

SYNLETT
Spotlight 374

Hexamethylenetetramine

Compiled by Baljinder Singh



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

Baljinder Singh was born in Haryana, India. He received his B. Pharm (2007) from Kurukshetra University, India and his M.S. Pharm (2009) from the National Institute of Pharmaceutical Education and Research (NIPER), Ahmedabad, India. After completion of his master degree, he joined the research group of Piramal Life Sciences Ltd., Mumbai, India. Presently he is pursuing his Ph.D. under the supervision of Dr. R. A. Vishwakarma at IIIM-Jammu (CSIR), India. His research interest focuses on the analogue synthesis of bio-active natural products, non-natural products, and on the development of new synthetic methodologies.

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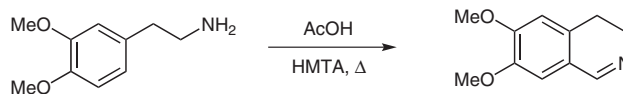
Introduction

Hexamethylenetetramine (HMTA) is a heterocyclic organic compound having a symmetric tetrahedral cage-like structure, whose four 'corners' are nitrogen atoms and 'edges' are methylene groups. It is also known as hexamine. It behaves like an amine base and known for its versatile role in organic chemistry. It plays an important role in formylation (Duff reaction),^{1,2} conversion of benzyl halides into corresponding aldehydes (Sommelet reaction),³ and synthesis of amines (Delépine reaction).⁴

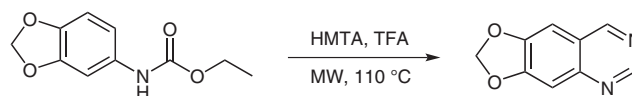
HMTA is a useful reagent in the conversion of ethyl 2-(4-hydroxyphenyl)-4-methylthiazole-5-carboxylate into ethyl 2-(3-formyl-4-hydroxyphenyl)-4-methylthiazole-5-carboxylate, an important step in the synthesis of febuxostat (hypouricemic agent).⁵ Apart from these applications, hexamethylenetetramine is also known for the synthesis of explosives like RDX (hexogen).⁶ Further, it has wide applications in polymer chemistry.⁷ HMTA is commercially available and first synthesized by Butlerov via reaction of formaldehyde with ammonia.⁸

Abstracts

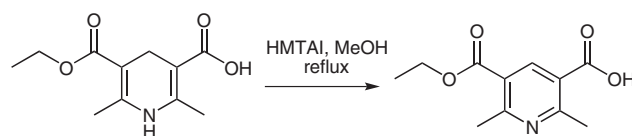
(A) Miyazaki et al. reported the preparation of 3,4-dihydroisoquinolines in excellent yield (>90%) using HMTA.⁹



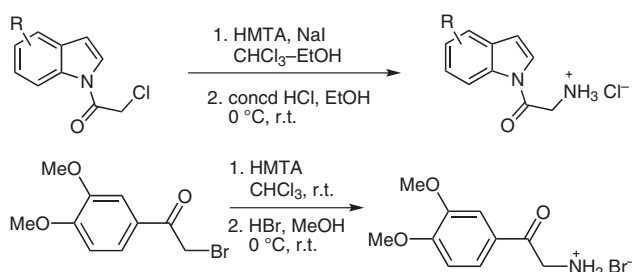
(B) The biologically active pharmacophore quinazoline was synthesized from benzocarbamate by treatment with HMTA.¹⁰



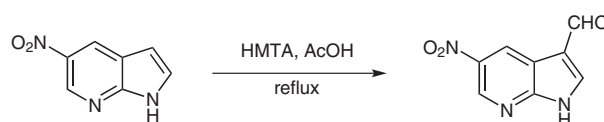
(C) Efficient aromatization of 1,4-dihydropyridines has been achieved using HMTA iodide.¹¹



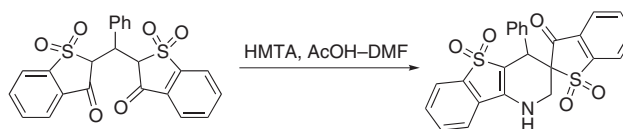
(D) Replacement of the chloro substituent with an ammonium group in the α -chloro ketone was achieved by reaction with HMTA.¹² Similarly, Zhang et al. reported the ammoniation of 2-bromo-1-(3,4-dimethoxyphenyl)ethanone using HMTA.¹³



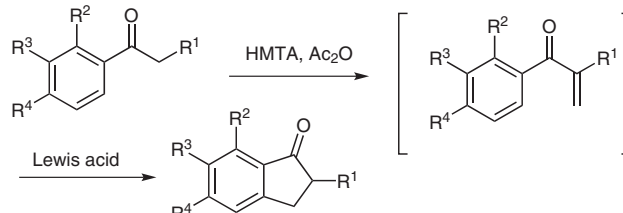
(E) HMTA has wide applications in mono- as well as diformylations of aromatic compounds. For example, the formylation of 5-nitro-7-azaindole using Duff reaction (HMTA/acetic acid) is reported.¹⁴



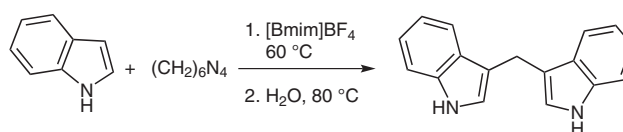
(F) Cekavicus et al. used HMTA in acidic medium for generating heterocyclic spiro systems via an internal Mannich reaction.¹⁵



(G) HMTA has been proven to be an excellent and inexpensive promoter of the Mannich reaction of aryl alkyl ketones, which was followed by a Nazarov cyclization, providing the 2-alkyl indanones in excellent yields.¹⁶



(H) 3,3'-Diindolylmethane derivatives have been prepared in one pot from indoles and HMTA. HMTA acts as a methylene group donor.¹⁷



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