SYNLETT
Spotlight 332

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

Synthetic Applications of Diethyl Ethoxymethylenemalonate

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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.

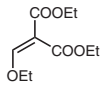
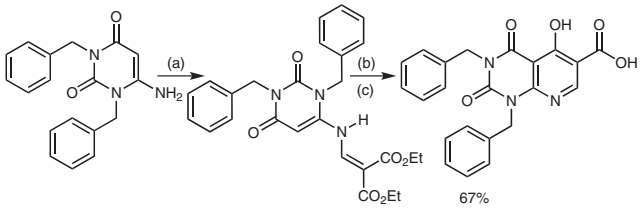


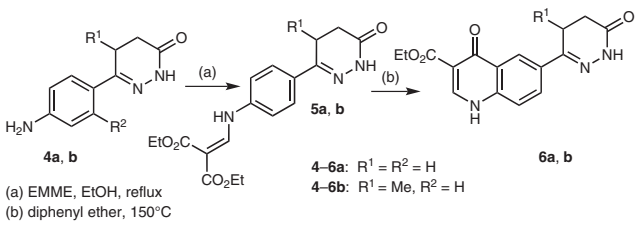
Figure 1 EMME

Abstracts

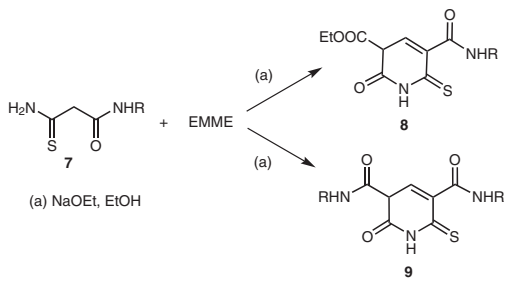
(A) Nair and co-workers reported the synthesis of 1,3-dibenzyl-5-hydroxy-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidine-6-carboxylic acid (**3**) with EMME. The synthesis followed the stages of cyclization and hydrolysis of the ester under acidic conditions. The target compound **3** was obtained 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(2*H*)-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]



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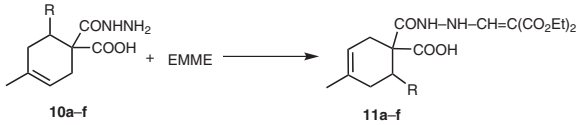
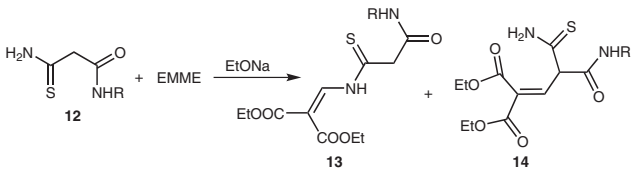
(D) Zicane et al. showed the condensation of EMME with hydrazides **10a–f** occuring exclusively at the enolic ethoxy group of this ester to yield *N*-(2,2-diethoxycarbonylethylenyl)hydrazides of 4-methylcyclohex-4-ene-1,1 dicarboxylic acids **11a–f**. [4]



10a–f **11a–f**

10,11: **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-$O_2NC_6H_4$

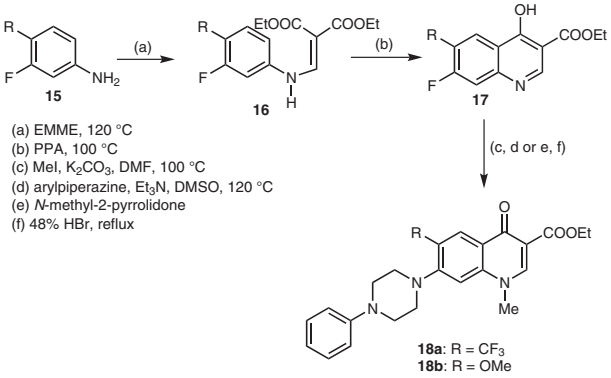
(E) Reactions of various thioamides **12a–e**, bearing an activated methylene group, with EMME afforded the intermediates **13a–e**, which underwent readily cyclization involving the ethoxycarbonyl group. Finally, 1*H*-pyridine-2-ones **14a–e** were obtained.[5]



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(trifluormethyl)aniline with EMME gave the compound **16**, which then cyclized with polyphosphoric acid (PPA) to give the key intermediate **17**. The subsequent sequencial steps are N1-methylation (c), nucleophilic substitution with arilpiperazines (d), and basic hydrolysis (e, f) to the target acids **18a–c**.[6]



15 **16** **17**

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

References

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