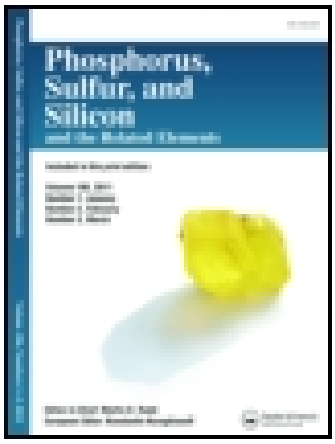


Phosphorus, Sulfur, and Silicon and the Related Elements

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 Molnár[a], Julien Behra[b], László Takács[a], Mihály Kádár[a], Zsuzsanna Kardos[a] & Ferenc Faigl[c]

[a] Sanofi/Chinoin - Prostaglandin Business Unit, Budapest, Hungary

[b] National Graduate School of Chemistry and Chemical Engineering of Montpellier, Montpellier, France

[c] 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

Running head: Synthesis of trifluoroethyl methyl phosphonates

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]

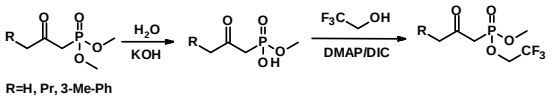
[a]Sanofi / Chinoin - Prostaglandin Business Unit, Budapest, Hungary

[b]National Graduate School of Chemistry and Chemical Engineering of Montpellier, Montpellier, France

[c]MTA-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_2SO_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 $NaHCO_3$ and brine, dried over Na_2SO_4 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

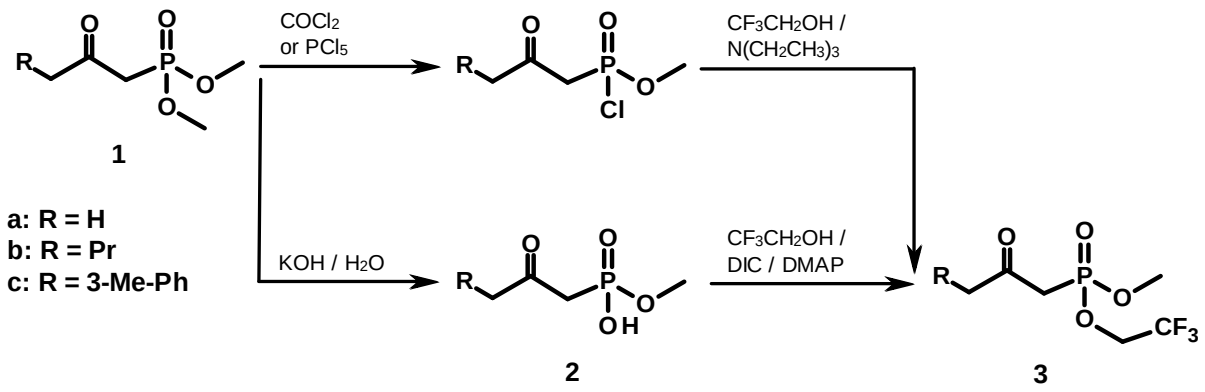
A two-step procedure was worked out for the preparation of novel, mixed, trifluoroethyl methyl 2-oxoalkylphosphonates. Our procedure using alkaline hydrolysis and a carbamide derivative activated esterification is mild and can be generally used even with less nucleophilic alcohols. Investigation of the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

1. Still, W. C.; Gennari, C. *Tetrahedron Lett*. **1983**, *24*, 4405.
2. Yu, W.; Su, M.; Jin, Z. *Tetrahedron Lett*. **1999**, *40*, 6725.
3. Iorga, B., Carmichael, D.; Savignac, P. *C. R. Acad. Sci. Paris, Série IIc, Chimie : Chemistry 3*, **2000**, 821.
4. Greene, T. W.; Wuts, P. G. M. *Protective groups in organic synthesis*, 3rd ed.; Wiley & Sons: New York, **1999**, pp 660.
5. Cox, J. R. JR.; Ramsay, O. B. *Chem. Rev.*, **1964**, *64*, 317.
6. a, Campbell, D. A. *J. Org. Chem*. **1992**, *57*, 6331; b, Mitsunobu, O. *Synthesis* **1981**, *1*, 1.
7. Kampe, W. *Chem. Ber.*, **1965**, *98*, 1031.
8. Neises. B.; Steglich, W. *Org. Synth.*, **1985**, *63*, 183.



Scheme 1

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

Compound	R	Reaction time (h)	Yield (%)
2a	H	5	73
2b	Pr	6	89
2c	3-Me-Ph	24	93

Table 2. *Synthesis of mixed esters **3a-c***

Compound	R	Purity (%)*	Yield (%)
3a	H	73	38
3b	Pr	89	42
3c	3-Me-Ph	93	36

** Determined by ^{1}H NMR*

