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Tetrahedron
Tetrahedron 63 (2007) 12731–12734

Reduction of 2,2,2-trifluoro-1-arylethanones with alkyl phosphines

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Received 18 August 2007; revised 28 September 2007; accepted 29 September 2007
Available online 6 October 2007

Abstract—In the presence of alkyl phosphines, reduction of 2,2,2-trifluoro-1-arylethanones proceeded smoothly to give the corresponding reduction products in moderate to high yields at room temperature. The possible mechanism was discussed on the basis of deuterium labeling and control experiments, indicating that one hydrogen transfer took place from alkyl phosphine to the carbonyl group activated by a strongly electron-withdrawing trifluoromethyl group.

1. Introduction

Previously, we reported the reduction of activated carbonyl groups such as α-keto esters, benzils, 1,2-cyclohexanedione, and α-ketophosphonates by alkyl phosphines to afford the corresponding α-hydroxy esters or ketones in good to excellent yields in THF at room temperature as well as the reductive coupling of acyl cyanides promoted by alkyl phosphines to give the substituted cyanohydrins in moderate to high yields by using trimethylphosphine or tributylphosphine as a promoter under mild reaction conditions.[1] More recently, organocatalysts, metal-free organic compounds, which exhibit catalytic abilities in organic reactions, have received much attention because of their advantages from an environmental as well as a resource standpoint.[2] On the basis of these backgrounds, we attempted to further develop such reduction of other substrates using alkyl phosphines. We envisioned that the carbonyl group in 2,2,2-trifluoro-1-arylethanone could be also reduced with various alkyl phosphines since its carbonyl group is connected with a strongly electron-withdrawing trifluoromethyl group. Namely, this carbonyl group is quite activated and it could be reduced by alkyl phosphines. Herein we wish to describe the details on the reduction of 2,2,2-trifluoro-1-arylethanones with alkyl phosphines along with a mechanistic investigation.

2. Results and discussion

Initial examinations using 2,2,2-trifluoro-1-phenylethanone **1a** as the substrate in the presence of various alkyl phosphines, such as PMe_3, PPh_2Me, $PPhMe_2$, and PBu_3 were aimed at determining the optimal conditions for the reduction of **1a**. The results are summarized in Table 1. As can be seen from Table 1, **1a** could be reduced with PMe_3 (1.0 equiv) in a variety of solvents to give the corresponding 2,2,2-trifluoro-1-phenyl-ethanol **2a** in 20–58% yields within 24–48 h (Table 1, entries 1–6). A prolonged reaction time slightly improved the yield of **2a** (Table 1, entry 2). Using PPh_2Me and $PPhMe_2$ as the reducing reagents, **2a** was obtained in 30% and 33% yields in THF, respectively (Table 1, entries 7 and 8). To our delight, we found that using PBu_3 as a reducing reagent, **2a** could be obtained in 98% yield in toluene after 48 h under the standard conditions (Table 1, entries 9–13). In the presence of methyl diphenylphosphinite (1.0 equiv), 2,2,2-trifluoro-1-*o*-tolyl-ethanone was also produced in 21% yield under identical conditions (Table 1, entry 14).

With the optimized reaction conditions in hand, we next examined the scope and limitations of this interesting reduction reaction. The results are summarized in Table 2. A variety of 2,2,2-trifluoro-1-arylethanones **1b–h** were tested under the standard conditions. For **1b** and **1c** bearing an electron-withdrawing group on the benzene ring, the corresponding reduction products **2b** and **2c** were obtained in good yields (Table 2, entries 1 and 2). For electron-rich 2,2,2-trifluoro-1-arylethanones **1d–g**, the corresponding reduction products **2d–g** were obtained in moderate to good

Keywords: 2,2,2-Trifluoro-1-arylethanone; Alkyl phosphine; Hydrogen transfer; Deuterium labeling experiment.
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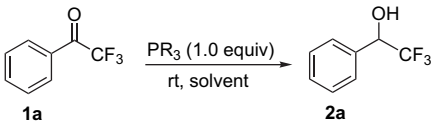
0040–4020/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2007.09.084

Table 1. Reduction of 2,2,2-trifluoro-1-phenylethanone by various phosphines in a variety of solvents[a]

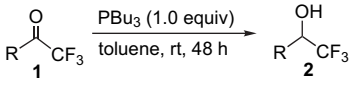


1a 2a

Entry	PR_3	Solvent	Time (h)	Yield[b] (%)
1	PMe_3	THF	24	58
2	PMe_3	THF	48	61
3	PMe_3	DCM	24	28
4	PMe_3	Toluene	24	31
5	PMe_3	MeOH	24	20
6	PMe_3	CH_3CN	24	56
7	PPh_2Me	THF	24	30
8	$PPhMe_2$	THF	36	33
9	PBu_3	THF	24	49
10	PBu_3	CH_3CN	24	57
11	PBu_3	Toluene	24	55
12	*PBu_3*	*Toluene*	*48*	*98*
13	PBu_3	DCM	24	19
14[c]	$PPh_2(OMe)$	Toluene	24	21

[a] 2,2,2-Trifluoro-1-phenylethanone (0.3 mmol), phosphine (0.3 mmol), and solvent (0.3 mL) were used.
[b] Isolated yields.
[c] 2,2,2-Trifluoro-1-*o*-tolyl-ethanone was used.

Table 2. Reduction of 2,2,2-trifluoro-1-phenylethanone under optimized conditions[a]



1 2

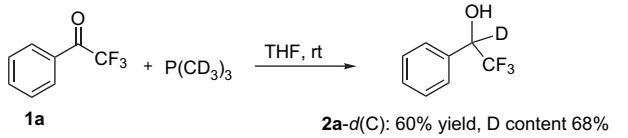
Entry	R	Time (h)	Yield[b] (%)
1	4-ClC_6H_4 (**1b**)	48	**2b**, 99
2	4-BrC_6H_4 (**1c**)	48	**2c**, 91
3	4-$CH_3C_6H_4$ (**1d**)	48	**2d**, 68
4	2-$CH_3C_6H_4$ (**1e**)	48	**2e**, 71
5	2,4-$(CH_3)_2C_6H_3$ (**1f**)	48	**2f**, 50
6	4-$CH_3OC_6H_4$ (**1g**)	48	**2g**, 40
7	1-Naphthyl (**1h**)	48	**2h**, 68

[a] The reactions were conducted with PBu_3 (1.0 equiv), 2,2,2-trifluoro-1-phenylethanone (0.5 mmol) in toluene (0.5 mL) for 48 h at rt.
[b] Isolated yields.

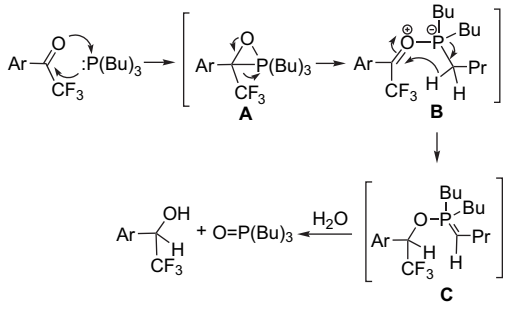
yields (Table 2, entries 3–6). Naphthyl derivative **1h** also can be reduced in good yield under the standard conditions (Table 2, entry 7).

The reaction mechanism is the most interesting issue in this context. In order to clarify the reaction mechanism, a deuterium labeling experiment was carried out with trimethylphosphine-d_9, prepared from the reaction of CD_3MgI with tri-*o*-tolyl phosphite,[3] under the standard conditions. The corresponding product of **2a**-*d*(C) was produced in 60% isolated yield with 68% D incorporation at the C_1 position (Scheme 2).[4] This result suggests that one hydrogen is directly transferred from trimethylphosphine to product **2a**, and an additional equivalent of water is required for the release of the phosphorus atom through formation of the phosphine oxide during work-up (Scheme 1 and also see Scheme 2).

According to the relative control experiments and our previous investigations[1] as well as the in situ ^1H, ^{31}P, and ^{19}F NMR monitoring, a plausible mechanism for the



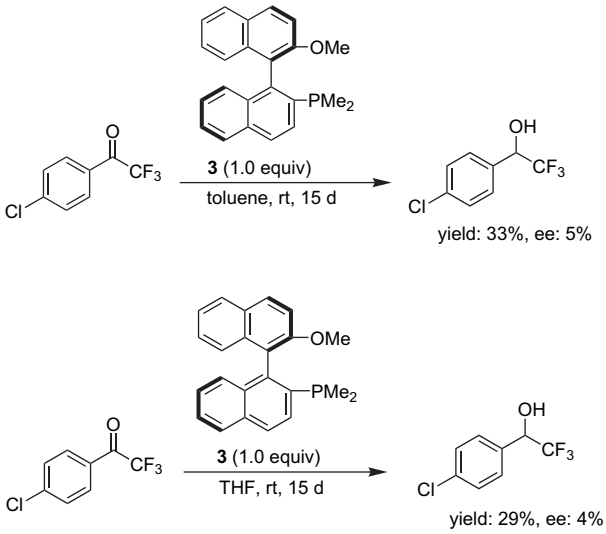
Scheme 1. Reduction of 2,2,2-trifluoro-1-phenylethanone with trimethylphosphine-d_9 in THF and the isotopic labeling experiment.



Scheme 2. A proposed reaction mechanism.

reduction of 2,2,2-trifluoro-1-arylethanone **1** was proposed in Scheme 2. Initially, the addition of phosphorus atom of tributylphosphine to the carbonyl group in **1** takes place to give intermediate **A**. This process is beneficial from the strongly electron-withdrawing trifluoromethyl group on the basis of previous investigations and computational calculation.[5] The rearrangement of intermediate **A** provides intermediate **B** from which intramolecular hydrogen transfer from the butyl group of tributylphosphine to the corresponding carbonyl group activated by a strongly electron-withdrawing trifluoromethyl group produces intermediate **C**, which subsequently undergoes O–P bond hydrolytic cleavage by ambient moisture or during work-up to generate **2** and the corresponding phosphine oxide. It should be noted that the carbonyl groups activated by a strongly electron-withdrawing trifluoromethyl group are essential for this reduction because no reaction occurred if phenylethanone was used as the substrate under the standard conditions.[6] Concerning the reduction of 2,2,2-trifluoro-1-*o*-tolyl-ethanone with $Ph_2P(OMe)$ indicated in entry 14 of Table 1, the hydrogen transfer can also take place from the MeO group in phosphite, although this process is not as effective as alkyl phoshines under the same conditions.[7]

According to the proposed reaction mechanism mentioned above, when the alkyl phosphine was replaced by a chiral alkyl phosphine, an asymmetric reduction might be realized. Therefore, we selected [2-(2-methoxynaphthalen-1-yl)-3-methyl-1-methylene-hexa-2,4-dienyl]dimethylphosphane **3**[8] as a chiral alkyl phosphine in this reaction to examine the achieved enantioselectivity of the reduced product. It was found that the corresponding product 1-(4-chlorophenyl)-2,2,2-trifluoroethanol was obtained in 5% ee and 33% yield in toluene as well as 4% ee and 29% yield in THF after 15 days under the standard conditions (Scheme 3). The reaction is sluggish and the achieved ee is low, suggesting that a sterically bulky chiral back skeleton affects the reactivity. In any sense, although the achieved ee is low, this preliminary result implied that the reaction mechanism shown in Scheme 2 is reasonable.



Scheme 3. Reduction of 1-(4-chlorophenyl)-2,2,2-trifluoroethanone by a chiral phosphine.

3. Conclusion

In summary, we disclosed an efficient reductive process of 2,2,2-trifluoro-1-arylethanones to form the corresponding reduction products with alkyl phosphine under mild conditions. These reactions could take place at room temperature in the presence of alkyl phosphines such as trimethylphosphine and tributylphosphine in various solvents within 36 or 48 h to give the corresponding reduction products in good yields. We confirmed that this process involved with a hydrogen transfer from alkyl phosphine to the carbonyl group. Efforts are underway to elucidate the mechanistic details of this reductive system and to extend the scope of substrates in this interesting reduction reaction.

4. Experimental section

4.1. General remarks

Melting points were obtained with a Yanagimoto micro melting point apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded for a solution in $CDCl_3$ with tetramethylsilane (TMS) as internal standard. *J*-values are in Hertz. Mass spectra were recorded with a HP-5989 instrument and HRMS was measured by a Finnigan MA$^+$ mass spectrometer. The solid compounds reported in this paper gave satisfactory CHN microanalyses with a Carlo-Erba 1106 analyzer. Commercially obtained reagents were used without further purification. All reactions were monitored by TLC with Huanghai GF_{254} silica gel coated plates. Flash column chromatography was carried out using 300–400 mesh silica gel at increased pressure. Reaction experiments were performed under argon condition. The starting materials **1a–h** were synthesized according to the previous literature.[9] Since these alkyl phosphines are lachrymatory and sometimes spontaneously flammable in air, these reactions must be carried out under argon atmosphere in an efficient fume hood.

4.2. Typical reaction procedure for the preparation of 2

A mixture of 2,2,2-trifluoro-1-phenylethanone (0.5 mmol) and PBu_3 (0.5 mmol) in solvent was stirred under argon atmosphere at room temperature for the required time indicated in the tables. After the reaction solution was concentrated under reduced pressure, the residue was purified by flash chromatography on silica gel (eluent: EtOAc/petroleum=1:20) to afford pure product **2**.

4.3. Typical reaction procedure for the asymmetric reduction of 1b

A mixture of 1-(4-chlorophenyl)-2,2,2-trifluoroethanone (**1b**) (20.8 mg, 0.1 mmol) and axially chiral phosphine (34.4 mg, 0.1 mmol) in toluene was stirred under argon atmosphere at room temperature for 15 days. After the reaction solution was concentrated under reduced pressure, the residue was purified by flash chromatography on silica gel (eluent: EtOAc/petroleum=1:20) to afford pure product **2b**. Yield 33%, 7.0 mg; $[\alpha]_D^{20}$ −3.0 (*c* 0.30, $CHCl_3$); HPLC: OD column; λ=254 nm; eluent: hexane/isopropanol=95:5; flow rate: 0.7 mL/min; t_{major}=9.13 min, t_{minor}=11.18 min; ee=5%.

4.3.1. The in situ ^{1}H, ^{31}P, and ^{19}F NMR monitoring of this reduction. In a NMR tube, 1-(4-chlorophenyl)-2,2,2-trifluoroethanone (1.0 equiv) was added to Ph_2PMe (20.02 mg, 0.1 mmol) in C_6D_6 (3.0 mL) under argon atmosphere. Then, ^{1}H, ^{19}F, and ^{31}P NMR measurements were performed in different required time.

4.3.2. 2,2,2-Trifluoro-1-(2,4-dimethylphenyl)ethanol (2f) (a unknown compound). ^{1}H NMR ($CDCl_3$, 300 MHz, TMS): δ 2.32 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 2.82 (s, 1H, OH), 5.27 (q, 1H, *J*=6.6 Hz, CH), 7.02 (s, 1H, Ar), 7.09 (d, 1H, *J*=8.4 Hz, Ar), 7.48 (d, 1H, *J*=8.4 Hz, Ar); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 19.2, 21.1, 68.6 (q, *J*=31.6 Hz), 124.8 (q, *J*=280.1 Hz), 126.9 (q, *J*=1.3 Hz), 127.2, 129.7 (q, *J*=1.1 Hz), 131.3, 136.3, 139.1; ^{19}F NMR ($CDCl_3$, 282 MHz, $CFCl_3$): δ −78.23 (d, *J*=7.6 Hz). IR (film) 3400, 2960, 2926, 2853, 1708, 1617, 1506, 1379, 1217, 1166, 1135, 1117, 1064, 1039, 862, 833, 810, 733, 694, 594. MS (EI) *m*/*z* (%): 204 (25.4) [M$^+$], 135 (100), 107 (83.5), 105 (30.2), 91 (69.0), 79 (25.1), 77 (28.8); HRMS (EI) calcd for $C_{10}H_{11}F_3O$ 204.0762, found 204.0769.

Acknowledgements

We thank the Shanghai Municipal Committee of Science and Technology (04JC14083, 06XD14005), and the National Natural Science Foundation of China (20472096, 203900502, and 20672127, 20732008) for financial support.

Supplementary data

The spectroscopic charts (^{1}H, ^{13}C NMR spectra data), HRMS, analytic data of the compounds shown in Tables 1 and 2 and Scheme 1, HPLC analysis, in situ ^{31}P and ^{19}F NMR monitoring of this reduction are included in the

supplementary data. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.09.084.

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