Journal of Fluorine Chemistry, 48 (1990) 149–152

Received: November 16, 1989; accepted February 1, 1990

PRELIMINARY NOTE

The Synthesis from 2,5-Dichloro-1,1,1,6,6,6-hexafluoro-3,4-diazahexa-2,4- diene of 4H-3,5-Bis(trifluoromethyl)-1,2,4-triazole and some 1- and 4-Substituted Derivatives

MOHAMAD ABDUL-GHANI AND ANTHONY EDGAR TIPPING*

Department of Chemistry, The University of Manchester Institute of Science and Technology, Manchester M60 1QD (U.K.)

SUMMARY

Treatment of the title azine **(3)** with an excess of ammonia or ethyl glycinate affords the corresponding diaminoazines **(4a)** and **(4b)**, which undergo thermal cyclisation to give ammonium 3,5-bis(trifluoromethyl)1-2,4-triazolate **(6a)** [from which the parent 4H-1,2,4-triazole **(1a)** can be liberated by aqueous acid treatment] and 4-carboethoxymethyl-3,5-bis(trifluoromethyl)-1,2,4-triazole **(1e)**, respectively in high yield. Reaction of the 4H-1,2,4-triazole **(1a)** with ethyl propynoate and of its sodium salt **(6b)** with ethyl bromoethanoate and pentafluoropyridine yield the acrylate **(7a)**-, carboethoxymethyl **(7b)**- and fluoropyridyl **(9-11)**- derivatives of 1H-3,5-bis(trifluoromethyl)-1,2,4-triazole with competing attack on the pentafluoropyridine ring taking place at the 2- and 4-positions.

4H-3,5-Bis(trifluoromethyl)-1,2,4-triazole **(1a)** and its 4-methyl derivative **(1b)** were first synthesised from the oxadiazole **(2)** via reaction with ammonia and methylamine, respectively [1], and this route has been extended recently to the preparation of a wide range of 4-alkyl-, 4-alkenyl- and 4-aryl-1,2,4-triazoles [2].

In a previous communication we reported the reactions of 2,5-dichloro-1,1,1,6,6,6-hexafluoro-3,4-diazahexa-2,4-diene **(3)** with a variety of nucleophiles including primary amines and described the preparation of 4-phenyl **(1c)**- and 4-(2,6-dichloropyridyl)methyl **(1d)**- triazoles [3].

* To whom enquiries should be addressed.

0022-1139/90/$3.50

We now report the synthesis of the parent 4H-1,2,4-triazole **(1a)** and its 4-carboethoxymethyl derivative **(1e)** by the same route from azine **(3)** and the conversion of triazole **(1a)** into certain derivatives of 1H-3,5-bis(trifluoromethyl)-1,2,4-triazole.

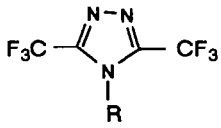
Reaction of dichloroazine **(3)** with an excess of aqueous ammonia or ethyl glycinate in diethyl ether at room temperature afforded the diaminoazine **(4a)** (95%) and a mixture of the monoglycinatoazine **(5)** (16%) and diglycinatoazine **(4b)** (75%) respectively. Thermolysis of the diaminoazines **(4a)** and **(4b)** in a sealed tube in vacuo at ca. 150 °C gave ammonium 3,5-bis(trifluoromethyl)-1,2,4-triazolate **(6a)** (98%) and 4-carboethoxymethyl-3,5-bis(trifluoromethyl)-1,2,4-triazole **(1e)** (82%) respectively. Treatment of the salt **(6a)** with 4M hydrochloric acid yielded the 4H-triazole **(1a)** (75%).

Thus, the reaction of the dichloroazine **(3)** with primary amines followed by thermal cyclisation of the resulting diaminoazines provides a satisfactory alternative general route to that from the oxadiazole **(2)** [2] for the preparation of 4-substituted-3,5-bis(trifluoromethyl)-1,2,4-triazoles.

The reaction of triazole **(1a)** with ethyl propynoate was investigated to determine whether the triazole was an effective nucleophile for Michael addition and whether attack on the substrate would involve N-1 or N-4. A mixture of **(1a)** and ethyl propynoate heated in vacuo in a sealed tube at 120 °C (14 days) gave the Michael adduct, ethyl 3-[1H-3,5-bis(trifluoromethyl)-1,2,4-triazolino]acrylate **(7a)** (95%), as a mixture of the (E)- and (Z)-isomers (ratio 46:49) which were separated by dry column flash chromatography (DCFC) (eluant:n-C_6H_{14}/$CHCl_3$ 1:1 v/v). This reaction occurred exclusively at N-1 of the triazole ring possibly due to N-4 being β to two strongly electron-withdrawing CF_3 groups which reduce the availability of the lone pair on N-4 and sterically hinder reaction at this position; N-1 is β to only one CF_3 group., It has been reported that reaction of the 4H-1,2,4-triazole **(8)** with N-chloromethylacetanilides afforded 4-substituted triazoles [4].

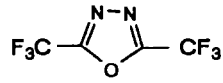
The resonance-stabilised salts of 3,5-disubstituted-1,2,4-triazoles undergo reaction at N-1 because of the greater nucleophilicity of the N-N linkage relative to N-4 [5]. Therefore, the reactions of the sodium salt **(6b)** [prepared by treatment of triazole **(1a)** with sodium hydride in diethyl ether or THF] with ethyl bromoethanoate [a potential route to the 1-substituted isomer **(7b)** of triazole **(1e)**] and with pentafluoropyridine (to determine if nucleophilic attack at the 2-position of the pyridine ring could compete with 'normal' attack at the 4-position) were investigated.

Treatment of salt **(6b)** with ethyl bromoethanoate at room temperature in diethyl ether gave 1-carboethoxymethyl-3,5-bis(trifluoromethyl)-1,2,4-triazole **(7b)** (87%), while with pentafluoropyridine in THF heated under reflux a mixture was

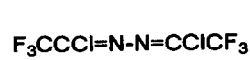


(1)

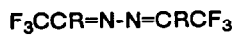
a, R = H
b, R = Me
c, R = Ph
d, R = 
e, R = CH_2CO_2Et



(2)

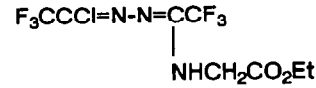


(3)

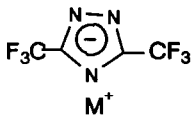


(4)

a, R = NH_2
b, R = $NHCH_2CO_2Et$

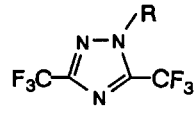


(5)



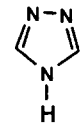
(6)

a, M = NH_4
b, M = Na

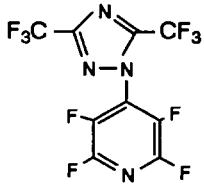


(7)

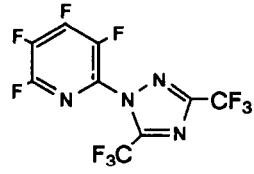
a, R = $CH{=}CHCO_2Et$
b, R = CH_2CO_2Et



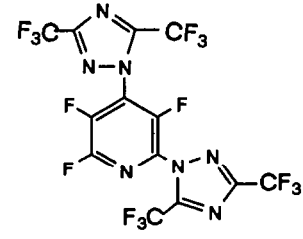
(8)



(9)



(10)



(11)

formed from which the major products were separated by DCFC (eluant n-C_6H_{14}) and identified as the 4-triazolinotetrafluoropyridine **(9)** (19%), the 2-triazolinotetrafluoropyridine **(10)** (5%) and the 2,4-bis(triazolino)trifluoropyridine **(11)** (6%) all formed via attack by N-1 of the triazolate on the pyridine ring.

It has been reported recently [6] that treatment of the sodium or potassium salts of the oximates RR'C=NOH (R=R'=Me; R=R'=Ph; R=Me, R'=Ph) and the lithium salts of the hydrazones Ph_2C=NNHR (R=H or Ph) with pentafluoropyridine afforded mixtures of the corresponding 2- and 4-substituted tetrafluoropyridines in contrast to reaction with other nucleophiles which involved exclusive initial attack in the 4-position [7]. The present reaction involving the salt **(6b)** thus extends the examples of nucleophiles which attack the 2-position of pentafluoropyridine in competition with the 4-position.

Further reactions of triazole **(1a)** and its sodium salt **(6b)** are under investigation and will be reported in due course in a full paper.

All products possessed satisfactory elemental compositions and their structures were determined spectroscopically [i.r., n.m.r. (^1H, ^{13}C, ^{19}F) and mass].

We thank the committee of Vice Chancellors and Principals for an O.R.S. award (to M. A-G.).

1 H.C. Brown and M.T. Cheng, J. Org. Chem., 27 (1962) 3240.

2 D.B. Reitz and M.J. Finkes, J. Heterocyclic Chem., 26 (1989) 225.

3 M.G. Barlow, D. Bell (in part), N.J. O'Reilly and A.E. Tipping, J. Fluorine Chem., 23 (1983) 293.

4 R. Thomas, W. Draber, R.R. Schmidt, L. Eue and J. Stetter, Ger. Offen. 2 704 281 (1978); Chem. Abstr., 89 (1978) 163578w.

5 Carroll Temple, Jr., 'The Chemistry of Heterocyclic Compounds, Vol. 37, Triazoles, 1,2,4', Ed. J.A. Montgomery, John Wiley - Interscience, New York, 1981.

6 R.E. Banks, W.J. Jondi and A.E. Tipping, J. Chem. Soc., Chem. Commun., (1989) 1268.

7 R.D. Chambers, J.S. Waterhouse and D.L.H. Williams, J. Chem. Soc.Perkin Trans. II, (1977) 585.