SYNLETT Spotlight 419

Ethoxymethylenemalononitrile

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

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Introduction

Ethoxymethylenemalononitrile (**3**) is an orange solid with a melting point of 64–66 °C. It is a functionalized malononitrile widely used to synthesize pyrazoles,¹ pyrimidines² as well as a variety of fused heterocyclic systems, like pyrazolooxazines,³ pyrazolopyrimidines⁴ and benzodiazepines.⁵ It is an inexpensive reagent, but can be prepared in 94% yield by the reaction of 1,1',1''-[methanetriyl-

tris(oxy)]triethane (**1**) and malononitrile (**2**) under reflux in the presence of acetic anhydride for four hours.³

Scheme 1 Synthesis of ethoxymethylenemalononitrile (**3**)

Abstracts

(A) A simple reaction of *o*-phenylenediamine (**4**) with ethoxymethylenemalononitrile at room temperature formed 2-[(2-aminophenyl-amino)methylene]malononitrile (**5**). Then an intramolecular cyclization of **5** happened under microwave conditions to generate the benzimidazole ring in quantitative yield by elimination of malononitrile.⁶

(B) This reaction proceeds via attack of hydroxytropone **7** onto the electrophilic alkene to form a Michael-type adduct and subsequent loss of ethanol to give the potassium salt of [(8-hydroxy-1,3-dimethyl-4-oxo-4*H*-cyclohepta[*c*]furan-7-yl)methylene]malononitrile (**8**).⁷

(C) The reaction between 3-methoxypropionitrile (**12**), *t*-butyl bromoacetate (**13**) and ethoxymethylenemalononitrile allowed the synthesis of *t*-butyl 6-amino-5-cyano-2-(2-methoxyethyl)nicotinate (**14**).²

(D) According to Zaki and co-workers,⁸ two different products can be obtained by the reaction between derivatives **9** and ethoxymethylenemalononitrile, depending on the reaction conditions. At low temperature, a nucleophilic substitution provides the enaminone derivative *N'*-(2,2-dicyanovinyl)hexanohydrazide (**10a**). Under reflux conditions using DBU as a catalyst, the reaction mixture allows the cyclization to the seven-membered 1,2-diazepine rings **11a–d**.

(E) Bruno et al.⁹ reported the synthesis of 2-phenyl-2,3-dihydro-1*H*-imidazo[1,2-*b*]pyrazole-7-carboxamide (**18**) by condensation of hydrazine **15** with ethoxymethylenemalononitrile (**3**) to give **16**, followed by an alkaline hydrolysis providing **17** and subsequent cyclization to give the fused pyrazoloimidazole **18**, which exhibits potent anti-inflammatory properties.

(F) The condensation of 4-hydrazino-8-(trifluoromethyl)quinoline (**19**) with ethoxymethylenemalononitrile afforded intermediate **20** that reacted with formamide to provide fused pyrazolopyrimidine **21**, a potential antimicrobial agent.¹⁰

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