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A New Bis(2,2,2-trifluoroethyl)phosphonate for the Synthesis of *Z*-Unsaturated *N*-Methoxy-*N*-methylamides

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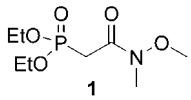
Abstract: The *N*-methoxy-*N*-methyl bis(2,2,2-trifluoroethyl)phosphonamide was easily obtained via the *Arbuzov* reaction with use of commercially available tris(2,2,2-trifluoroethyl)phosphite, 2-bromo-*N*-methoxy-*N*-methylacetamide, and KF/alumina. The reaction of bis(2,2,2-trifluoroethyl)phosphonate with several aldehydes demonstrates the versatility of the method, which gives *Z*-unsaturated amides in good yields.

One of the best methods for the synthesis of conjugated unsaturated esters or nitriles is the Wittig−Horner−Emmons reaction.[1] The Wittig−Horner−Emmons olefination gives preferentially the *E*-alkene, but a combination of modifications on the structure of the phosphonate (2,2,2-trifluoroethyl instead of ethyl), associated with a highly dissociated countercation with a crown ether, gives the *Z*-alkene in high yield.[2] On the other hand, *N*-methoxy-*N*-methylamide is a useful synthetic precursor for aldehydes and ketones.[3] We wish to report a new class of bis(2,2,2-trifluoroethyl)phosphonate containing the *N*-methoxy-*N*-methylamide moiety, which gives access to *Z*-unsaturated aldehydes or ketones in high yield.

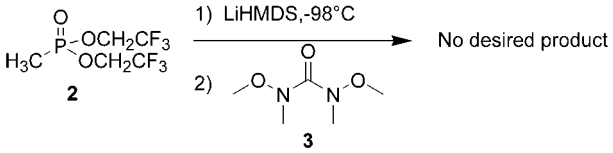
The method reported by Still[2] to make the bis(2,2,2-trifluoroethyl)phosphonate, i.e, reaction of the corresponding triethylphosphonoacetate with PCl_5 to form the dichlorophosphonate followed by treatment with 2,2,2-trifluoroethanol and a base, does not work with *N*-methoxy-*N*-methylamide. Indeed, when phosphonate **1**



1

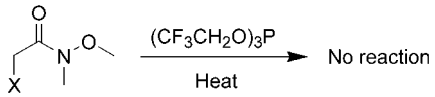
is treated with phosphorus pentachloride, complete degradation occurred. Another method for the synthesis of bis(2,2,2-trifluoroethyl)phosphonate developed by Savignac,[4] and which was utilized by Jin,[5] also failed when

SCHEME 1



2 **3**

SCHEME 2



4 X=Br
5 X=I

the *N*,*N*′-dimethoxy-*N*,*N*′-dimethylurea[6] (**3**) was used as the electrophile (Scheme 1).

We decided to investigate the classical method for the synthesis of phosphonates, i.e, the *Arbuzov* reaction,[7] that involve trialkyl phosphite as the nucleophile and a α-halocarbonyl compound as the electrophile. The experimental procedure is very simple, the two reagents are mixed together without solvent and then the desired phosphonate is distilled. 2-Bromo-*N*-methoxy-*N*-methylacetamide (**4**) was easily obtained[8] and the tris(2,2,2-trifluoroethyl)phosphite is commercially available. However, the desired phosphonate was never detected in standard conditions and degradation of the tris(2,2,2-trifluoroethyl)phosphite occurred when the temperature reached 200 °C. Also the use of 2-iodo-*N*-methoxy-*N*-methylacetamide (**5**) (formed by the reaction of sodium iodide and **4** in acetone under reflux) did not change the outcome of the reaction (Scheme 2).

Tius and Busch-Petersen used KF/alumina to form α-heterosubstituted Weinreb amides.[9] We found that (2,2,2-trifluoroethyl) phosphite reacts with bromides **4** and **6** in the presence of KF/alumina in acetonitrile to give the desired phosphonates **7** and **8** in moderate yield (33%). This method was also applied to commercially available ethyl 2-bromopropionate (**9**) for the synthesis of phosphonate **10** developed by Still[2] (Scheme 3).

In search for another phosphonate, giving access to highly functionalized trisubstituted alkenes, we decided to investigate the reactivity of α-bromophosphonates. Starting with phosphonate **7**, bromophosphonate **11** was easily synthesized (Scheme 4) under modified Balczewski conditions.[10]

Bis(2,2,2-trifluoroethyl)phosphonates **7**, **8**, and **11** were used to form several *Z*-unsaturated *N*-methoxy-*N*-methylamides as indicated in Table 1. Only the *Z* isomer is detectable by ^{1}H NMR for all entries, except for the case of bromoamide **17**, where the *E* isomer is the major product (ratio 7:1). The two isomers are easily separable

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(2) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405−4408.
(3) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1982**, *22*, 3815−3818.
(4) Patois, C.; Savignac, P.; About-Jaudet, E.; Collignon, N. *Synthetic Commun.* **1991**, *21*, 2391−2396.
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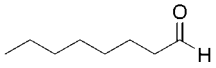
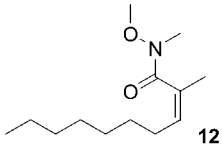
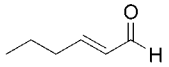
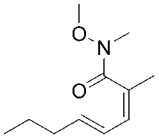
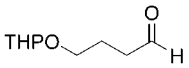
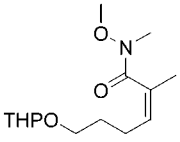
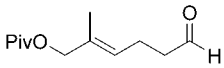
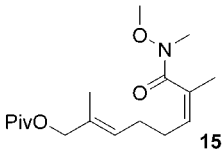
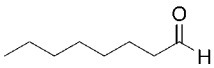
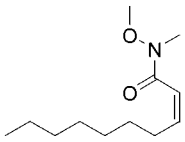
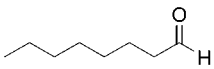
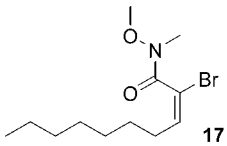
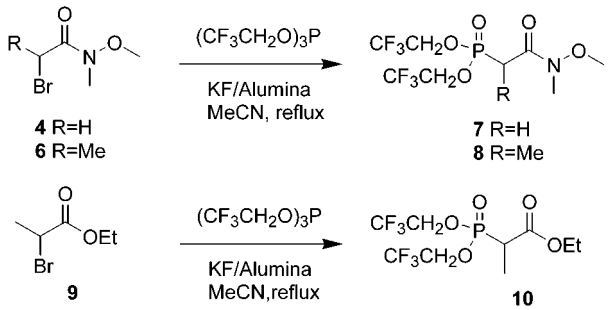
TABLE 1. Preparation of Z-Unsaturated *N*-Methoxy-*N*-methylamide

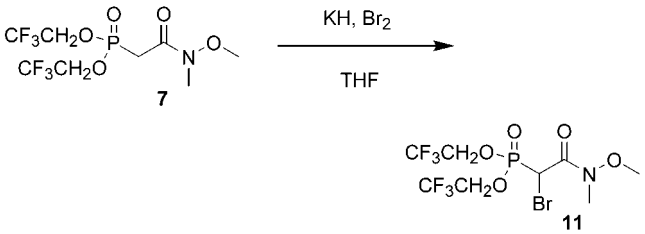
Entry	Aldehyde	Phosphonate	Product	Yield (%)[a]	Ratio (Z/E)
1		**8**	 **12**	83	>20/1
2		**8**	 **13**	83	>20/1
3		**8**	 **14**	83	>20/1
4		**8**	 **15**	81	>20/1
5		**7**	 **16**	89	>20/1
6		**11**	 **17**	70	1/7[b]

[a] Isolated yields. [b] **17** has the *E* configuration by virtue of the high priority of Br in the stereochemical assignment.

SCHEME 3



SCHEME 4



by flash chromatography. To ensure the predominance of the *Z* geometry, the corresponding diethyl phosphonate **18** was allowed to react with octanal under Massiot conditions[12] to afford *E*-unsaturated amide **19** (Scheme 5). Amides **12** and **19** possessed chemical shifts of 5.4 and 5.8 ppm, respectively, in agreement with literature precedents[12] and thus confirming the assigned geometries.

Experimental Section

General. All reactions were performed under nitrogen atmosphere with flame-dried glassware. All solvents were distilled prior to use; tetrahydrofuran was dried by distilling over sodium benzophenone ketyl. Dichloromethane and acetonitrile were distilled over calcium hydride. Analytical and preparative thin-

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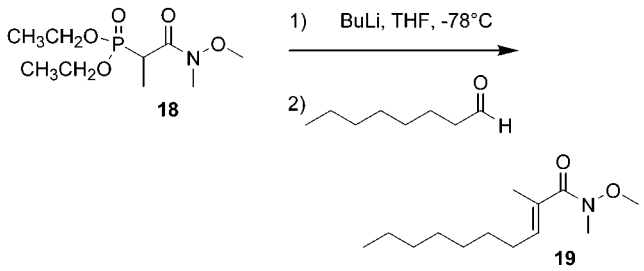
(12) Nuzillard, J.-M.; Boumendjel, A.; Massiot, G. *Tetrahedron Lett.* **1989**, *30*, 3779−3780.

SCHEME 5



layer chromatographies were carried out on precoated glass plates (0.25 mm) with 60 F-250 silica gel (Merck). Materials were detected by visualization under an ultraviolet lamp and/or by spraying with a solution of phosphomolybdic acid (10% in ethanol) followed by heating on a hot plate. Column chromatography was performed with 60 silica gel (230−400 mesh, Merck).

Typical Procedure for the Preparation of the Phosphonate. To a solution of bromide **6** (5.57 g, 79.4 mmol) in acetonitrile (50 mL) was added the KF/alumina[11] (34.5 g, 2:3 w/w, 238 mmol) with heating to strong reflux (oil bath set at 100 °C). After 15 min, the tris(2,2,2-trifluoroethyl) phosphite (26.7 mL, 119.1 mmol) was added and the reaction mixture was refluxed for 18 h. The reaction mixture was cooled to room temperature, diluted with ether (100 mL), and filtered over a pad of Celite; the solvent was evaporated. The residue was purified by bulb-to-bulb distillation (115−125 °C, 0.1 mmHg) to afford phosphonate **8** (9.59 g, 33%) as a colorless oil.

Typical Procedure for the Preparation of *Z*-Unsaturated *N*-Methyl-*N*-methoxyamide. To a solution of phosphonate **8** (600 mg, 1.66 mmol) in THF (8 mL) was added 18-C-6 (334 mg, 1.27 mmol) and the solution was cooled to 0 °C. KH (54 mg, 1.35 mmol) freshly washed with dry hexanes was added in one shot and the reaction mixture was stirred at 0 °C for 20 min. The solution was cooled to −78 °C and octanal (143 mg, 1.11 mmol) in THF (2 mL), cooled to −78 °C, was added via cannula. After 30 min the reaction was quenched with saturated ammonium chloride solution (15 mL) and extracted (3×) with ether. The combined organic phase was dried over sodium sulfate, filtered, and concentrated. The yellow residue was purified by flash chromatography (50% ethyl ether in hexane) to give amide **12** (209 mg, 83%) as a colorless oil.

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Supporting Information Available: ^{1}H NMR, ^{13}C NMR, IR, MS, and HRMS for compounds **7, 8,** and **11**−**19**. This material is available free of charge via the Internet at http://pubs.acs.org.

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