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TRIFLUOROMETHYLATION OF ALIPHATIC HALIDES WITH TRIFLUOROMETHYL COPPER

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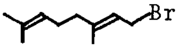
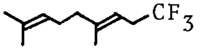
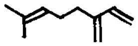
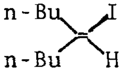
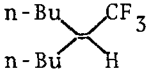
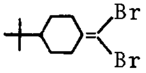
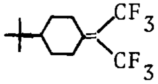
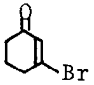
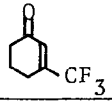
Summary: A solution of trifluoromethyl copper complex in hexamethylphosphoric triamide was found to be useful for trifluoromethylation of aliphatic halides.

Many trifluoromethyl compounds have been shown to be biologically active. However, highly corrosive or toxic reagents must be used in most of the synthetic methods for these compounds, and in some cases, a drastic condition like very high temperature and/or high pressure is necessary. Therefore, a new method for trifluoromethylation using a less toxic reagent in a milder condition has been searched after for a long time. We have reported a trifluoromethylation of aromatic halides1), and its application to the pyrimidine and purine nucleosides2). This method is composed of shaking a mixture of aryl halide and trifluoromethyl iodide with copper power in an aprotic solvent at 110-140° in a stainless steel tube. However, application of this method to a aliphatic halides did not give satisfactory results.

Now, we would like to report some improvements on this method: First, trifluoromethyl iodide and copper powder3) in hexamethylphosphoric triamide was shaken at 120° in a stainless steel tube for 2.5 h and excess copper powder was removed by filtration through celite layer in a glove box with exclusion of air. A solution of aliphatic halide was added to this dark green solution of trifluoromethyl copper complex and the mixture was mechanically stirred at room temperature, or at 70° if necessary, under N_2 atomsphere. The trifluoromethyl compound was obtained in a moderate to good yield. This method is superior to the previous one1), in the points that a glass apparatus can be used at trifluoromethylation of the halide and that the reaction can be followed much more easily by g.l.c. or t.l.c. Thus, the reaction condition can be chosen as mild as possible. Some results of this method with aliphatic halides are shown in Table I. The yields were not optimized.

In conclusion, trifluoromethyl copper complex smoothly reacted with various aliphatic halides to give the corresponding trifluoromethyl compounds, although alkyl fluorides were obtained as by-products with primary halides. These results show a large difference in reactivity between trifluoromethyl copper complex and other perfluoroalkyl copper complexes4). This modification of trifluoromethylation is useful for the synthesis of various aromatic and aliphatic trifluoromethyl compounds in a relatively mild condition.

Table I. Trifluoromethylation of Alkyl Halides

Starting Material	Reaction Conditions Temp (°C)	Time (h)	Product[a]	Yield (%)
$PhCH_2Br$	r.t.	12	$PhCH_2CF_3$	65[b]
$Ph\text{-}CH{=}CHCH_2Br$	r.t.	12	$PhCH{=}CHCH_2CF_3$	37[b]
	50	12		50[c]
				3.7[c]
$n\text{-}C_{10}H_{21}Br$	45-70	62	$n\text{-}C_{10}H_{21}CF_3$	13[c]
			$n\text{-}C_{10}H_{21}F$	32[c]
$n\text{-}C_{10}H_{21}I$	50	32	$n\text{-}C_{10}H_{21}CF_3$	48[c]
			$n\text{-}C_{10}H_{21}F$	6[c]
PhCOBr	45	24	$PhCOCF_3$	24[c]
			PhCOF	22[c]
PhCH=CHBr (c/t)	50	24	$PhCH{=}CHCF_3$ (c/t)	65[b]
	r.t.	12		62[b]
	r.t.-50	20		81[b]
	30	12		40[b]

a) Spectral data of all new products are in good agreement with the assigned structures. Some of them were identified with the samples synthesized by another routes. b) Isolated. c) Estimated by g.l.c.

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