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Alkoxide-induced nucleophilic trifluoromethylation using diethyl trifluoromethylphosphonate

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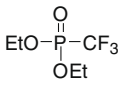
ABSTRACT

A novel alkoxide-induced nucleophilic trifluoromethylation of carbonyl compounds, disulfides and diselenides using diethyl trifluoromethylphosphonate is presented. In these reactions diethyl trifluoromethylphosphonate acts as a [CF_3^-] synthon.

The unique properties of the trifluoromethyl group such as its powerful electron-withdrawing character, relatively small size, increased lipophilicity and metabolic stability have been exploited in the design of new targets for pharmaceutical and agrochemical industries as well as materials science.[1] Traditional methods leading to trifluoromethyl-containing molecules often rely on highly reactive, toxic and hazardous chemicals[1c] (HF, F_2, SF_4, halogen fluorides, high-valence metal fluorides). In recent years, direct CF_3 group introduction by nucleophilic,[2] radical[3] or electrophilic[4] trifluoromethylations have been explored.[5] Nucleophilic trifluoromethylation is a powerful strategy despite the inherent instability of CF_3M (M = Na, K, MgX, etc.) reagents which readily decompose to difluorocarbene and metal fluorides.[6] The most efficient, mild and versatile nucleophilic trifluoromethylating reagent is the Ruppert–Prakash reagent (Me_3SiCF_3), which upon initiation, typically with fluoride ions, oxygen nucleophiles or Lewis bases, delivers the trifluoromethyl group to electrophilic substrates such as aldehydes, ketones, esters, amides, acid chlorides or anhydrides, imines, nitrones and others.[2] Nucleophilic trifluoromethylation has been achieved using other systems including: (a) trifluoromethane in the presence of a strong base,[7] (b) bromo or iodotrifluoromethane in the presence of tris(dialkylamino)phosphines[8] or tetrakis(dimethylamino)ethylene,[9] respectively, (c) trifluoromethyl carbonyl reagents such as hemiaminals of trifluoroacetaldehyde,[10] trifluoroacetophenone[11] and its aminoketals,[12] esters, salts and amides of trifluoroacetic acid,[13] (d) sulfur reagents such as trifluoromethyl sulfides in the presence of germyl anions,[14] trifluoromethanesulfoxides and sulfones in the presence of alkoxides,[15] and trifluoromethanesulfinates and sulfinamides.[10f,16] We herein report the use of the phosphorus-containing nucleophilic trifluoromethylating reagent—diethyl trifluoromethylphosphonate (**1**) for the efficient trifluoromethylation of carbonyl compounds and other electrophiles. The only reported CF_3–P-containing nucleophilic trifluoromethylating reagents are the phosphonium salts $[CF_3P(NR_2)_3]^+Br^-$ (R = Me, Et, *n*-Pr) prepared by the reaction of CF_3Br with $P(NR_2)_3$. These phosphonium salts were used for the trifluoromethylation of benzaldehyde in the presence of fluoride ions.[17]



1

During the course of our investigation of nucleophilic difluoromethylation and difluoromethylenation with diethyl difluoromethylphosphonate[18] we became interested in the possibility of analogous nucleophilic trifluoromethylations with diethyl trifluoromethylphosphonate (**1**).[19] We expected that addition of a nucleophilic reagent to **1** would effect cleavage of the carbon–phosphorus bond to generate an unstable trifluoromethyl carbanion, and in the presence of an electrophilic substrate, provide the corresponding trifluoromethylated product.

Our initial attempts to effect the trifluoromethylation of benzophenone with **1** in the presence of CsF (2 equiv) in DMF at room temperature led only to recovery of the starting material. Substituting CsF for *t*-BuOK did not lead to any improvement and conducting the reaction at −40 °C or 0 °C for 30 min and quenching the reaction at that temperature led only to trace amounts of the

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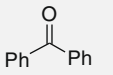
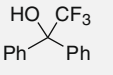
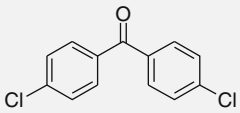
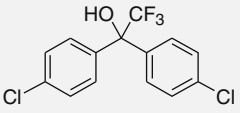
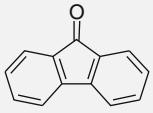
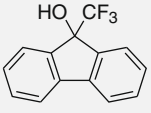
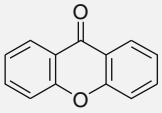
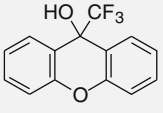
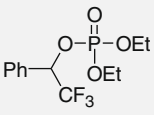
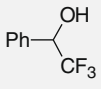
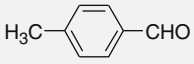
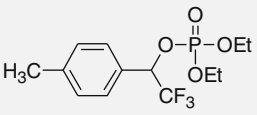
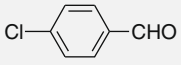
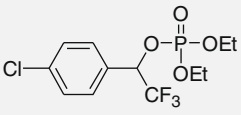
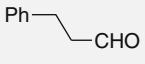
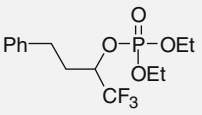
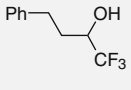
trifluoromethylated alcohol product. We were gratified to observe an excellent[19] F NMR yield of the trifluoromethylated alcohol product when using *t*-BuOK (2 equiv) in DMF as the solvent at −40 °C, and slowly warming to room temperature over 1 h (Table 1, entry 1). Reduction of the amount of base, changing the base to the less basic potassium phenolate or changing the solvent system to THF–DMF (9:1) led to dramatic decreases in product yields (5–20%). The optimized reaction conditions were used for the trifluoromethylation of a range of non-enolizable ketones and the corresponding trifluoromethylated alcohols were obtained in very good isolated yields (Table 1, entries 2–4).

Next, our attention turned to the use of aromatic aldehydes as electrophilic substrates. Although Prakash et al.[15b] have demonstrated the compatibility of aryl aldehydes and *t*-BuOK in the trifluoromethylation using phenyl trifluoromethyl sulfone, in our case, the use of *t*-BuOK (2 equiv) (or CsF) with phosphonate **1** and benzaldehyde did not lead to any trifluoromethylated product. We therefore investigated other alkoxides as initiators including the less sterically demanding MeONa, and the less basic and nucleophilic CF_3CH_2OK, PhOK and C_6F_5OK. While the use of MeONa or C_6F_5OK did not meet with success, the other two alkoxides gave unexpected products. In the presence of potassium trifluoroethanolate the expected 2,2,2-trifluoro-1-phenylethanol was obtained in 15% yield, however a small amount (3%) of diethyl 2,2,2-trifluoro-1-phenylethyl phosphate was formed. In the presence of potassium phenolate, 2,2,2-trifluoro-1-phenylethanol was obtained in only 9% NMR yield, while diethyl 2,2,2-trifluoro-1-phenylethyl phosphate was formed in 81% NMR yield (65% isolated yield) (Table 1, entry 5). The major product (phosphate) presumably originates by reaction of the intermediate alcoholate [$PhCH(CF_3)O^-$] with **1**. Therefore we investigated the possibility of using the nucleophilic initiator in catalytic amounts. However, the use of 0.1 equiv of PhOK under otherwise identical reaction conditions led to the formation of trace amounts of 2,2,2-trifluoro-1-phenylethanol and no phosphate. We have evaluated the reaction scope using the optimized reaction conditions and various aryl aldehydes (Table 1, entries 6–8). 4-Methylbenzaldehyde and 4-chlorobenzaldehyde underwent smooth reaction to give the corresponding trifluoromethyl-containing phosphates as the sole products in good yields. On the other hand, deactivated 4-methoxybenzaldehde was found to be unreactive (not shown in Table 1). Even the enolizable aldehyde (3-phenylpropanal) provided the trifluoromethyl-containing phosphate in good yield together with a small quantity of the trifluoromethylated alcohol.

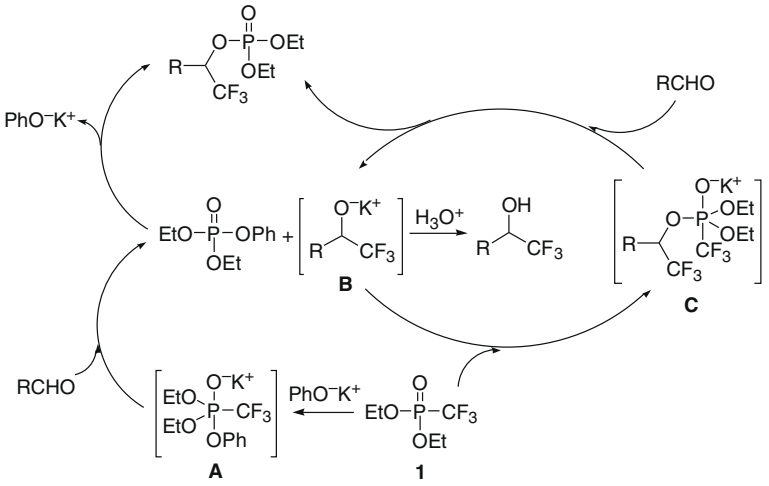
Attempts to effect trifluoromethylation of enolizable ketones such as acetophenone or cyclohexanone with **1** under various reaction conditions unfortunately led to low yields (<10%) of the corresponding trifluoromethylated products.

Finally, we briefly evaluated phosphonate **1** for the trifluoromethylation of diphenyl disulfide and diphenyl diselenide. In the presence of *t*-BuOK the corresponding trifluoromethyl sulfide and selenide were obtained in low yields (Table 1, entries 9 and 10).

Table 1
Nucleophilic trifluoromethylation using diethyl trifluoromethylphosphonate (**1**)[a]

Entry	Substrate	Alkoxide	Product and yields[b]		
1		*t*-BuOK		91%[15b]	
2		*t*-BuOK		99%[15b]	
3		*t*-BuOK		89%[10c]	
4		*t*-BuOK		91% (83%)[20]	
5	PhCHO	PhOK		81% (65%)[20]	 9%[15b]
6		PhOK		72% (57%)[20]	
7		PhOK		99% (86%)[20]	
8		PhOK		60% (53%)[20]	 16%[21]
9	PhSSPh	*t*-BuOK	$PhSCF_3$	26%[7c]	
10	PhSeSePh	*t*-BuOK	$PhSeCF_3$	34%[22]	

[a] Reaction conditions: (1) Substrate (0.5 mmol), $CF_3P(O)(OEt)_2$ (0.6 mmol), alkoxide (1 mmol), DMF (1.7 mL), −40 °C to rt, 1 h; (2) HCl, H_2O, rt.
[b] ^{19}F NMR yield using $PhCF_3$ as the internal standard. Yield of isolated product in brackets.



Scheme 1. A plausible mechanism for the trifluoromethylation of aldehydes with **1** in the presence of potassium phenolate.

The use of PhOK did not result in any improvement in the product yields.

Concerning the mechanism of the alkoxide-induced trifluoromethylation reactions with **1**, it is reasonable to assume that the reaction starts with nucleophilic attack of the alkoxide (PhOK) on **1**. In the presence of an aldehyde the alcoholate **B** is formed together with diethyl phenylphosphate (detected in the crude reaction mixture by GC–MS and NMR $\delta_P = -1.28$ ppm, singlet) presumably via pentavalent phosphorus intermediate **A**. Protonation of the alcoholate **B** gives the trifluoromethyl-containing alcohol, while for the formation of the trifluoromethyl-containing phosphate, two routes can be envisaged. The first involves transesterification of diethyl phenylphosphate with **B** and the second is the reaction of **B** with phosphonate **1** to give the intermediate **C**, followed by reaction with another molecule of aldehyde to provide the phosphate product and alcoholate **B** (Scheme 1). This mechanistic scenario implies the regeneration of phenolate, however, the observed dramatic decrease of product yield when using catalytic amounts of phenolate is an indication of the poor efficiency in the formation and/or decomposition of intermediate **A**.

In conclusion, we have demonstrated that diethyl trifluoromethylphosphonate (**1**) in the presence of alkoxide ions (potassium *tert*-butoxide or phenoxide) represents a new system for the nucleophilic trifluoromethylation of various electrophilic substrates. In the presence of potassium *tert*-butoxide, non-enolizable ketones provide the corresponding trifluoromethyl carbinols in high yields whereas in the presence of potassium phenolate, aryl and alkyl aldehydes furnish the phosphates of trifluoromethyl carbinols[23] in good yields (in some cases accompanied by small amounts of trifluoromethyl carbinols). The mode of action of our system is similar to the use of trifluoroacetophenone[11] or phenyl trifluoromethyl sulfone[15b] for nucleophilic trifluoromethylation and provides a unique reaction pattern in the case of trifluoromethylation of aldehydes. Although phosphonate **1** does not display as good a performance as $TMSCF_3$ in terms of availability and substrate range applicability, it expands the array of available trifluoromethylating reagents with a new phosphorus-containing member.

Acknowledgements

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19. Compound **1** was prepared by reaction of CF_3I with $P(OEt)_3$ under photolytic conditions: (a) Burton, D. J.; Flynn, R. M. *Synthesis* **1979**, 615; (b) Mahmood, T.; Shreeve, J. M. *Synth. Commun.* **1987**, *17*, 71–75.
20. *General procedure for nucleophilic trifluoromethylation*: A solution of alkoxide (1 mmol) in anhydrous DMF (0.7 mL) was added dropwise to a solution of substrate (0.5 mmol) and **1** (123.7 mg, 0.6 mmol) in anhydrous DMF (1 mL) cooled to −40 °C. The reaction mixture was warmed to room temperature over 1 h and then added slowly to aqueous HCl (5 mL, 0.2 M), followed by extraction with *t*-BuOMe (3 × 10 mL). The combined organic phase was washed with water (10 mL), brine (10 mL), dried ($MgSO_4$), filtered, and the solvent removed in vacuo. The crude product was purified by column chromatography over silica gel.
9-Trifluoromethyl-9H-xanthen-9-ol (entry 4, Table 1): 83%, white solid; mp 90–91 °C; R_f = 0.36 (10% EtOAc in hexane); FTIR (film, ν_{max} cm^{-1}) 3545, 3425, 3077, 3044, 1644, 1606, 1575, 1478, 1452, 1253, 1174, 1057, 756, 717; ^1H NMR (400 MHz, $CDCl_3$): δ = 3.16 (s, 1H, O*H*), 7.18–7.25 (m, 4H, $C_{Ar}H$), 7.40–7.46 (m, 2H, $C_{Ar}H$), 7.80–7.83 (m, 2H, $C_{Ar}H$); ^{13}C {^1H} NMR (100 MHz, $CDCl_3$): δ = 69.5 (q, $^2J_{CF}$ = 31.2 Hz, *C*OH), 116.6 ($C_{Ar}H$), 119.1 (C_{Ar}), 123.4 ($C_{Ar}H$), 124.3 (q, $^1J_{CF}$ = 286.0 Hz, CF_3), 127.9 ($C_{Ar}H$), 130.8 ($C_{Ar}H$), 151.1 (C_{Ar}); ^{19}F NMR (376 MHz, $CDCl_3$): δ = −81.9 (s); EI-MS: *m/z* 266 (M+, 5%), 197 (100), 181 (8), 139 (9), 115 (9), 77 (7); ESI-HRMS: *m/z* calcd for $C_{14}H_8F_3O_2$ $(M-H)^-$: 265.0482; found: 265.0483.
Diethyl 2,2,2-trifluoro-1-phenylethyl phosphate (entry 5, Table 1): 65%, colorless oil; R_f = 0.14 (20% EtOAc in hexane); FTIR (film, ν_{max} cm^{-1}) 3070, 3040, 2987, 1606, 1590, 1498, 1481, 1266, 1184, 1039, 704, 635; ^1H NMR (400 MHz, $CDCl_3$): δ = 1.15 (dt, 3H, $^3J_{HH}$ = 7.1 Hz, $^4J_{HP}$ = 1.1 Hz, CH_3), 1.31 (dt, 3H, $^3J_{HH}$ = 7.1 Hz, $^4J_{HP}$ = 1.1 Hz, CH_3), 3.83–3.97 (m, 2H, CH_2), 4.06–4.22 (m, 2H, CH_2), 5.56–5.64 (m, 1H, C*H*), 7.40–7.45 (m, 3H, $C_{Ar}H$), 7.48–7.50 (m, 2H, $C_{Ar}H$); ^{13}C {^1H} NMR (100 MHz, $CDCl_3$): δ = 15.7–15.9 (m, *C*H_3), 64.2–64.5 (m, *C*H_2), 76.2 (dq, $^2J_{CF}$ = 33.9 Hz, $^2J_{CP}$ = 4.4 Hz, *C*H), 123.0 (dq, $^1J_{CF}$ = 281.1 Hz, $^3J_{CP}$ = 10.0 Hz, *C*F_3), 128.0 ($C_{Ar}H$), 128.6 ($C_{Ar}H$), 130.1 ($C_{Ar}H$), 131.5 (C_{Ar}); ^{19}F NMR (376 MHz, $CDCl_3$): δ = −77.7 (d, $^3J_{FH}$ = 6.4 Hz); ^{31}P {^1H} NMR (162 MHz, $CDCl_3$): δ = −1.73 (s); EI-MS: *m/z* 312 (M^+, 2%), 292 (45), 236 (46), 216 (100), 159 (54), 125 (36), 109 (81), 77 (18); ESI-HRMS: *m/z* calcd for $C_{12}H_{16}F_3NaO_4P$ (M+Na)+: 335.0631; found: 335.0630.
Diethyl 2,2,2-trifluoro-1-p-tolylethyl phosphate (entry 6, Table 1): 57%, colorless oil; R_f = 0.36 (30% EtOAc in hexane); FTIR (film, ν_{max} cm^{-1}) 3044, 2986, 1618, 1518, 1480, 1267, 1182, 1036, 808; ^1H NMR (400 MHz, $CDCl_3$): δ = 1.16 (dt, 3H, $^3J_{HH}$ = 7.1 Hz, $^4J_{HP}$ = 1.1 Hz, CH_3), 1.31 (dt, 3H, $^3J_{HH}$ = 7.1 Hz, $^4J_{HP}$ = 1.1 Hz, CH_3), 3.82–3.99 (m, 2H, CH_2), 4.03–4.22 (m, 2H, CH_2), 5.52–5.59 (m, 1H, C*H*), 2.38 (s, 3H, CH_3), 7.22 (d, 2H, $^3J_{HH}$ = 8 8.0 Hz, $C_{Ar}H$), 7.37 (d, 2H, $^3J_{HH}$ = 8.0 Hz, $C_{Ar}H$); ^{13}C {^1H} NMR (100 MHz, $CDCl_3$): δ = 15.7–15.9 (m, *C*H_3), 21.2 (s, CH_3), 64.1–64.4 (m, *C*H_2), 76.1 (dq, $^2J_{CF}$ = 33.8 Hz, $^2J_{CP}$ = 4.4 Hz, *C*H), 122.9 (dq, $^1J_{CF}$ = 281.0 Hz, $^3J_{CP}$ = 10.0 Hz, *C*F_3), 129.3 ($C_{Ar}H$), 128.0 ($C_{Ar}H$), 128.5 (C_{Ar}), 140.4 (C_{Ar}); ^{19}F NMR (376 MHz, $CDCl_3$): δ = −77.8 (d, $^3J_{FH}$ = 6.5 Hz); ^{31}P {^1H} NMR (162 MHz, $CDCl_3$): δ = −1.92 (s); EI MS: *m/z* 326 (M^+, 2%), 306 (60), 230 (100), 258 (39), 249 (40), 173 (63), 123 (49), 119 (36), 91 (30), 77 (15); ESI-HRMS: *m/z* calcd for $C_{13}H_{19}F_3O_4P$ $(M+H)^+$: 327.0968; found *m/z*: 327.0966.
Diethyl 1-(4-chlorophenyl)-2,2,2-trifluoroethyl phosphate (entry 7, Table 1): 86%, colorless oil; R_f = 0.37 (30% EtOAc in hexane); FTIR (film, ν_{max} cm^{-1}) 3060, 3040, 2987, 1600, 1582, 1495, 1264, 1187, 1038, 817; ^1H NMR (400 MHz, $CDCl_3$): δ = 1.19 (dt, 3H, $^3J_{HH}$ = 7.1 Hz, $^4J_{HP}$ = 1.1 Hz, CH_3), 1.32 (dt, 3H, $^3J_{HH}$ = 7.1 Hz, $^4J_{HP}$ = 1.1 Hz, CH_3), 3.86–4.02 (m, 2H, CH_2), 4.06–4.23 (m, 2H, CH_2), 5.55–5.62 (m, 1H, C*H*), 7.41–7.43 (m, 4H, $C_{Ar}H$); ^{13}C {^1H} NMR (100 MHz, $CDCl_3$): δ = 15.8–15.9 (m, *C*H_3), 64.3–64.6 (m, *C*H_2), 75.5 (dq, $^2J_{CF}$ = 34.1 Hz, $^2J_{CP}$ = 4.3 Hz, *C*H), 122.7 (dq, $^1J_{CF}$ = 281.2 Hz, $^3J_{CP}$ = 9.9 Hz, *C*F_3), 129.0 ($C_{Ar}H$), 129.3 ($C_{Ar}H$), 130.0 (C_{Ar}), 136.3 (C_{Ar}); ^{19}F NMR (376 MHz, $CDCl_3$): δ = −77.8 (d, $^3J_{FH}$ = 6.3 Hz); ^{31}P {^1H} NMR (162 MHz, $CDCl_3$): δ = −1.93 (s); EI-MS: *m/z* 346 (M^+, 3%), 326 (40), 270 (60), 250 (100), 193 (59), 143 (64), 125 (35), 109 (26), 81 (25); ESI-HRMS: *m/z* calcd for $C_{12}H_{15}ClF_3NaO_4P$ $(M+Na)^+$: 369.0241; found: 369.0242.
Diethyl 3-phenyl-1-trifluoromethylpropyl phosphate (entry 8, Table 1): 53%, colorless oil; R_f = 0.45 (30% EtOAc in hexane); FTIR (film, ν_{max} cm^{-1}) 3088, 3065, 3029, 2985, 1604, 1497, 1481, 1272, 1177, 1037, 751, 700; ^1H NMR (400 MHz, $CDCl_3$): δ = 1.33–1.39 (m, 6H, 2 × *C*H_3), 2.08–2.14 (m, 2H, PhCH_2), 2.73–2.81 (m, 1H, $PhCH_2CH^aH^b$), 2.86–2.94 (m, 1H, $PhCH_2CH^aH^b$), 4.11–4.22 (m, 4H, 2 × OCH_2), 4.69–4.76 (m, 1H, C*H*), 7.20–7.24 (m, 3H, $C_{Ar}H$), 7.29–7.33 (m, 2H, $C_{Ar}H$); ^{13}C {^1H} NMR (100 MHz, $CDCl_3$): δ = 15.9–16.1 (m, *C*H_3), 30.5 (s, *C*H_2), 31.2–31.3 (m, *C*H_2), 64.4 (d, $^2J_{CP}$ = 6.1 Hz, OCH_2), 74.3 (dq, $^2J_{CF}$ = 32.8 Hz, $^2J_{CP}$ = 5.3 Hz, *C*H), 123.7 (dq, $^1J_{CF}$ = 281.2 Hz, $^3J_{CP}$ = 6.0 Hz, *C*F_3), 126.4 ($C_{Ar}H$), 128.3 ($C_{Ar}H$), 128.6 ($C_{Ar}H$), 140.2 (C_{Ar}); ^{19}F NMR (376 MHz, $CDCl_3$): δ = −78.1 (d, $^3J_{FH}$ = 6.3 Hz); ^{31}P {^1H} NMR (162 MHz, $CDCl_3$): δ = −1.77 (s); EI-MS: *m/z* 340 (M^+, 4%), 186 (39), 155 (50), 127 (25), 117 (100), 99 (42), 91 (36); ESI-HRMS: *m/z* calcd for $C_{14}H_{21}F_3O_4P$ $(M+H)^+$: 341.1124; found: 341.1124.
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23. These phosphates were previously prepared either by the reaction of $RC(O)CF_3$ with $HP(O)(OEt)_2$ in the presence of Et_3N or DBU (analytical data not reported): (a) Kuroboshi, M.; Ishihara, T.; Teiichi, A. *J. Fluorine Chem.* **1988**, *39*, 293–298; (b) El Kaïm, L.; Gaultier, L.; Grimaud, L.; Dos Santos, A. *Synlett* **2005**, 2335–2336; or from $RCH(OH)CF_3$ and $ClP(O)(OR)_2$ under harsh reaction conditions: (c) Goryunov, E. I.; Petrovskii, P. V.; Shcherbina, T. M.; Laretina, A. P.; Zakharov, L. S.; Kabachnik, M. I. *Bull. Acad. Sci. USSR, Chem.* **1990**, *39*, 787–794; (d) Goryunov, E. I.; Zakharov, L. S.; Petrovskii, P. V.; Kabachnik, M. I. *Bull. Acad. Sci. USSR, Chem.* **1985**, *34*, 799–802.