SYNLETT
Spotlight 419

Ethoxymethylenemalononitrile

Compiled by Jéssica Venância Faria

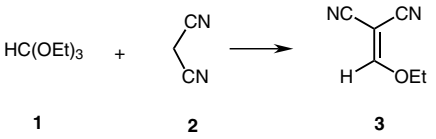
This feature focuses on a reagent chosen by a postgraduate, highlighting the uses and preparation of the reagent in current research

Jéssica Venância Faria was born in 1985 in Rio de Janeiro, Brazil. She obtained her Chemistry degree from the Universidade Federal Fluminense in 2010. She is currently working toward her M.Sc. in Chemistry under the supervision of Dr. Alice Maria Rolim Bernardino and Dr. Maurício Silva dos Santos. Her research interests focus on the synthesis of pyrazolyl and tetrazolyl derivatives with potential antileishmanial activity.

Instituto de Química, Universidade Federal Fluminense, UFF, CEP 24020-150 Niterói, Rio de Janeiro, Brazil
E-mail: jessikvenancia@gmail.com

Introduction

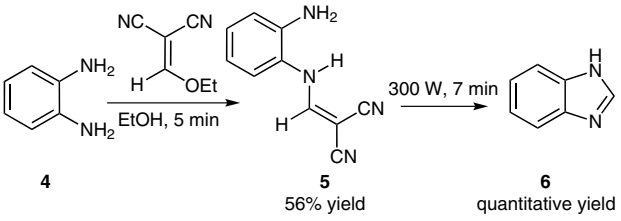
Ethoxymethylenemalononitrile (**3**) is an orange solid with a melting point of 64–66 °C. It is a functionalized malononitrile widely used to synthesize pyrazoles,[1] pyrimidines[2] as well as a variety of fused heterocyclic systems, like pyrazolooxazines,[3] pyrazolopyrimidines[4] and benzodiazepines.[5] It is an inexpensive reagent, but can be prepared in 94% yield by the reaction of 1,1′,1″-[methanetriyltris(oxy)]triethane (**1**) and malononitrile (**2**) under reflux in the presence of acetic anhydride for four hours.[3]



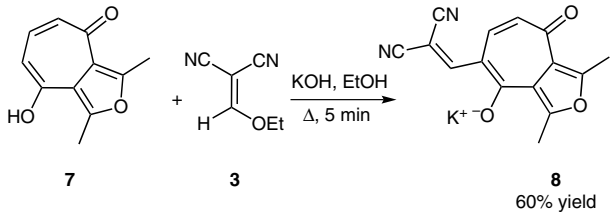
Scheme 1 Synthesis of ethoxymethylenemalononitrile (**3**)

Abstracts

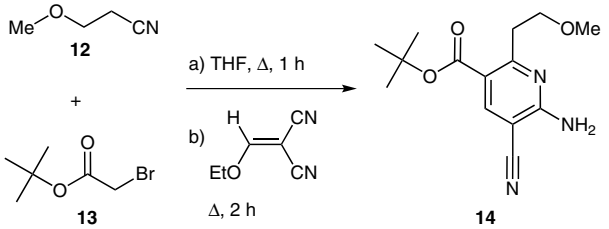
(A) A simple reaction of *o*-phenylenediamine (**4**) with ethoxymethylenemalononitrile at room temperature formed 2-[(2-aminophenylamino)methylene]malononitrile (**5**). Then an intramolecular cyclization of **5** happened under microwave conditions to generate the benzimidazole ring in quantitative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



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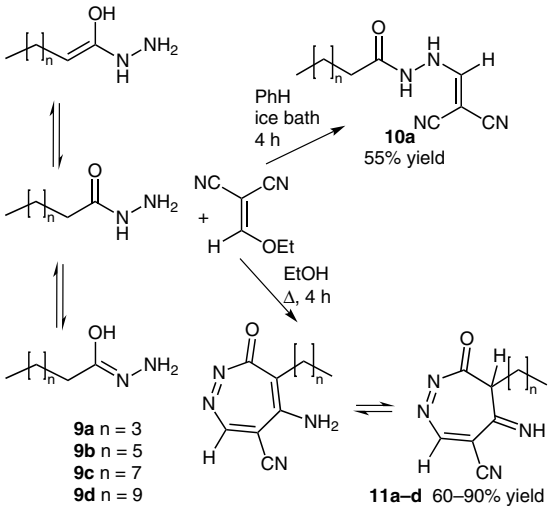
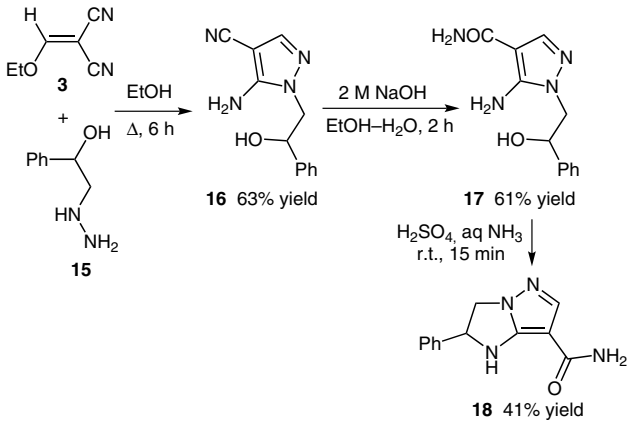
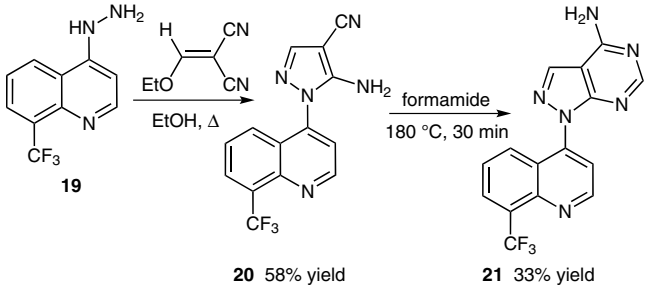
(D) According to Zaki and co-workers,[8] two different products can be obtained by the reaction between derivatives **9** and ethoxymethylenemalononitrile, depending on the reaction conditions. At low temperature, a nucleophilic substitution provides the enaminone derivative *N*′-(2,2-dicyanovinyl)hexanohydrazide (**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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