Synthetic Applications of Diethyl Ethoxymethylenemalonate

Compiled by Roberta Katlen Fusco Marra

Roberta Katlen Fusco Marra was born in 1985 in Rio de Janeiro, Brazil. She obtained her degree in Industrial Chemistry in 2007 and her M.Sc. degree in 2010, from the Universidade Federal Fluminense. She is currently working toward her Ph.D. degree in Chemistry under the supervision of Prof. Alice Maria Rolim Bernardino. Her research interests focus on the synthesis of pyrazolyl derivatives with potential antileishmanial activity.

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

Introduction

Diethyl ethoxymethylenemalonate (EMME, Figure 1), a liquid with a boiling point of 279–281 °C, is a very versatile reagent, extensively used for the synthesis of heterocyclic systems. The main application of this reagent is its use in the Gould–Jacobs reaction.

Abstracts

(A) Nair and co-workers reported the synthesis of 1,3-dibenzyl-5-hydroxy-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine-6-carboxylic acid (3) with EMME. The synthesis followed the stages of cyclization and hydrolysis of the ester under acidic conditions. The target compound 3 was obtained as a crystalline solid in 67% yield. This compound exhibits strong activity against the dengue virus.1

(B) Ethyl 6-(6-oxo-1,4,5,6-tetrahydropyridazin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate (6) can be obtained by nucleophilic addition of the 6-(4-aminophenyl)-4,5-dihydropyridazin-3(2H)-one (4) to the β-carbon of EMME followed by elimination of ethanol. The compound 6 was obtained in 80% yield by heating the diester 5 in diphenyl ether.2

(C) In the literature it is reported that EMME can react with 2-thiocarbamoyl-N-arylacetamides (7) in two concurrent directions forming 1,2-dihydropyridine-6-thiones 8 and 9. The yields depend on the excess of the thioamide 7.3
(D) Zicane et al. showed the condensation of EMME with hydrazides 10a–f occurring exclusively at the enolic ethoxy group of this ester to yield N-(2,2-diethoxycarbonyl-ethenyl)hydrazides of 4-methylcyclohex-4-ene-1,1 dicarboxylic acids 11a–f.  

\[
\text{CONHNH}_2 + \text{EMME} \rightarrow \text{CONH}–\text{NH–CH(CO_2Et)_2} \text{COOH}
\]

10a–f: a R = H, b R = Ph, c R = 4-FC_6H_4, d R = 4-ClC_6H_4, e R = 4-BrC_6H_4, f R = 4-O_2NC_6H_4

(E) Reactions of various thioamides 12a–e, bearing an activated methylene group, with EMME afforded the intermediates 13a–e, which underwent readily cyclization involving the ethoxycarbonyl group. Finally, 1H-pyridine-2-ones 14a–e were obtained.  

\[
\text{CONHOS} + \text{EMME} \rightarrow \text{CONH–OS} \text{COOEt}
\]

12 13 14

R = H, Ph, 2-MeC_6H_4, 3-MeC_6H_4, 4-MeOC_6H_4

(F) Recently, 6-trifluoromethylquinolines were obtained by a modified Gould–Jacobs reaction. The reaction of 3-fluoro-4,4(trifluoromethyl)aniline with EMME gave the compound 16, which then cyclized with polyphosphoric acid (PPA) to give the key intermediate 17. The subsequent sequential steps are N1-methylation (c), nucleophilic substitution with arilpiperazines (d), and basic hydrolysis (e, f) to the target acids 18a–c.  

\[
\text{NH}_2F + \text{EMME} \rightarrow \text{NMe} \text{COOEt}
\]

15 16 17

(a) EMME, 120 °C  (b) PPA, 100 °C  (c) MeI, K_2CO_3, DMF, 100 °C  (d) arylpiperazine, Et_3N, DMSO, 120 °C  (e) N-methyl-2-pyrrolidone  (f) 48% HBr, reflux

18a: R = CF_3  18b: R = OMe

References