

SYNLETT Spotlight 332

Synthetic Applications of Diethyl Ethoxymethylenemalonate

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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

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 hetero-

cyclic systems. The main application of this reagent is its use in the Gould–Jacobs reaction.

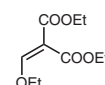
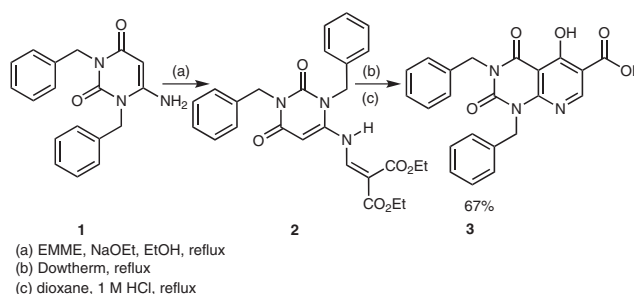


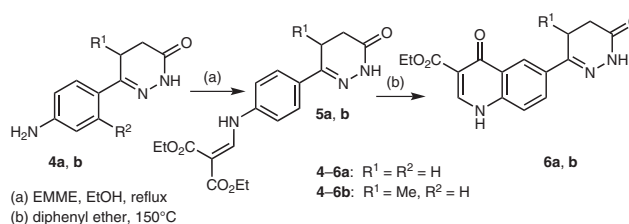
Figure 1 EMME

Abstracts

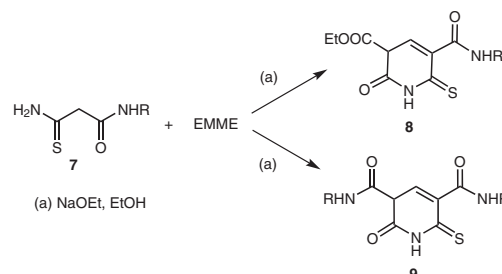
(A) Nair and co-workers reported the synthesis of 1,3-dibenzyl-5-hydroxy-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidine-6-carboxylic acid (**3**) with EMME. The synthesis followed the stages of cyclization and hydrolysis of the ester under acidic conditions. The target compound **3** was obtained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



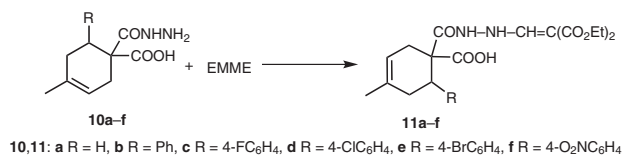
(B) Ethyl 6-(6-oxo-1,4,5,6-tetrahydropyridazin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate (**6**) can be obtained by nucleophilic addition of the 6-(4-aminophenyl)-4,5-dihydropyridazin-3(2*H*)-one (**4**) to the β -carbon of EMME followed by elimination of ethanol. The compound **6** was obtained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



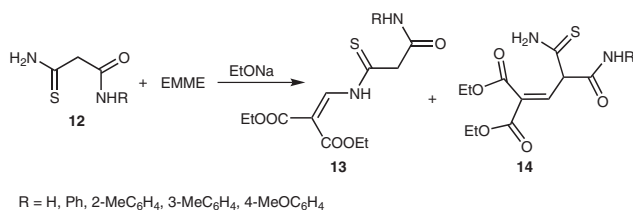
(C) In the literature it is reported that EMME can react with 2-thiocarbamoyl-*N*-arylacetamides (**7**) in two concurrent directions forming 1,2-dihydropyridine-6-thiones **8** and **9**. The yields depend on the excess of the thioamide **7**.³



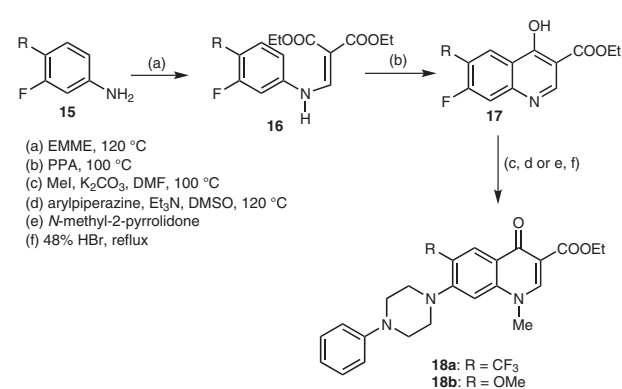
(D) Zicane et al. showed the condensation of EMME with hydrazides **10a–f** occurring exclusively at the enolic ethoxy group of this ester to yield *N*-(2,2-diethoxycarbonylethyl)hydrazides of 4-methylcyclohex-4-ene-1,1 dicarboxylic acids **11a–f**.⁴



(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



(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 arylpiperazines (d), and basic hydrolysis (e, f) to the target acids **18a–c**.⁶



References

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- (4) Zicane, D.; Ravina, I.; Teter, Z.; Petrova, M. *Chem. Heterocycl. Compd.* **2005**, *41*, 187.
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