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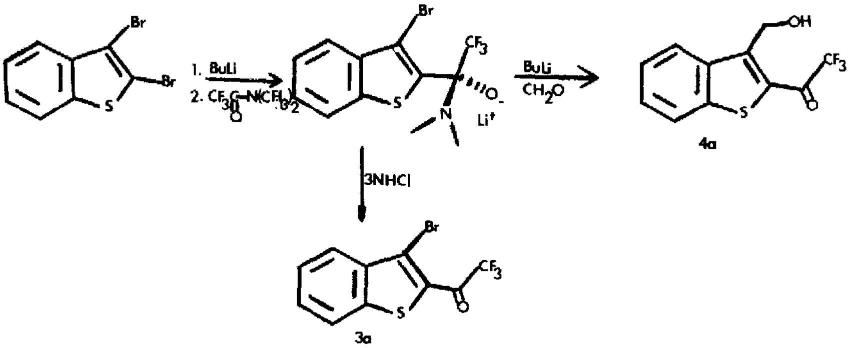
A CONVENIENT PREPARATION OF ARYLTRIFLUOROMETHYLKETONES

William S. DiMenna
P. M. Gross Chemical Laboratory
Duke University
Durham, North Carolina 27706

Summary: The reaction of aryllithium reagents prepared by halogen metal exchange or direct metallation with α,α,α-trifluoro-N,N-dimethylacetamide give the corresponding aryltrifluoromethylketones in good yield.

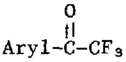
The introduction of the trifluoroacetyl moiety into aromatics has generally been accomplished by Friedal Crafts acylation and by the reaction of Grignard or organolithium reagents with trifluoroacetic acid or its salt.[1] The use of a large excess of lithium or magnesium reagent and inverse addition is generally required to effect moderate yields of the desired ketone. It has been found that the reaction of aryllithium reagents (1-7) with α,α,α-trifluoro-N,N-dimethylacetamide (8) at low temperature gives a good yield of desired ketone after workup. The main advantages of the method are that only one equivalent of aryllithium reagent is necessary and inverse addition is not required. Gas chromotography generally shows 90-100 percent conversion to product. Isolated yields of analytically pure product are 50-75 percent.

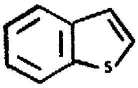
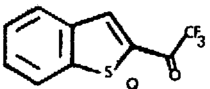
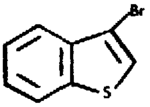
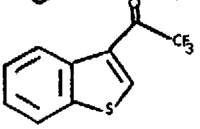
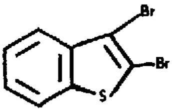
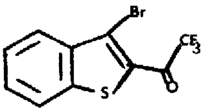
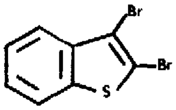
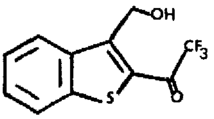
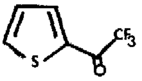
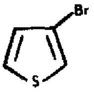
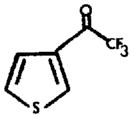
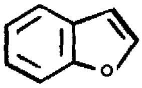
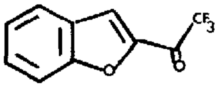
The use of N,N substituted formamides for the synthesis of ketones and aldehydes is well documented, and the adduct formed prior to hydrolysis is a protected carbonyl which can be used to prepare disubstituted derivatives by a one pot procedure.[2,3] This is especially advantagous for the synthesis of disubstituted aryltrifluoroacetyl derivatives since ketalization of these compounds is not feasible.[4] For example, 2-trifluoroacetyl-3-hydroxymethylbenzo[b]thiophene was prepared in forty percent overall yield from 2,3-dibromobenzo[b]thiophene.[5,6]



The other aryl trifluoromethylketones prepared are listed in table 1. The IR, ^{1}H and ^{13}C spectra were consistent with the assigned structures. The ^{13}C was especially valuable for distinguishing between the 2 and 3 substituted thiophenes and benzo[b]thiophenes. Studies on this reaction indicate it to be quite general, and should be readily extended to other systems, including pyrimidines,[8] purines,[9] and other heterocycles,[10] where low temperatures are necessary for regioselectivity. The experimental for two cases is given below.

2-trifluoroacetylbenzo[b]thiophene (1a) Butyllithium (commercial solution in hexane, 0.16 mol) was added to a stirred solution of benzo[b]thiophene (20.0g, 0.15 mol) in 100 ml of dry ether at 20°. The reaction was exothermic and began to gently reflux. After the addition was complete the red solution of 2-lithiobenzo[b]thiophene[10] was cooled to -100° with a ether-liquid nitrogen bath. 8 (32.0g 0.16 mol) in 50 ml of ether was added at such a rate that the temperature did not exceed -85°. After stirring between -85° and -65° for one hour the reaction was slowly warmed to 0°, 50 ml of water was added and the reaction mixture was poured into 50 ml of cold 3 N HCl. The layers were separated and the water layer was washed with ether. The combined ether layers were washed with 3 N HCl, water, brine, then dried over MgSO$_4$. After filtering the drying agent and removing the solvent in vacuo, the orange-yellow residue was crystallized from pet-ether/ether to afford 22.4g (65%) of analytically pure product (C,H,F).

Table 1. Synthesis of  $\mathrm{Aryl{-}\overset{\overset{O}{\|}}{C}{-}CF_3}$

Starting material	product	m.p. [b.p.]	%yield [b]	oxime m.p.
1. 	1a 	47-49°	75	149-150°
2. 	2a 	53-54°	61	83-85°
3. 	3a 	59-60°	50	103-106°
4. 	4a 	105-107°	40	148-153°
5. 	5a 	[163-165°]	55	113-120°
6. 	6a 	[164-165°]	50	97-98°
7. 	7a 	46-48° [71-81°/.35mm]	40	-

[a] exchange reaction with butyllithium was done at -100°

[b] yield of analytically pure material

3-hydroxymethyl-2-trifluoroacetyl benzo[b]thiophene(4a), Butyllithium (0.10) in hexane was added dropwise to a mechanically stirred solution of 2,3-dibromobenzo[b]thiophene[5] (29.2g, 0.10 mol) in 250 ml of dry ether at 0° over a period of forty minutes.[6] After stirring for thirty minutes the reaction was cooled to -78° and 8 was added dropwise. An aliquot was taken after 30 minutes. GC showed 2a as the major species after workup. Butyllithium in hexane was added at -78°. After 30 minutes a yellow suspension developed. GC of a small amount showed that complete lithiation had occurred. Formaldehyde gas (generated from 27.0g of paraformaldehyde at 140°) was bubbled through the system under a swift stream of nitrogen. The reaction was slowly warmed to 0° and 350 ml of 3N HCl was added with stirring. After 15 minutes the reaction was worked up to give a thick orange oil as a 3:2 mixture of 1a and 4a. Fractional crystallization from $CHCl_3$ afforded 9.2g (40%) of 4a.

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References

1. B. J. Wakefield, "The Chemistry of Organolithium Compounds", Pergamon Press, London, (1974) p140.

2. U. Micheal and S. Gronowitz, Acta Chem.Scand. 22 1353 (1968).

3. S. Gronowitz, etal., Acta Pharm. Suec., 8, 623 (1971).

4. J. P. Guthrie, Can. J. Chem., 53, 898 (1975).

5. W. Reid and H. Bender, Chem Ber., 88, 34 (1955).

6. For the lithiation of 2,3 dibromobenzo[b]thiophene and 3-bromobenzo[b]thiophene see R. P. Dickinson and B. Iddon, J. Chem. Soc., (C) 2733 (1968).

7. D. A. Shirley and M. D. Cameron, J. Amer. Chem. Soc., 72, 2788 (1950).

8a. B. W. Langley, J. Amer. Chem. Soc., 78, 2136 (1956).
b. J. D. Bryant and N. J. Leonard, J. Org. Chem., 43, 511 (1978).

9. N. J. Leonard and J. D. Bryant, J. Org. Chem., 44, 4612 (1979).

10. H. W. Gschwend and H. R. Rodriguez, Org. Reactions 26, 1 (1979).

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