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Mechanistic studies of the ring opening reactions of [1,2,3]triazolo[1,5-*a*]pyridines

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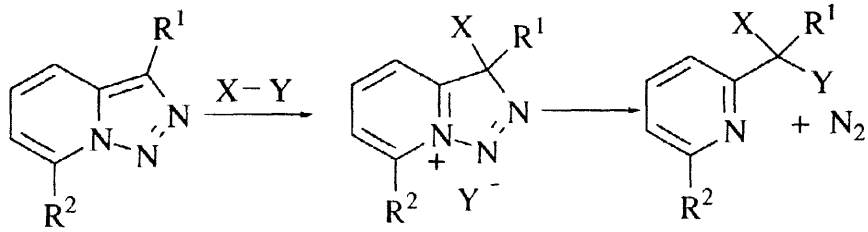
Abstract:

A mechanism with radical intervention is proposed for the opening of the triazole ring in [1,2,3] triazolo-[1,5-*a*]pyridines which results in the production of 2- or 2,6-disubstituted pyridines.

Keywords. Triazolopyridines; Radicals and free radical reactions; mechanism; ring transformations

Introduction

We have reported that [1,2,3]triazolo[1,5-*a*]pyridines react with many electrophiles by opening the triazole ring with subsequent loss of nitrogen, thus producing, regiospecifically, 2,6-disubstituted pyridines [1]. We have suggested that the reaction proceeds by an electrophilic attack at position 3, isomerisation to the diazo form, and subsequent nucleophilic substitution by the anion with displacement of nitrogen (Scheme 1). A similar sequence has been used to prepare 2,4-disubstituted thiazoles from [1,2,3]triazolo[1,5-*a*]thiazoles [2].



1, R^1=Me, R^2=H Scheme 1

Subsequent work has shown that electrophilic attack by alkyl halides in the absence of severe

‡ This paper, my swan song in triazolopyridine chemistry, is dedicated to my old friend Alan Katritzky on his 70th. birthday.

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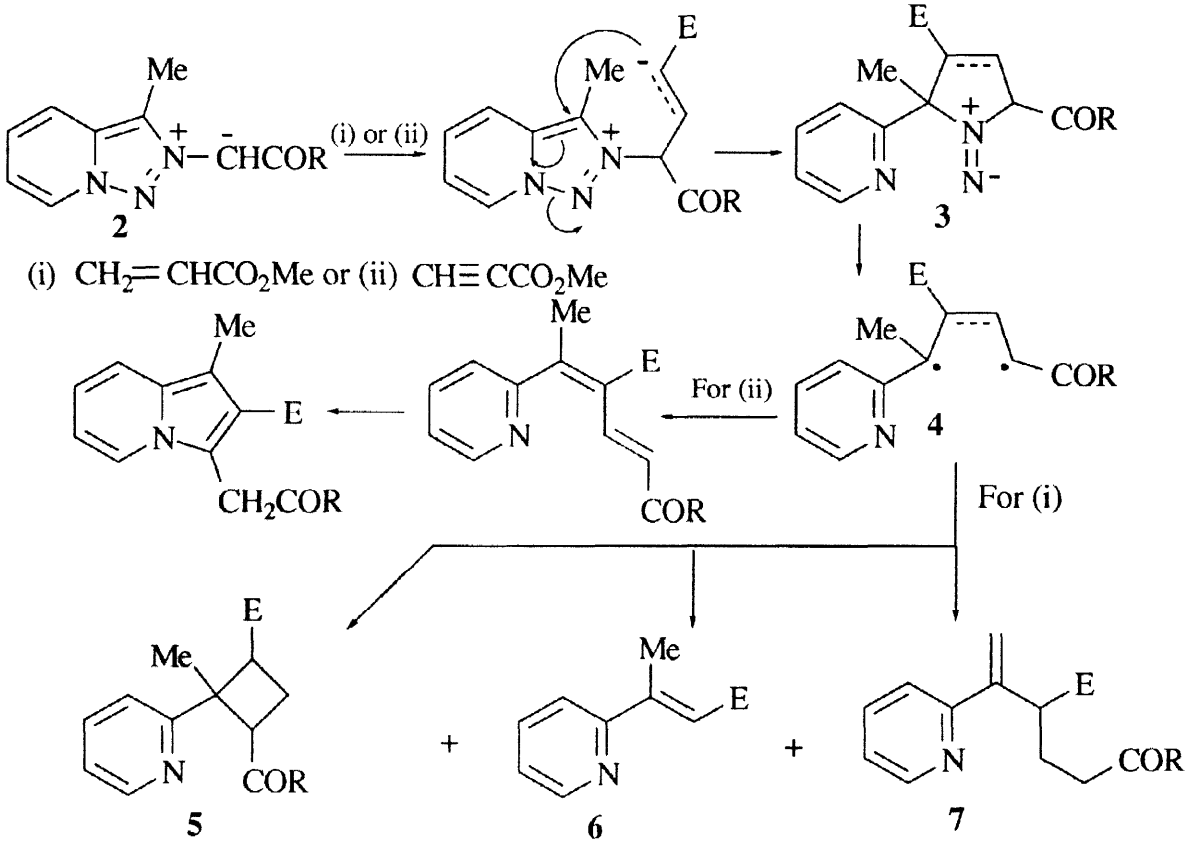
steric obstruction occurs exclusively at position 2, and this observation allowed us to prove that protonation also occurs at this position [3], an observation supported by molecular orbital calculations [4]. Furthermore, ylides derived from triazolopyridine **1** also undergo reactions in which opening of the five-membered ring can occur with loss of nitrogen. Thus, for example, ylides **2** react with methyl propiolate to give indolizines [5], and with methyl acrylate to give a mixture of products **5-7** [6]. Triazolothiazole ylides undergo similar fragmentations [7,8].These reactions were best explained by the sequence shown in Scheme 2, where the initial adduct cyclises with simultaneous opening of the five- membered ring to give a cyclic diazene **3**. Diazenes are known to decompose by a radical pathway, and the diradical **4** provides a plausible precursor for all the observed products, notably the mixture of products **5**, **6**, and **7** from the reaction with acrylate, the product **7** being reasonably explained only as the product of a hydrogen abstraction from the methyl group.



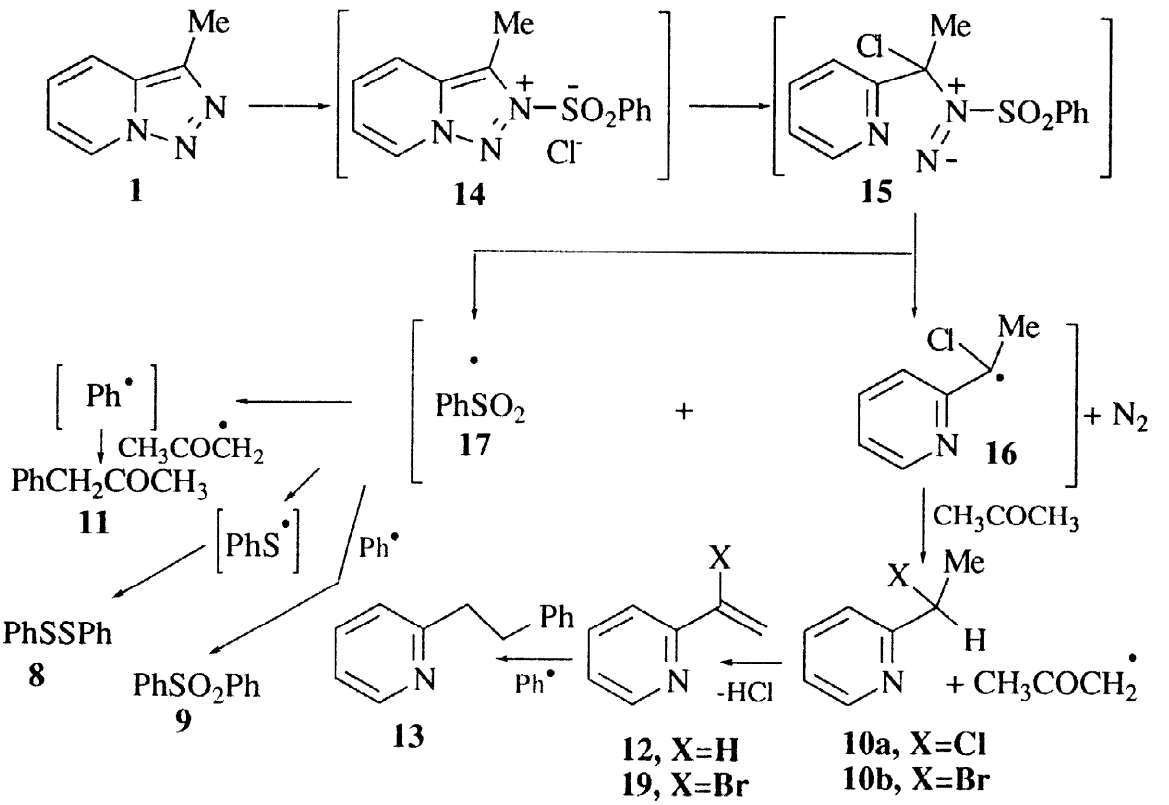
Scheme 2; E = CO_2Me

These observations have led to a suspicion that the mechanism of the simpler ring opening reactions may also involve free radical intermediates, and it is our investigation of this possibility which is described here.

RESULTS AND DISCUSSION

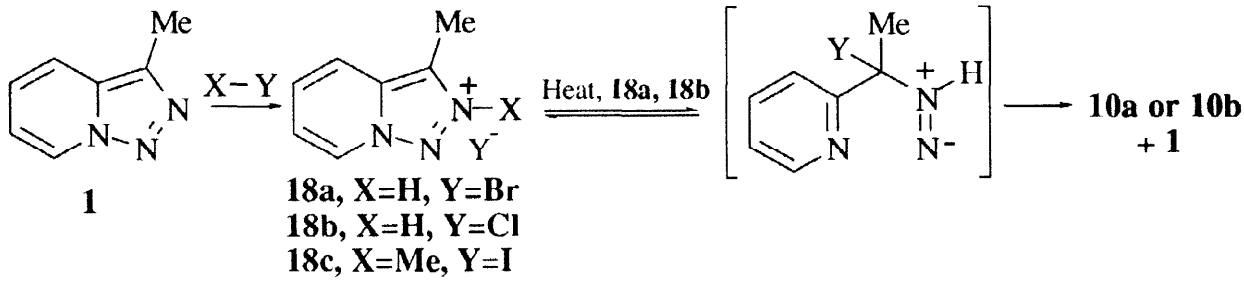
Our first experiments were aimed at the production of quaternary derivatives of intermediate

stability. Heating triazolopyridine **1** with benzenesulfonyl chloride in acetone as solvent produced a range of products, mainly in small isolated yield. In addition to the isolated diphenyl disulfide **8**, diphenyl sulfone **9**, 2-(1-chloroethyl)pyridine **10a** [9], and phenylpropanone **11**, the NMR signals of the crude product showed the presence of 2-vinylpyridine **12** and 2-(2-phenylethyl)pyridine **13**. These products are explained by the intervention of the quaternary derivative **14**, converted by chloride ion to the diazene **15**, which fragments as shown in Scheme 3 to produce the pyridylethyl radical **16** and the phenylsulfonyl radical **17**, itself the source of phenyl radicals and phenylsulfide radicals.



Scheme 3

We next prepared the simple salts **18** and studied their decomposition in solution in acetonitrile at 70°C, in dimethylsulfoxide at 100°C, and in carbon tetrachloride. The methiodide **18c** was stable under these conditions, but the hydrohalide salts decomposed to give as main product (50%, 67%) the triazolopyridine **1**, with a substantial minority (29%, 25%) of the appropriate 2-(1-haloethyl)pyridine, **10a** or **10b**. From the hydrochloride **18b** 2-ethenylpyridine **12** was also formed, and from the hydrobromide in DMSO a small amount of 2--(1-bromoethenyl)pyridine **19** which could be formed by hydrogen abstraction from the 1-(2-pyridyl)-1-bromoethyl radical. In the case of the hydrochloride, the experiment was conducted in an NMR tube, and all products have characteristic and distinct signals.



Scheme 4

We now sought physical evidence of the intermediacy of free radicals, using the simple systems. Both hydrohalides, heated in the presence of DPPH, a violet stable radical, showed the change to yellow characteristic of radical trapping by the DPPH. No detection of radical intermediates by ESR was possible, but decomposition of the hydrobromide **18a** in acetonitrile at 340K in the presence of nitrosobenzene as a radical trap [10] gave the aminoxyl radical PhNOH·[11].The experimental spectrum in CH_3CN at 340K with g-value = 2.0057 matched a simulated spectrum with the following hyperfine coupling constants[10]: 1N,α_N = 0.938; $\alpha_{o,p}{}^N$ = 0.295; $\alpha_m{}^H$ = 0.099; 1H,$\alpha_{NH}{}^H$ = 1.223mT. Repetition of the experiment using CD_3CN as solvent gave the same result, showing that the H was not abstracted from the solvent. We were unable to identify any second radical in the decomposition, and it now seems likely that the aminoxyl radical is formed from HBr (or HCl) formed by thermal equilibrium between the triazolopyridinium salt and the free base / HX pair.The signal can indeed be generated from HBr or HCl dissolved in the same solvent, and also from amine hydrobromides such as pyridinium hydrobromide, but not from triazolopyridine **1** itself, nor from triethylamine hydrobromide, this latter indicating dependency on basic dissociation constant. We feel that the accumulated evidence nevertheless indicates that a radical pathway is involved, if not solely operative, in the decomposition of simple triazolopyridinium salts. The mechanism would follow that shown in Scheme 3, with H· as the second radical, formed directly by fragmentation of an intermediate species similar to **15.**

Experimental

Mps were determined on a Kofler heated stage, and are uncorrected. NMR spectra were determined on a Bruker 250MHz spectrometer, and ESR spectra on a Bruker ESP-300E spectrometer operating in the X-band (9.3 GHz) with a rectangular TE102 cavity and equipped with a field-frequency lock accessory and a built-in NMR gaussmeter. Precautions to avoid undesirable spectral line broadening, such as that arising from microwave power saturation and magnetic field overmodulation were taken.

3-Methyl-[1,2,3]triazolo[1,5-a]pyridinium bromide ***18a.*** - A solution of HBr in acetic acid (48%) was added slowly to a solution of compound **1** in ether. The white precipitate which formed was filtered and recrystallised from ether to give the hydrobromide **18a**, m.p. 144-145°C (74%) (Found C,39.53; H,3.67 N,19.84. $C_7H_8N_3Br$ requires C,39.27; H,3.76; N,19.63%). ^1H nmr (DMSO-d_6) 2.64(s, 3H), 7.27-7.33(ddd, 1H, J_1=6.6, J_2=6.6, J_3=1.1Hz),

7.43-7.49(ddd, J_1=6.6, J_2=8.8, J_3=1.1Hz), 8.03, (dd, 1H, J_1=8.8, J_2=1.1Hz), 9.05(dd, 1H, J_1=6.6, J_2=1.1Hz). ^{13}C(DMSO-d_6) 10.3(CH_3), 117.3(CH), 118.5(CH), 125.6(CH), 125.9(CH), 131.93(C), 133.7(C).

3-Methyl-[1,2,3]triazolo[1,5-a]pyridinium chloride ***18b*** .- Prepared from anhydrous HCl gas and an ether solution of triazolopyridine **1**, the hydrochloride **18b** had m.p. 98-98°C (from ether) (68%). (Found; C,49.50; H,5.02; N,24.81. $C_7H_8N_3Cl$ requires C, 49.56;H,4.75; N,24.77%). ^{1}H nmr (DMSO-d_6) 2.76(s, 3H), 7.32-7.38(ddd, 1H, J_1=6.8, J_2=6.84, J_3=1.0Hz), 7.51-7.57(ddd, J_1=6.8, J_2=8.8, J_3= 1.0Hz), 8.13, (dd, 1H, J_1=8.8, J_2=1.0Hz), 9.18(d,1H, J_1=6.8, J_2=1.0Hz). ^{13}C NMR (DMSO-d_6) 10.1(CH_3), 116.3 (CH), 118.1(CH), 124.9(CH), 125.7(CH), 131.6(C), 133.6(C).

Reaction between Triazolopyridine ***1*** *and benzenesulfonyl chloride* .- Slow addition of benzenesulfonyl chloride (2.6g, 15mmol) to a solution of triazolopyridine **1** (2g, 15mmol) in anhydrous acetone was followed by boiling under reflux (80h).The solvent was evaporated and the crude residue chromatographed on a column of silica, eluting with hexane / ethyl acetate (9:1). Eluted were diphenyldisulfide **8** (1%) , 1-phenylpropanone **11**(3%), 2-(1-chloroethyl) -pyridine **10a** [8] (4%), and diphenylsulfone **9** (6%). In the crude, NMR signals characteristic of 2-ethenylpyridine **12** and 2-(2-phenylethyl)pyridine **13** were detected.

Thermal Decomposition of 3-Methyl-[1,2,3]triazolo[1,5-a]pyridinium bromide 18a.

a) A solution of 3-methyl-[1,2,3]triazolo[1,5-*a*]pyridinium bromide **18a** (0.1 g, 0.46mmol) in acetonitrile (12 ml) was heated (70°C, 4h). Evaporation and separation by Chromatotron, eluting with hexane and ethyl acetate (9:1) gave two compounds. The first was 2-(1-bromoethyl)pyridine **10b** (20mg, 25%), ^{1}H NMR ($CDCl_3$) δ 2.06(d,3H, J=7.0Hz), 5.3(q,1H, J=6.9Hz), 7.2(dd, 1H, J_1=4.7, J_2=7.7Hz), 7.4(d, 1H, J_1=7.7Hz), 7.69(dd, 1H, J_1=J_2=7.7Hz), 8.56(d, 1H, J=4.75Hz). ^{13}NMR ($CDCl_3$) δ 24.5(CH_3), 48.7(CH), 121.3(CH), 122.7(CH), 136.9(CH), 148.5(CH), 160.2(C). Further elution gave triazolopyridine **1** (42mg, 67%).

b) A solution of 3-methyl-[1,2,3]triazolo[1,5-*a*]pyridinium bromide **18a** (0.888 g, 4.1mmol) in DMSO (5ml) was heated (100°C, 4h). Water was added, and the solution extracted with ether. The solvent was dried, and the mixture of products purified using a Chromatotron as in (a). Two compounds were isolated, of which the first was 2-(1-bromoethenyl)pyridine (60mg, 8%) [12]. ^{1}H NMR ($CDCl_3$) δ 5.9 (d, 1H, J= 1.7Hz), 6.76 (d, 1H, J=1.7Hz), 7.13-7.19 (m, 1H), 7.65 (m, 2H), 8.50-8.54 (ddd, 1H, J_1=1.8, J_2=1.5, J_3=1.1Hz). ^{13}C NMR ($CDCl_3$) δ 120.8(CH), 122.0(CH), 123.4(CH), 129.6(C), 136.9(CH), 149.0(CH). The second compound eluted was triazolopyridine **1**.

Thermal Decomposition of 3-Methyl-[1,2,3]triazolo[1,5-a]pyridinium chloride ***18b*** .

A solution of the hydrochloride **18b** (15mg) in DMSO-d_6 was heated in an NMR tube at 100°C (4h), then the spectrum was recorded.Three compounds could be identified by distinct signals: 2-(1-chloroethyl)pyridine **12a**, triazolopyridine **1**, and 2-vinylpyridine **12**, in the ratio 29:50:21.

ACKNOWLEDGEMENTS

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