Phosphorus, Sulfur, and Silicon and the Related Elements

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gpss20

A Convenient Procedure For The Synthesis Of 2,2,2-Trifluoroethyl Methyl 2-Oxoalkylphosphonates

Katalin Molnár¹, Julien Behra², László Takács², Mihály Kádár³, Zsuzsanna Kardos³ & Ferenc Faigl³

¹ Sanofi/Chinoin - Prostaglandin Business Unit, Budapest, Hungary
² National Graduate School of Chemistry and Chemical Engineering of Montpellier, Montpellier, France
³ MTA-BME Organic Chemical Technology Research Group, Hungarian Academy of Sciences, Budapest University of Technology and Economics, Budapest, Hungary

Accepted author version posted online: 14 Nov 2014.

To cite this article: Katalin Molnár, Julien Behra, László Takács, Mihály Kádár, Zsuzsanna Kardos & Ferenc Faigl (2014): A Convenient Procedure For The Synthesis Of 2,2,2-Trifluoroethyl Methyl 2-Oxoalkylphosphonates, Phosphorus, Sulfur, and Silicon and the Related Elements, DOI: 10.1080/10426507.2014.978326

To link to this article: http://dx.doi.org/10.1080/10426507.2014.978326

Disclaimer: This is a version of an unedited manuscript that has been accepted for publication. As a service to authors and researchers we are providing this version of the accepted manuscript (AM). Copyediting, typesetting, and review of the resulting proof will be undertaken on this manuscript before final publication of the Version of Record (VoR). During production and pre-press, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal relate to this version also.

PLEASE SCROLL DOWN FOR ARTICLE

Taylor & Francis makes every effort to ensure the accuracy of all the information (the "Content") contained in the publications on our platform. However, Taylor & Francis, our agents, and our licensors make no representations or warranties whatsoever as to the accuracy, completeness, or suitability for any purpose of the Content. Any opinions and views expressed in this publication are the opinions and views of the authors, and are not the views of or endorsed by Taylor & Francis. The accuracy of the Content should not be relied upon and should be independently verified with primary sources of information. Taylor and Francis shall not be liable for any losses, actions, claims, proceedings, demands, costs, expenses, damages, and other liabilities whatsoever or howsoever caused arising directly or indirectly in connection with, in relation to or arising out of the use of the Content.

This article may be used for research, teaching, and private study purposes. Any substantial or systematic reproduction, redistribution, reselling, loan, sub-licensing, systematic supply, or distribution in any form to anyone is expressly forbidden. Terms & Conditions of access and use can be found at http://www.tandfonline.com/page/terms-and-conditions
A CONVENIENT PROCEDURE FOR THE SYNTHESIS OF 2,2,2-TRIFLUOROETHYL METHYL 2-OXOALKYLPHOSPHONATES

Katalin Molnár,∗a Julien Behra, b László Takács, a Mihály Kádár, a Zsuzsanna Kardos, a
Ferenc Faigl.c

aSanofi / Chinoin - Prostaglandin Business Unit, Budapest, Hungary

bNational Graduate School of Chemistry and Chemical Engineering of Montpellier, Montpellier, France

cMTA-BME Organic Chemical Technology Research Group, Hungarian Academy of Sciences, Budapest University of Technology and Economics, Budapest, Hungary

katimolnar88@gmail.com

Abstract: A convenient and versatile method was developed for the synthesis of 2,2,2-trifluoroethyl methyl 2-oxoalkylphosphonates starting from dimethyl phosphonates by alkaline hydrolysis followed by esterification with 2,2,2-trifluoroethanol using diisopropylcarbodiimide (DIC) in the presence of 4-(dimethylamino)pyridine (DMAP) catalyst following the Steglich protocol.

Keywords: trifluoroethyl ester, mixed phosphonoester, methyl phosphonic acid, 2,2,2-trifluoroethanol, Steglich protocol
INTRODUCTION

Stabilized phosphonates are key compounds in the Horner-Wadsworth-Emmons (HWE) reaction to form trans double bonds. The work of Still and Gennari\(^1\) and later of Jin\(^2\) showed that using bis(2,2,2-trifluoroethyl)phosphonoacetates or 2-oxoalkylphosphonates the stereochemical outcome of the HWE reaction is reversed and α,β-unsaturated esters or ketones can be prepared with moderate to good Z stereoselectivity. In order to understand this unexpected effect of the trifluoroethyl substituents more thoroughly, we wanted to examine the situation when only one trifluoroethyl group was present. Although many examples can be found for the preparation of dimethyl- and bis(trifluoroethyl)phosphonates, mixed trifluoroethyl methyl phosphonates are unknown and therefore elaboration of a simple method for their synthesis was undertaken.

RESULTS AND DISCUSSION

Mixed phosphonates can be conveniently prepared from their readily available dimethyl analogues using two methods (Scheme 1): (i) activation of the phosphonate moiety by mono chlorination followed by reaction with trifluoroethanol\(^3\) or (ii) partial hydrolysis of a diester followed by esterification with trifluoroethanol.\(^4\) Considering the unpleasant reaction conditions of chlorination and the stability of 2-oxoalkylphosphonates, partial hydrolysis of the dimethylester was preferred.

Acidic hydrolysis needs harsh conditions and yields the fully hydrolyzed product.\(^4,5\) Mono dealkylation can be performed in alkaline medium where the difference of an order of magnitude in the rate of hydrolysis of mono and diesters enables partial hydrolysis.\(^4,5\) Best results were obtained with KOH in water at 50 °C. No organic solvent was needed because of the water solubility of the dimethyl phosphonates studied (1). Solubility in water of the dimethyl ester 1a...
was considerable explaining the lower yield of the monoester 2a. Work-up was adjusted to the different solubilities of monoesters 2 (see in the Supplement). Conditions and results of hydrolysis are summarized in Table 1.

The next step was the alkylation of the mono phosphonic acids (2). Trifluoroethanol is a weak nucleophile therefore it was not surprising that direct esterification in the presence of H$_2$SO$_4$, the use of Mitsunobu reaction$^6$ and base catalyzed alkylation with trifluoroethyl mesylate or tosylate were all unsuccessful. Even with trifluoroethyl triflate only traces of the product was formed. Activation of the monoester (2) with carbamide derivatives as in Kampe’s procedure$^7$ was promising. Satisfying results were achieved by following Steglich’s protocol$^8$, which is frequently used for preparing carboxylic acid esters with hindered alcohols. The monoester (2) was dissolved in dichloromethane and activated with a carbamide derivative (DCC or DIC) and esterification was catalyzed by DMAP. Results are summarized in Table 2.

**EXPERIMENTAL**

**General procedure for the synthesis of trifluoroethyl methyl phosphonates 3a-c**

**Esterification.** To the solution of 2-oxoalkylphosphonic acid monomethyl esters 2a-c (30 mmol) in 20 mL DCM 2.93 g (24 mmol) DMAP and 2.62 mL (36 mmol) trifluoroethanol were added under nitrogen atmosphere. The reaction mixture was cooled to -10 °C and 5.57 mL (36 mmol) DIC was added, then it was let to warm up overnight. Reaction was quenched by 46 mL 1 M HCl. After stirring for 20 minutes, the reaction mixture was cooled to 0 °C. Precipitation was filtered off and washed with EtOAc. The phases were separated, the aqueous phase was extracted.
with EtOAc. The combined organic phases were washed with 1 M NaHCO₃ and brine, dried over Na₂SO₄ and evaporated. The crude product was purified by silica gel column chromatography giving the title compound as yellowish liquids.

*Supplemental data are available online with synthetic details and \(^1\)H, \(^{13}\)C and \(^{31}\)P NMR data of compounds 1a-c, 2a-c, and 3a-c and HRMS data of 3a-c.*

**CONCLUSIONS**

A two-step procedure was worked out for the preparation of novel, mixed, trifluoroethyl methyl 2-oxoalkylphosphonates. Our procedure using alkaline hydrolysis and a carbamide derivative activated esterification is mild and can be generally used even with less nucleophilic alcohols. Investigation of the stereochemistry in HWE reactions of mixed ester phosphonates is in progress.

**ACKNOWLEDGEMENTS**

We thank the financial support of Sanofi-Chinoin and Varga József Foundation.
REFERENCES


Scheme 1
Table 1. Partial hydrolysis of dimethyl 2-oxophosphonates 1a-c

<table>
<thead>
<tr>
<th>Compound</th>
<th>R</th>
<th>Reaction time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2a</td>
<td>H</td>
<td>5</td>
<td>73</td>
</tr>
<tr>
<td>2b</td>
<td>Pr</td>
<td>6</td>
<td>89</td>
</tr>
<tr>
<td>2c</td>
<td>3-Me-Ph</td>
<td>24</td>
<td>93</td>
</tr>
</tbody>
</table>

Table 2. Synthesis of mixed esters 3a-c

<table>
<thead>
<tr>
<th>Compound</th>
<th>R</th>
<th>Purity (%)*</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a</td>
<td>H</td>
<td>73</td>
<td>38</td>
</tr>
<tr>
<td>3b</td>
<td>Pr</td>
<td>89</td>
<td>42</td>
</tr>
<tr>
<td>3c</td>
<td>3-Me-Ph</td>
<td>93</td>
<td>36</td>
</tr>
</tbody>
</table>

* Determined by $^1$H NMR