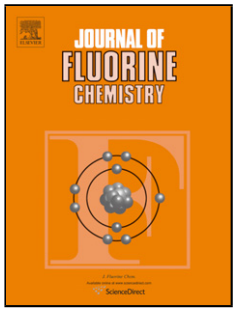

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PII: S0022-1139(15)00039-1
DOI: http://dx.doi.org/doi:10.1016/j.jfluchem.2015.01.015
Reference: FLUOR 8501

To appear in: *FLUOR*

Received date: 28-10-2014
Revised date: 26-1-2015
Accepted date: 30-1-2015

Please cite this article as: D. Yang, Y. Zhou, Y. Song, J. Qu, A practical synthesis of trifluoromethyl alkyl ketones, *Journal of Fluorine Chemistry* (2015), http://dx.doi.org/10.1016/j.jfluchem.2015.01.015

A practical synthesis of trifluoromethyl alkyl ketones

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Abstract:

Trifluoromethyl ketones (TFMKs) significantly contribute to biologically active compounds and special materials. TFMKs can be prepared by "trifluoroacetic ester/ketone metathesis" along with the accompanying products, aromatic acid esters. As an important extension of our previous studies on the use of aryl alkyl ketones, wherein the separation of the resulting TFMKs and aromatic acid esters proved problematic, *i*-Pr and *t*-Bu alkyl ketones were shown in this work to be competent reaction partners for easy TFMK separation from the product mixtures, thereby providing a practical synthesis route to TFMKs. With the removal of accompanying products, *i*-Pr and *t*-Bu carboxylic esters, TFMKs with high boiling points were efficiently obtained by distillation or recrystallization. Furthermore, a solvent-free condition was also effective for this reaction, which allowed TFMKs with low boiling points to be separated from the reaction mixture by distillation in good yield.

Keywords:
Trifluoromethyl alkyl ketones
Practical synthesis
Esters
Solvent free

1. Introduction

In view of the potent effects of the trifluoromethyl group on the pharmacological and physiochemical profiles [1], an extensive variety of synthesis methodologies have been used to target trifluoromethyl-containing compounds [2]. Of this group, trifluoromethyl ketones (TFMKs) have been the focus of considerable attention not only because of their outstanding performances in biological activity [3] but also because of their applications in the synthesis of other trifluoromethyl-containing compounds [4]. Thus, the generation of TFMKs, especially trifluoromethyl alkyl ketones, has been the focus of considerable attention. Over the past years, well-known synthesis methods such as the reaction of trifluoroacetic acid derivatives (acetate or their salts) with Grignard reagent or alkyl lithium [5], nucleophilic trifluoromethylation by Ruppert−Prakash reagent ($TMSCF_3$) [6], and the reaction of carboxylic acids or acyl chlorides with pyridine and trifluoroacetic anhydride [7] have been utilized to prepare TFMKs. Given the electron-withdrawing characteristic of the trifluoromethyl group, the oxidation of trifluoromethyl carbinol is difficult. Efficient reagents for the oxidation of trifluoromethyl carbinol include hypervalent iodine reagents and oxoammonium salt [8]. A similar method to generate TFMKs is the catalytic aerobic oxidative decarboxylation of α-trifluoromethyl-α-hydroxy acids [9]. In addition, more efficient methods have been developed, for example, enediolate trifluoroacetylation/decarboxylation of enolizable carboxylic acids [10]

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