

SYNLETT Spotlight 50

N,N-Dimethylformamide Dimethyl Acetal

Compiled by Davor Kidjemet



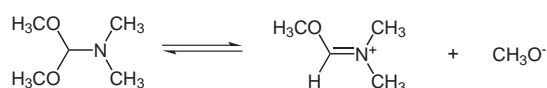
This feature focuses on a reagent chosen by a postgraduate, highlighting the uses and preparation of the reagent in current research

Davor Kidjemet was born in Varazdin, Croatia. He studied chemistry at the University of Zagreb where he received his BSc degree in 1994 and MSc degree in 1998. He is currently working on his PhD thesis under the supervision of Professor Srdjanka Tomic (University of Zagreb) at PLIVA d.d., Pharmaceutical Company.

PLIVA d.d, Research Division, Prilaz baruna Filipovica 25,
HR-10000 Zagreb, Croatia.
E-mail: Davor.Kidjemet@pliva.hr

Introduction

N,N-Dimethylformamide dimethyl acetal (DMF·DMA), as well as other *N,N*-dimethylformamide dialkyl acetals (e.g. ethyl, benzyl, *t*-butyl), are very useful reagents in organic synthesis. All of them are used in two main categories of reactions, namely alkylation and formylation. The mechanism of these reactions probably includes generation of an oxo-stabilized carbenium ion.^{1,2}



As alkylating agents they have been used in the synthesis of esters from acids, ethers from phenols, and thioethers from aromatic and heterocyclic thiols. As formylating

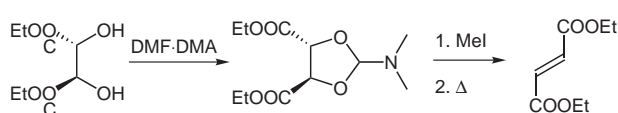
agents, formamide acetals are useful in the synthesis of enamines from active methylene compounds and amidines from amines and amides. These compounds are found to be useful intermediates in the formation and modification of many heterocyclic¹ and biologically active compounds.³

The *N,N*-dibenzyl formamidinium group was also found to be effective as a protecting group for primary amines. It is stable under variety of conditions and can be removed by catalytic hydrogenation.⁴ All conversions proceed under mild conditions and in high yields.

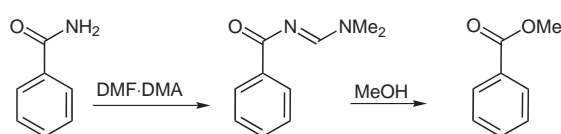
Many formamide acetals are commercially available. In addition, they can be prepared by addition of chloroform into a refluxing solution of sodium alkoxide in the appropriate alcohol and the secondary amine.⁵

Abstracts

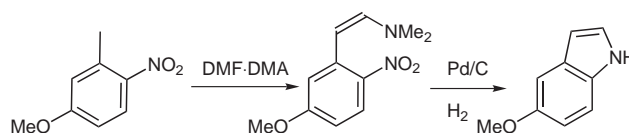
DMF·DMA converts a number of vicinal *cis*-diols, both cyclic and acyclic, into olefins. In a typical example, treatment of diethyl D-tartrate with an excess of DMF·DMA in dichloromethane provides the corresponding acetal. Upon addition of methyl iodide, trimethylammonium salt precipitates. Thermolysis of trimethylammonium salt in toluene at reflux temperature affords diethylfumarate.⁶



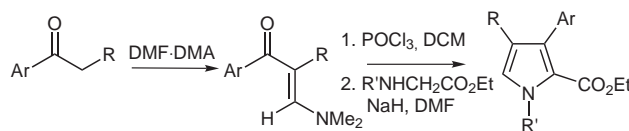
Treatment of phenoxyacetamide with DMF·DMA at room temperature affords *N,N*-acylformamidinium, which is converted into methyl phenoxyacetate by simple dissolution in methanol. This methodology can be extended to the preparation of carboxylic esters other than methyl (e.g. ethyl, *i*-propyl, *n*-butyl and benzyl). However, a limitation of its use is the presence in the substrate of functional groups which are reactive towards DMF·DMA (e.g. NH₂, NHR, COOH).⁷



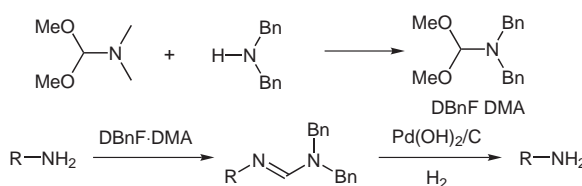
A general indole synthesis involves reaction of an *o*-nitrotoluene derivative with DMF·DMA in refluxing DMF forming a nitro *N,N*-dimethyl enaminone. Reduction of the nitro group is accompanied by spontaneous cyclization to an indole. Generally, catalytic hydrogenation is preferred for this step. One drawback in this synthesis is that electron-donating groups retard the aminomethylenation step. A more reactive reagent is obtained if reaction is performed with addition of pyrrolidine to the reaction mixture. Then, the main product is pyrrolidine enaminone, which can be reduced to an indole.⁸



Reaction of appropriate ketones with DMF·DMA affords the enaminone. It can be easily converted to the chloropropeniminium salt by the reaction with phosphorous oxychloride in dichloromethane. A 2,3,4-trisubstituted pyrrole can be obtained when this iminium salt is condensed with ethyl *N*-methylglycinate in the presence of sodium hydride and DMF.⁹



A trans-amidation reaction of DMF·DMA with dibenzylamine affords the intermediate, *N,N*-dibenzylformamide dimethyl acetal. It reacts smoothly with a primary amine at room temperature to give the corresponding amidine in high yield. Removal of the *N,N*-dibenzylformamidine protection by catalytic hydrogenation is accomplished using the Pearlman catalyst, Pd(OH)₂/C. This protection group is stable towards acidic, basic, and nucleophilic reaction conditions.⁴



References

- (1) Abdula, R. F.; Brinkmeyer, R. S. *Tetrahedron* **1979**, *35*, 1675.
- (2) Paquette, L. A. *Encyclopedia of Reagents for Organic Synthesis*, Vol. 3; John Wiley & Sons: New York, **1995**, 2075.
- (3) (a) Zimmermann, J.; Buchdunger, E.; Mett, H.; Meyer, T.; Lydon, N. B. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 187.
(b) MacDonald, A. A.; DeWitt, S.; Hogan, E. M.; Ramage, R. *Tetrahedron Lett.* **1996**, *37*, 4815.
- (4) Vincent, S.; Mons, S.; Lebean, L.; Mioskowski, C. *Tetrahedron Lett.* **1997**, *38*, 7527.
- (5) Scheeren, J. W.; Nivard, R. J. F. *Recl. Trav. Chim. Pays-Bas* **1969**, *88*, 289.
- (6) Hanessian, S.; Bargiotti, A.; La Rue, M. *Tetrahedron Lett.* **1978**, 737.
- (7) Anelli, P. L.; Brocchetta, M.; Palano, D.; Visigalli, M. *Tetrahedron Lett.* **1997**, *38*, 2367.
- (8) Showalter, H. D. H.; Sun, L.; Sercel, A. D.; Winters, R. T.; Denny, W. A.; Palmer, B. D. *J. Org. Chem.* **1996**, *61*, 1155.
- (9) Gupton, J. T.; Krumpe, K. E.; Burnham, B. S.; Dwornik, K. A.; Petrich, S. A.; Du, D. X.; Bruce, M. A.; Vu, P.; Vargas, M.; Keertikar, K. M.; Hosein, K. N.; Jones, C. R.; Sikorski, J. A. *Tetrahedron* **1998**, *54*, 5075.