Nucleophilic Difluoromethylation of Arylidene Meldrum's Acid Derivatives

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About 20% of novel pharmaceuticals and 40% of novel agrochemicals appearing every year contain at least one fluorine atom in their structure. However, the lack of existing methods for obtaining organofluorine compounds limits the expansion of pharmacology and agrochemistry. For instance, there has been no convenient method for nucleophilic addition of the difluoromethyl group (CF2H) to electron deficient alkenes. CF2H-group exhibits unique farmacophoric properties being bioisosteric to hydroxyl group. Herein we present a novel and convenient protocol for the synthesis of ß-CF2H functionalized esters and alcohols by nucleophilic difluoromethylation of electron-deficient olefins. The process is based on 1,4-addition of in situ generated difluoromethylene triphenylphosphorane Ph3P=CF2 to arylidene Meldrum's acid derivatives (the products of condensation between Meldrum’s acid and corresponding aldehydes). The primarily formed phosphobetaines are hydrolized/protodephosphorilated and decarboxylated without isolation, affording ß-CF2H substituted carboxylic acids in a one-pot manner. The latter may be easily transformed to the corresponding ethers and alcohols without preliminary purification. The effectiveness of the process was demonstrated on a large scope of different alkylidene and arylidene substrates. The products were purified by column chromatography and characterized by 1H, 19F, 13C NMR spectra and HRMS or elemental analysis data. One of the intermediates was isolated by slow diffusion crystallization and characterized by 1H, 19F, 13C, 31P NMR, HRMS and X-Ray analysis.

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