-

[a]NMR data obtained in benzene-d_6.

We have found that the imine-forming reaction in the cases when the aldehyde component is bound to the solid support and the amine is presented in solution (Table 2, compounds **16** and **17**) is slower than for the reaction with the opposite orientation (amine immobilized / aldehyde in solution). In most cases, a second treatment of the partially converted support-bound aldehyde with amine drives the imine formation to completion.

There have been a wealth of studies concerning the use of trialkylorthoformates as a synthetic reagent in the presence of amines and ketones.[13] The products of these reactions, in the presence of acid catalysis or with heating, are enamines which incorporate the methine of the orthoformate. This useful reaction has been used for the synthesis of heterocyclic compounds.[13] Trialkylorthoformates also have been used for *N*-formylation of amines.[14] Under our reaction conditions we detected no reaction products resulting from either of these pathways.

Imines are the pivotal intermediates in the *N*-alkylation of amines with ketones or aldehydes by reductive amination. Under protic conditions, *in situ* reductive aminations can lead to over alkylation of the aldehyde component to the amine.[15] Based on the putative mechanism for reductive amination we felt that using trimethylorthoformate would circumvent this problem.[11] Indeed, when alkyl amines or esters of amino acids were treated with an excess of aldehyde and sodium cyanoborohydride in trimethylorthoformate, only the monoalkylated products were observed by HPLC.

In summary, trimethylorthoformate has been found to be a particularly useful solvent for imine formation. The use of this powerful dehydrating solvent allows one to form imines under mild and non-acidic conditions for both solution phase and resin-bound synthesis.[16,17]

Acknowledgments: The authors would like to thank Dr. Christopher P. Holmes and Mr. Jason P. Chinn for useful discussions and experimental assistance.

References and Notes:

1. For a treatise on imines and their chemistry, see: Patai, S. *The Chemistry of the Carbon-Nitrogen Double Bond* Wiley Interscience: New York, 1970.

2. For a recent example of organometallic reagent additions to imines, see: Kuznetsov, V. V.; Pal'ma, A. R.; Aliev, A. E.; Varlamov, A. V.; Prostakov, N. S. *Zh. Org. Khim.* **1991**, *27*, 1579-1581.
3. For recent examples of the use of imines and azomethine ylides in cycloaddition and cyclocondensation reactions, see: a) Aly, M. F.; Younes, M. I.; Matwally, S. A. O. *Tetrahedron* **1994**, *50*, 3159. b) Tsuge, O.; Kanemasa, S. *Adv. Heterocyc. Chem.* **1989**, *45*, 231.
4. Moffett, R. B. *Org. Synth., Coll. Vol. 4*, **1963**, 605.
5. For the use of molecular sieves to drive acetal formation, see: Roelofsen, D. P.; Wils, E. R. J.; Van Bekkum, H. *Recl. Trav. Chim. Pays-Bas*, **1971**, *90*, 1141.
6. For an alternative strategy for forming imines on solid support, see: DeWitt, S. H.; Kiely, J. S.; Stankovic, C. J.; Schroeder, M. C.; Cody, D. M. R.; Pavia, M. R. *Proc. Natl. Acad. Sci. USA* **1993**, *90*, 6909.
7. Love, B. E.; Ren, J. *J. Org. Chem.* **1993**, *58*, 5556.
8. a) Thurkauf, A.; Jacobsen, A. E.; Rice, K. C. *Synthesis* **1988**, 233. b) Gemal, A. L.; Luche, J. -L. *J. Org. Chem.* **1979**, *44*, 4187. c) Wenkert, E.; Goodwin, T. E. *Synth. Commun.* **1977**, *7*, 409. d) Taylor, E. C.; Chiang, C. -S. *Synthesis* **1977**, 467.
9. In general, the free base of the amine component is used. However, we have run experiments using amino acids which were converted to their free bases *in situ*. When the solubility of the amino acid salt is not an issue, we obtain comparable results to that of the independently generated free base amino acids.
10. G. Look and C. Holmes, unpublished results.
11. Trimethylorthoformate-mediated *in situ* reductive amination reactions is the subject of another paper.
12. For the use of ^{13}C enriched compounds for the monitoring of gel phase reactions by NMR, see: Look, G. C.; Holmes, C. P.; Chinn, J. P.; Gallop, M. A. *J. Org. Chem.* **1994**, *59*, 7588.
13. For recent examples, see; a) Wentrup, C.; Briehl, H.; Lorencak, P.; Vogelbacher, U. J.; Winter, H.-W.; Maquestiau, A.; Flammang, R. *J. Am. Chem. Soc.* **1988**, *110*, 1337. b) Spéziale, V.; Sakellariou, R.; Hamdi, M. *Synthesis* **1992**, 921. c) Bouzard, D.; Di Cesare, P.; Essiz, M.; Jacquet, J. P.; Ledoussal, B.; Remuzon, P.; Kessler, R. E.; Fung-Tomc, J. *J. Med. Chem.* **1992**, *35*, 518. d) Zupet, R.; Tisler, M.; Golic, L *J. Heterocycl. Chem.* **1991**, *28*, 1731.
14. a) Chancellor, T.; Morton, C. *Sythesis* **1994**, 1023. b) Roberts, R.; Vogt, P. *J. Am. Chem. Soc.* **1956**, *78*, 4778.
15. Salvi, J. -P.; Walchshofer, N.; Paris, J. *Tetrahedron Lett.* **1994**, *35*, 1181.
16. **General Procedure for Imine Formation in Solution Phase.** The amino acid alkyl ester (4 mmol) was added to a stirred solution of trimethylorthoformate (8-10 mL). After 5 min, benzaldehyde (4 mmol) was added and the mixture stirred for 8 hours. The mixture was taken up in ethyl ether (25 mL) and extracted with water (4 X 50 mL), dried over anhydrous magnesium sulfate, concentrated and analyzed without further purification.
17. **General Procedure for Imine Formation on Solid Support.** To a suspension of a support-bound amine (50 mg, 650 mmol/g, 0.03 mmol) in trimethylorthoformate (0.5 mL) was added benzaldehyde (0.06 mmol). The bead suspension was mixed by vortexing for 2 hours, the resin was filtered, rinsed with anhydrous ethanol, and dried under high vacuum. The dried bead mass was then suspended in benzene-d_6 and analyzed by fast ^{13}C NMR spectroscopy.

(*Received in USA* 1 *February* 1995; *revised* 1 *March* 1995; *accepted* 3 *March* 1995)