Ethoxymethylenemalononitrile

Compiled by Jéssica Venância Faria

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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 pyrazolo[1,5-a]pyrimidines,3 pyrazolopyrimidines4 and benzodiazepines.5 It is an inexpensive reagent, but can be prepared in 94% yield by the reaction of 1,1′,1″-tris(ethanetriyl-tris(oxy))tris(ethylenediamine) (1) and malononitrile (2) under reflux in the presence of acetic anhydride for four hours.3

\[
\begin{align*}
    \text{HC(OEt)}_3 \quad + \quad \text{CN} & \quad \xrightarrow{\Delta, \text{5 min}} \quad \text{CN} \quad \text{CN} \\
    1 & \quad 2 & \quad 3
\end{align*}
\]

Scheme 1 Synthesis of ethoxymethylenemalononitrile (3)

Abstracts

(A) A simple reaction of o-phenylenediamine (4) with ethoxymethylenemalononitrile at room temperature formed 2-[(2-aminophenylamino)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-4H-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, two different products can be obtained by the reaction between derivatives 9 and ethoxymethyleneamalonitrile, depending on the reaction conditions. At low temperature, a nucleophilic substitution provides the enamine derivative \(N^\prime-(2,2\text{-dicyanovinyl})\text{hexanohydrazide (10a).}\) 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-1H-imidazo[1,2-b]pyrazole-7-carboxamide (18) by condensation of hydrazine 15 with ethoxymethyleneamalonitrile (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 ethoxymethyleneamalonitrile afforded intermediate 20 that reacted with formamide to provide fused pyrazolopyrimidine 21, a potential antimicrobial agent.\(^10\)

References