Tetrahedron Letters, Vol.32, No.18, pp 2003-2004, 1991
Printed in Great Britain

0040-4039/91 $3.00 + .00
Pergamon Press plc

A FACILE SYNTHESIS OF ARYL TRIFLUOROMETHYL KETONES

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Summary: The reaction of arylcopper reagents with α,α,α-trifluoroacetic anhydride gives the corresponding aryl trifluoromethyl ketones in good yields.

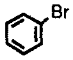
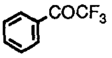
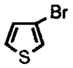
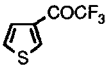
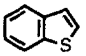
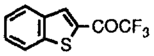
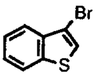
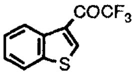
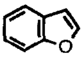
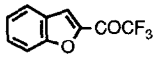
Trifluoromethyl ketones are of considerable current interest due to their ability to act as potent enzyme inhibitors.[1] The trifluoromethylacetyl moiety has been introduced directly into organic molecules by a variety of methods.[2] These earlier procedures were generally inefficient requiring a large excess of lithium or magnesium reagent. More recently, palladium-catalyzed Carroll-type reaction,[3] Wittig condensation,[4] and lithium acetylide alkylation[5] have been used but they provide only alkyl ketones. Creary[6] was able to prepare alkyl and phenyl substituted trifluoromethyl ketones in good yields by reaction of ethyl trifluoroacetate with Grignard or organolithium reagents (inverse addition) at -78°C. Unfortunately, with their only heterocyclic example (2-thienylmagnesium bromide), a substantial amount of tertiary alcohol (37%) was produced. DiMenna[7] has reported the synthesis of aryl trifluoromethyl ketones in 40-75% isolated yields by the reaction of aryllithium reagents with N,N-dimethyltrifluoroacetamide(prepared) between -85° and -65° C. We report herein that treatment of arylcopper reagents with trifluoroacetic anhydride at -15°C provides the corresponding trifluoromethyl ketones in excellent yield after mild workup with no significant amount of tertiary alcohol byproduct produced. These arylcopper reagents are readily prepared *in situ* from the aryllithio precursors and CuBr·DMS. Our procedure offers advantages compared to other syntheses in that trifluoroacetic anhydride is inexpensive and commercially available, no appreciable amount of tertiary alcohol is formed, the reaction is carried out at more convenient temperatures, and the yields are generally higher.

The use of arylcopper reagents for the synthesis of methyl ketones has literature precedent[8] and such an approach we felt would be useful in preparing trifluoromethyl ketones. The reaction appears to be general and can be extended to other heterocyclic systems (Table I).

The typical experimental procedure used for the examples in Table I is described as follows. In cases employing bromo substrates, the use of t-butyl lithium instead of n-butyl lithium is preferred. BuLi (50 mmol) was added dropwise at -25°C under nitrogen to a solution of the starting material (50 mmol) in THF (100ml). After 30 min, $CuBr\cdot(CH_3)_2S$ (50 mmol) was added in one portion. After 10 min, the flask was removed from the cooling bath and kept at 23°C for 10 min. The flask was cooled to -25°C and kept at that temperature for another 30 min. The anhydride (50 mmol) was added dropwise and the reaction mixture stirred at -15°C for 8 h. The reaction mixture was warmed to 0°C and stirred at this temperature for 20 min. Aqueous saturated NH_4Cl (50 ml) was added and the crude product extracted into ethylacetate (3X 50 ml). The organic layer was washed with brine (50 ml) and dried ($MgSO_4$). The solvent was removed and the residue was chromatographed or distilled to afford the product.

Table I. Synthesis of Aryl Trifluoromethyl Ketones.

$$Ar \xrightarrow[2.\ (CF_3CO)_2O]{1.\ BuLi,\ CuBr \cdot DMS} ArCOCF_3$$

Entry	Compound	Product[a]	mp(bp)°C	Yield (%)[b]
1			(165-166)	84
2			(163-164)	74
3			(164-165)	72
4			(129-131)	65
5			49-50	85
6			53-54	78
7			47-48	68

[a] All spectral and analytical data were consistent with the assigned structures. [b] Yield of isolated pure material.

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(Received in USA 2 January 1991)