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SHORT COMMUNICATION

Fluorination with Xenon Difluoride. Reaction with Halogenated Hydrocarbons

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Filler and coworkers [1–5] have demonstrated the utility of xenon difluoride as a selective fluorinating agent for aromatic hydrocarbons in the liquid phase, while Mackenzie and coworker [6] have fluorinated aromatic compounds in the vapour phase. We have developed a fluorination reaction of phenyl substituted olefins resulting in high yields of vicinal difluorides [7,8] and trifluoroacetates, depending on the catalyst. In our continued interest in the use of xenon difluoride as a mild fluorinating agent for fluorination of organic compounds, we have tried to fluorinate some heterocyclic ring systems, e.g. imidazo–(1,2–b)–pyridazine, under conditions similar to those used for fluorination of phenyl substituted olefins [7,8,9] (room temperature, methylene chloride as solvent, hydrogen fluoride as catalyst). It is well known that heteroaromatic compounds are less reactive toward electrophilic substitution reactions then aromatic hydrocarbon systems. However, it has been shown that bromination of imidazo–(1,2–b)–pyridazine results in 3–bromo products [10], while in chlorination with phosphorus pentachloride [11], the entering order of chlorine atoms is at position 3 > 2, 7 > 8 > 6 (Radical reactions).

A three hour reaction of xenon difluoride in methylene chloride with imidazo–(1,2–b)–pyridazine [A, X = H] with hydrogen fluoride as catalyst gave two products, the main product being the unconverted starting material and the second one, in low yield, being a chlorinated product. On the basis of the n.m.r., mass and i.r. spectral data we have concluded that the product formed was 3–chloro–imidazo–(1,2–b) pyridazine [B, X = H, Y = Cl]. A seventy–two hour reaction resulted in the formation of 50–60 % of 3–chloro product. Meinert with coworkers [12] has remarked on the slow reaction of xenon difluoride with halogen substituted alkanes. The observed unusual reactivity of xenon difluoride with the solvent, which resulted in the formation of 3–chloro–products, led us to investigate the reaction with various halogen alkanes which differ in the energy [13] of their carbon–halogen bond, i.e. carbon tetrachloride (78.2 kcal/mol), chloroform (78.3 kcal/mol), methylene chloride (77.9 kcal/mol) and bromoform (66.1 kcal/mol). The experimental results of these studies are presented in the Scheme. It can be seen that under similar conditions (72 hr.) in cloroform the reaction yielded only 5–10 % of 3–chloro–product, while the formation of 3–bromo–product was in higher yield of 65–75 %. On the other hand, when trifluoroacetic acid was used as catalyst in methylene chloride, a lower amount of 3–chloro–product was formed, namely, 30–35 %. The data show that the amount of the 3–halo–product formed depends on the energy of the carbon–halogen bond. We were unable to detect any trace of fluoro–substituted products by g.l.c., t.l.c., ^{19}F n.m.r. and mass spectrometry in the crude reaction mixture, formed under the above conditions. Analogous results were obtained wich 6–chloro–imidazo–(1,2–b)–pyridazine [X = Cl].

Experimental Section

I.r. spectra were recorded by using a Perkin–Elmer 257 spectrometer, ^1H and ^{19}F n.m.r. spectra by a Jeol–JNM–C–60 HL from $CDCl_3$ solution with TMS or CCl_3F as internal standard. Mass spectra were taken on a CEC 21–110 spectrometer. Melting points were determined on a Kofler melting point apparatus and are uncorrected. T.l.c. separations were carried out on Merck Fertigplatten SiO_2.

Materials

Imidazo–(1,2–b)–pyridazine and 6–chloro–imidazo–(1,2–b)- pyridazine were synthesised [10], and solvents were purified [14] to conform with published physical and spectral data. Xenon difluoride was prepared by a photosynthetic method [15] and its purity was better than 99.5 %.

General reaction procedures

To a solution of 1 mmol of imidazo–(1,2–b)–pyridazine or 6–chloro–imidazo–(1,2–b)–pyridazine in 5 ml of solvent (CCl_4, $CHCl_3$, CH_2Cl_2, $CHBr_3$) 3 mmols of XeF_2 were added under stirring at 20°C and a catalytic amount of hydrogen fluoride or 0.3 ml of 1 M trifluoroacetic acid in methylene chloride was added. After 72–hr. the reaction mixture was diluted with 15 ml of methylene chloride, washed with a 5 % aqueous solution of $NaHCO_3$, washed with water, dried over anhydrous sodium sulphate and solvent was evaporated in vacuo. The crude products were separated by preparative t.l.c. (SiO_2, chloroform: methanol–9.7 : 0.3, eluation by methanol). All of the products were sublimed. Yields are presented in the Scheme.

3–chloro–imidazo–(1,2–b)–pyridazine n.c.

mp 124–125°C, mass spectrum, calcd. for $C_6H_4N_3Cl$ m/e 153.0094, found m/e 153.0097. N.m.r. spectra: δH2 = 7.65 ppm, δH6 = 8.38 ppm, δH7 = 7.00 ppm, δH8 = 7.88 ppm, J(H6, H7) = 4.5 Hz, J(H7, H6) = 9.8 Hz, J(H6, H8) = 1.5 Hz.

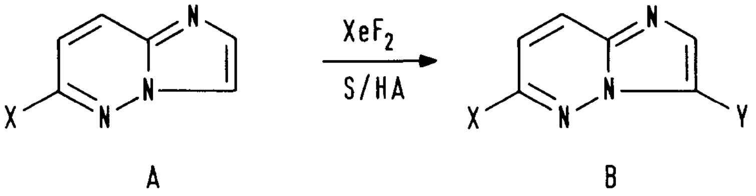
3–bromo–imidazo–(1,2–b)–pyridazine

mp 146.5–147°C, lit.(16) mp = 163°C, mass spectrum, calcd. for $C_6H_4N_3Br$ m/e 196.9589, found m/e 196.9586, n.m.r. spectrum: δH2 = 7.70 ppm, δH6 = 8.38 ppm, δH7 = 7.0 ppm, δH6 = 7.88 ppm, J(H6, H7) = 4.5 Hz, J(H7, H8) = 9.8 Hz, and J(H6, H8) = 1.5 Hz.

3.6–dichloroimidazo–(1,2–b)–pyridazine

mp 119–120°C, lit. (11) mp = 120–121°C mas spectrum, calcd. for $C_6H_3N_3Cl_2$ m/e 186.9704, found m/e 186.9699, m.n.r. spectrum: δH2 = 7.58 ppm, δH7 = 7.0 ppm, δH8 = 7.8 ppm, J(H7, H8) = 9.6 Hz.

SCHEME



X = H, Cl Y = Cl, Br

S = CCl_4, $CHCl_3$, CH_2Cl_2, $CHBr_3$

HA = HF, CF_3COOH

		B	
A	S	Y = Cl	Y = Br
X = H	CCl_4	15-20%	—
	$CHCl_3$	5-10%	—
	CH_2Cl_2	a) 50-60%	—
		b) 30-35%	—
	$CHBr_3$	—	65-75%

		B	
A	S	Y = Cl	Y = Br
X = Cl	CCl_4	15-20%	—
	$CHCl_3$	5-10%	—
	CH_2Cl_2	a) 55-65%	—
		b) 30-35%	—
	$CHBr_3$	—	60-70%

a) HA = HF
b) HA = CF_3COOH

<u>3–bromo–6–chloroimidazo–(1,2–b)–pyridazine</u>

mp 157–157.5°C, lit. (10) mp = 156°C mass spectrum, calcd. for $C_6H_3N_3BrCl$ m/e 230.9199, found m/e 230.9188, n.m.r. spectrum: δH2 = 7.73 ppm, δH7 = 7.0 ppm, δH8 = 7.85 ppm, J(H7, H8) = 9.8 Hz.

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1 M.J. Shaw, J.A. Weil, H.H. Hyman and R. Filler, J.Amer.Chem.Soc., 92 (1970), 5096.

2 M.J. Shaw, H.H. Hyman and R. Filler, J. Amer.Chem.Soc., 92 (1970) 6498.

3 M.J. Shaw, Ph.D. Thesis, Illinois Institute of Technology, May 1970.

4 M.J. Shaw, H.H. Hyman and R. Filler, J.Org.Chem., 36 (1971), 2917.

5 S.P. Anand, L.A. Quaterman, H.H. Hyman, K.G. Migliorese, and R. Filler, J.Org.Chem. 40 (1975), 807.

6 D.R. Mackenzie and J. Fajer, J. Amer.Chem.Soc., 92 (1970), 4994.

7 M. Zupan and A. Pollak, J.Chem.Soc., Chem.Comm., 1973, 845.

8 M. Zupan and A. Pollak, Tetrahedron Lett. 1974, 1015.

9 M. Zupan and A. Pollak, J. Org.Chem., 39 (1974) 2646.

10 B. Stanovnik and M. Tišler, Tetrahedron, 24 (1967) 387.

11 B. Stanovnik, M. Tišler and V. Žigon, Mh.Chem., 103 (1972) 1624.

12 H. Meinert, G. Kauschka and St. Rüdiger, Z.Chem., 7 (1967), 111;
H. Meinert, St. Rüdiger, Z.Chem., 7 (1967) 239.

13 W.A. Sheppard, and C.M. Sharts, Organic Fluorine Chemistry, W.A. Benjamin, Inc., New York, 1969, p. 19.

14 Technique of Organic Chemistry, Vol. VII, Organic Solvents, Physical Properties and Methods of Purification, A. Weissberger, Editor, Interscience Publishers, Inc., New York, 1955.

15. S.M. Williamson, Inorg. Syn., 11 (1968), 147.

16. J. Kobe, B. Stanovnik and M. Tišler, Tetrahedron, 24 (1968) 239.