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A NEW METHOD OF INTRODUCING A TRIFLUOROMETHYL GROUP INTO AN AROMATIC RING

Marko Zupan and Zvonko Bregar

Laboratory for Organic and Bioorganic Chemistry, "Jožef Stefan" Institute and Department of Chemistry, University of Ljubljana, 61000 Ljubljana, Yugoslavia.

Abstract- Trifluoromethyl derivatives of aromatic molecules were prepared from aromatic halides, converted to dithiocarboxylic acids through formation of Grignard reagents, followed by fluorination with xenon difluoride at room temperature.

The physicochemical properties and biological activities of various aromatic and heteroaromatic molecules, when functionalised with a trifluoromethyl group, resulted in an increasing popularity of these types of compounds[1]. However, methods available for direct introduction of a trifluoromethyl group into aromatic or hetreoaromatic compounds are still scarce. Another strategy for the introduction of a trifluoromethyl function into a molecule is based on the use of an appropriate "trifluoromethyl building block" such as trifluoroacetic acid, N-substituted trifluoroacetimidoyl chlorides[2] etc. Classical approaches for synthesis are based on the following types of reactions[3]: conversion of an acid group using sulphur tetrafluoride; halogen exchange by the use of Swartz-type catalysts, generation of trifluoromethyl radical either photochemically or thermally by the use of peroxides, reactions proceeding via a "trifluoromethyl-metal" intermediate. Recently the following approaches were recommended: trifluoromethyl-M-X[4], where M = Zn, Cu, Cd, tri-n-butyl(trifluoromethyl) silane[5], methyl fluorosulphonyldifluoroacetate[6] and trifluoroacetic acid or trimethylsilyl trifluoroacetate in the presence of xenon difluoride[7].

We now wish to report a new method of introducing a trifluoromethyl substituent into an aromatic molecule based on the following sequence. Aromatic halides, preferentially bromides, were converted with magnesium into the corresponding Grignard reagents, further addition to carbon disulphide resulted in formation of dithiocarboxylic acids that, without prior purification, reacted with xenon difluoride at room temperature in methylene chloride as solvent, giving trifluoromethyl substituted aromatics.

$$\mathbf{Ar\text{–}X} \xrightarrow[3.\ XeF_2]{1.\ Mg/Et_2O;\ 2.\ CS_2} \mathbf{Ar\text{–}CF_3}$$

Ar = C_6H_5-, p-H_3C-C_6H_4-, p-H_3CO-C_6H_4-, m-F_3C-C_6H_4-, α-naphthyl-; **X** = halogen.

In a typical experiment p-bromo toluene (25 mmols) was converted into the Grignard reagent, which reacted with carbon disulphide yielding p-methyl dithiobenzoic acid[8]. Crude p-methyl dithiobenzoic acid (3 mmols) was dissolved in 25 ml methylene chloride and under a

nitrogen atmosphere, stepwice (twice) 12 mmols of xenon difluoride were added at 0°C and then the reaction mixture was stirred at room temperature for 72 hours. After the usual work-up the crude reaction mixture was analysed by ^{19}FNMR spectroscopy (octafluoro naphthalene as an internal standard) and the formation of 2.2 mmols of p-trifluoromethyl toluene (73% yield, calculated on the the basis of the crude p-methyl dithiobenzoic acid) was found. The crude reaction mixture also contained 21% (based on the internal reference) of p-methyl benzoyl fluoride, which was removed from the crude reaction mixture after treatment of the methylene chloride solution with a 5% aqueous solution of sodium hydroxide. In order to obtain more information about the course of the reaction, we analysed the crude reaction mixtures formed after reactions where the following ratios of dithiocarboxylic acid to xenon difluoride were used: 1 : 1, 1 : 2, 1 : 3 and finally 1 : 4. The reaction mixtures where lower ratios were used resulted in crude reaction mixtures where apart-from signals for trifluoromethyl and acid fluoride, up to 10 additional signals corresponding to unidentified products appeared in the ^{19}FNMR spectra. Final optimization of the reaction was achieved when a 1 : 4 molar ratio was used and 72 hours' reaction time, when only trifluoromethyl and acid fluoride signals were present. Further, we tested the effect of substituents on the aromatic ring on the course of the transformation and found that dithiobenzoic acid was converted into trifluoromethyl benzene (60%), p-methoxy dithiobenzoic acid into p-trifluoromethyl anisole (40%) and m-trifluoromethyl dithiobenzoic acid into m-di(trifluoromethyl) benzene (77%); pure products were isolated by preparative g.l.c. Finally the effect of the aromatic ring on the preparation of trifluoromethyl derivatives was tested and it was found that under the above mentioned conditions, 1-bromo naphthalene was converted to 1-trifluoromethyl naphthalene (50%), while reaction with 9-bromo anthracene was much more complex and the crude reaction mixture showed up to five signals in its ^{19}FNMR spectrum, and after separation only the formation of 9,9-difluoro anthrone was established.

We believe that the methodology presented for the introduction of a trifluoromethyl group into an aromatic ring could be applied to other aromatic and heteroaromatic molecules, and for this reason our investigations are being continued in this direction. Investigations of the role of the fluorinating agent (elemental fluorine, caesium fluoroxysulphate, fluoroxy acids etc.) on the methodology are also in progress.

REFERENCES

1 ed.: Filler, R.; Kobayashi, Y. "Biomedicinal Aspects of Fluorine Chemistry", Elsevier, Amsterdam: 1982; A Ciba Foundation Symposium: "Carbon-Fluorine Compounds", Elsevier, Amsterdam: 1972; ed.: Taylor, N. F., ACS Symposium Series: "Fluorinated Carbohydrates: Chemical and Biochemical Aspects", American Chemical Society, Washington DC: 1988; ed.: Banks, R. E.; Sharp, D. W. A.; Tatlow, J. C. "Fluorine: The First Hundred Years (1886-1986)", Elsevier Sequoia, Lousane: 1986; Kobayashi, Y.; Kumadaki, I. *Acc. Chem. Res.*, 1978, *11*, 197.

2 Uneyama, K.; Morimoto, O.; Yamashita, F. *Tetrahedron Lett.* 1989, 4821.

3 Chambers, R. D. "Fluorine in Organic Chemistry", Willey-Interscience, New York: 1973; ed.: Knunyants, I. L.; Yakobson, G. G. "Syntheses of Fluoroorganic Compounds", Springer-Verlag, Berlin: 1985; ed. Liebman, J. F.; Greenberg, A.; Dolbier, W. R. "Fluorine Containing Molecules", VCH: Weinhaim: 1988; Sheppard, W. A.; Sharts, C. M. "Organic Fluorine Chemistry", W. A. Benjamin, New York: 1969.

4 Wiemers, D. M.; Burton, D. J. *J. Am. Chem. Soc.* 1986, *108*, 832; Burton, D. J. *J. Fluorine Chemistry* 1989, *45*, 83; Clark, J. H.; McClinton, M. A., Blade, R. J. *J. Chem. Soc. Chem. Commun.* 1988, 638.

5 Stahly, G. P.; Bell, D. R. *J. Org. Chem.* 1989, *54*, 2873.

6 Quing-Yun Chen; Sheng-Wen Wu *J. Chem. Soc. Chem. Commun.* 1989, 705.

7 Tanabe, Y.; Matsuo, N.; Ohno, *J. Org. Chem.* 1988, *53*, 4582.

8 Houben-Weyl: "Methoden der Organischen Chemie", Band IX, ed.: Mueller, E., Georg Thieme Verlag, Stutgart: 1955.

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