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Radical-mediated synthesis of trifluoroethyl amines and trifluoromethyl ketones from alkyl iodides

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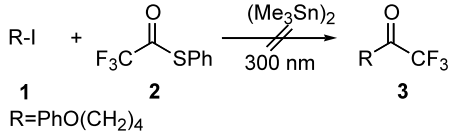
Abstract—Radical reaction of alkyl iodides with trifluoromethyl phenylsulfonyl oxime ether **10** and hexamethylditin at 300 nm in benzene afforded the corresponding trifluoromethyl oxime ethers **11** in high yields, which were reduced into the 2,2,2-trifluoroethyl amines with lithium aluminium hydride. The trifluoroethyl amines could be converted into the corresponding trifluoromethyl ketones by treatment with NBS and DBU. © 2002 Elsevier Science Ltd. All rights reserved.

Trifluoromethylation of organic compounds has attracted a great deal of attention among synthetic chemists because the presence of a trifluoromethyl group in organic molecules influences their chemical and biological properties due to a strong electron-withdrawing ability of the trifluoromethyl group.[1] Thus, the development of the methodologies for the introduction of the trifluoromethylated building blocks would be very important for the synthesis of many trifluoromethylated target molecules. Among trifluoromethylated compounds, trifluoromethyl ketones have been widely utilized as simple fluorine building blocks for further synthetic elaboration in addition to their unique chemical and biological properties.[2] Among several synthetic methods for the trifluoromethyl ketones, the nucleophilic trifluoromethylation of esters has been widely utilized,[3] while trifluoromethyl aryl ketones can be prepared by Friedel–Crafts acylations.[4] A recently reported method for direct preparation of trifluoromethyl ketones from carboxylic esters with (trifluoromethyl)trimethylsilane seems to be very attractive.[5] In addition, a new radical approach involving trifluoroacetonyl radicals and alkenes was also reported.[6]

Although numerous reports on the synthesis of ketones have appeared to date,[7] a free radical-mediated ketone synthesis is not presently available, and only two indirect approaches have been reported. Free radical carbonylation approach to a ketone synthesis has been reported by Ryu.[8] We have also developed a novel free radical acylation approach utilizing radical reactions of alkyl iodides with phenylsulfonyl oxime ethers to provide the corresponding oxime ethers.[9]



(1)

Since the synthesis of trifluoromethylated compounds using radical acylation approach has not been reported, we have studied the radical-mediated synthesis of trifluoromethylated compounds. We initially investigated the possibility of a direct trifluoroacetylation of an alkyl iodide using trifluoromethyl thiol ester **2** (Eq. (1)).[10] We hoped that the presence of an electron-withdrawing trifluoromethyl group would activate a carbonyl carbon toward a nucleophilic alkyl radical.[11] However, irradiation of a solution of 4-phenoxybutyl iodide (**1**), **2**, and hexamethylditin in benzene at 300 nm for 4 h did not give the trifluoromethyl ketone **3** and the reaction was messy. Therefore, we next turned our attention to an indirect acylation reaction using sulfonyl imine **6** and/or sulfonyl oxime ether **10**.

In order to use sulfonylimine **6** as a trifluoroacetyl equivalent radical acceptor, we began our study with previously known trifluoroacetimidoyl chloride **4**.[12] Treatment of **4** with sodium thiophenoxide in THF at room temperature for 1 h afforded **5** in 88% yield.

Keywords: radicals and radical reactions; fluorine and compounds; acylation; ketones; amines; sulfones; oximes.

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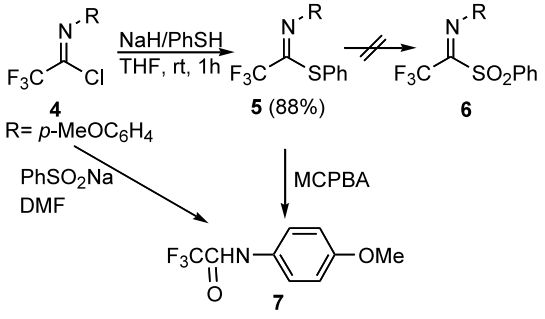
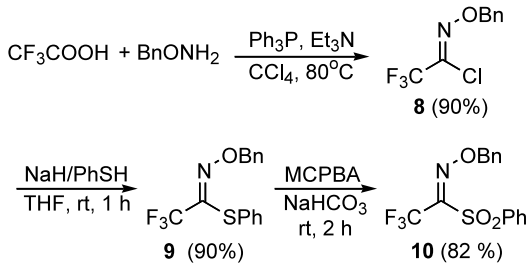
However, MCPBA oxidation of **5** did not yield **6** but only *p*-methoxytrifluoroacetanilide (**7**) was isolated in 90% yield. Similarly, the direct substitution of **4** with sodium phenyl sulfinate in DMF afforded **7** without giving the desired product **6**. Apparently, **6** was unstable and was hydrolyzed to give **7** (Scheme 1).

Since oxime ether groups are very stable and synthetically useful functional groups to transform either to carbonyl groups or to amino groups,[13] we prepared trifluoromethyl phenylsulfonyl oxime ether **10**. Chlorooxime ether **8** was prepared in 90% yield by treatment of *N*-benzyloxyamine with triphenylphosphine and triethylamine in carbon tetrachloride at reflux for 2 h.[12] Treatment of **8** with sodium thiophenoxide in THF at room temperature for 1 h afforded **9** in 90% yield, which was oxidized with MCPBA/$NaHCO_3$ to yield **10** in 82% yield.[14] Oxime ether **10** was obtained as a stable crystalline solid (Scheme 2).

According to our previous results,[9] the energy of LUMO in phenylsulfonyl oxime ether is lowered by introducing an electron-withdrawing group, which would increase the rate of the addition of an alkyl radical onto the sulfonyl oxime ether. Therefore, we anticipated that **10** would be highly reactive due to the presence of a strong electron-withdrawing trifluoromethyl substituent. Irradiation of a solution of 4-phenoxybutyl iodide, **10** (1.5 equiv.) and hexamethylditin (1.5 equiv.) in benzene at 300 nm for 4 h afforded oxime ether **11** in 93% yield (Eq. (2)). As shown in Table 1, the present method worked well not only with primary and secondary alkyl iodides but also with sterically hindered tertiary alkyl iodides (entries 4 and 8), yielding the corresponding trifluoromethyl oxime ethers in high yields. However, benzylic iodides (entries 9 and 10) gave relatively low yields of the



Scheme 1.



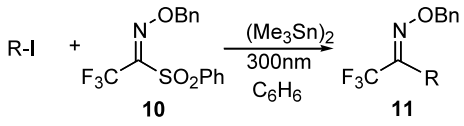
Scheme 2.

Table 1. Preparation of trifluoromethyl amines and ketones

Entry	Substrate	Isolated yield (%)[a]		
		11	**13**	**3**
1	PhO(CH2)4I	93	79	59
2	(CH2)6I	90	66	62
3	Ph(CH2)3I	88	71	64
4	1-adamantyl-I	75	65	61
5	R(CH2)3I, R=Ph	91	75	64
6	R= OCH_2Ph	89	64	72
7	cyclohexyl-I	91		
8	tert-butyl-I	70		
9	R-C6H4-CH2I, R= Br	42 (30%)[b]		
10	R= *t*-Bu	47 (22%)[c]		
11	C6H5-I	52		

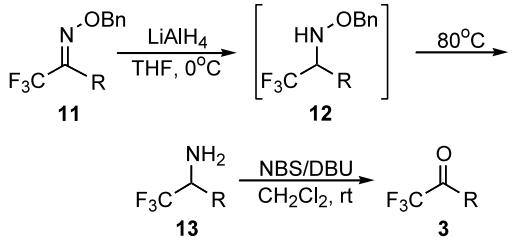
[a] Reaction time: 5 h for **11**, 4 h for **13**, 2 h for **3**.
[b,c] The yield of the dimerized product.

products together with the formation of a significant amount of dimeric products, apparently due to relatively low reactivity of benzylic radicals. Also, radical reaction of iodobenzene (entry 11) with **10** did not proceed smoothly, yielding the corresponding oxime ether in 52% yield after 10 h.



(2)

As we observed previously that oxime ethers substituted by strong electron-withdrawing groups were extremely inert to various acidic and oxidative cleavage conditions,[15] our attempts for the direct conversion of oxime **11** into trifluoromethyl ketone **3** with reported methods were unsuccessful.[16] Since trifluoroethyl amines are known to have important biological activities,[17] we next tried to reduce the oxime ether group into the amino group by the known method (Scheme 3).[18] When **11** was treated with an excess amount of lithium aluminium hydride in THF at 0°C, we initially observed the formation of benzyloxy amine **12**. Further reduction of **12** with lithium aluminium hydride in THF at 80°C for 4 h provided the 2,2,2-trifluoroethyl amine **13** in good yield. Previously, an amino group was converted into a keto group by treatment with NBS followed by dehydrobromination with DBU.[19] As shown in Table 1, when **13** was treated with NBS (1.2



Scheme 3.

equiv.) and DBU (2 equiv.) in dichloromethane at room temperature for 2 h, trifluoromethyl ketone **3** was isolated in modest yield.

In conclusion, we have found that trifluoromethyl sulfonyl oxime ether **10** is highly efficient for the radical-mediated synthesis of trifluoromethylated oxime ethers which can be converted into the synthetically useful 2,2,2-trifluoroethyl amines and trifluoromethyl ketones.

Acknowledgements

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