$BF_3.OEt_2$-promoted synthesis of acridines via *N*-aryl nitrenium-BF_3 ions generated by dissociation of 2-oxo azidoarenes in benzene

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Abstract

2-Oxo-substituted aryl azides such as 2-azidobenzenecarbaldehyde **1**, 1-(2-azidophenyl)-1-ethanone **2** and (2-azidophenyl) (phenyl)methanone **3** react with benzene in the presence of BF_3•OEt_2, mainly affording 9-substituted acridines via formal 2-anilino-oxobenzene-BF_3 complexes rapidly followed by intramolecular cyclo-dehydration at the activated carbonyl groups. Under the same conditions, 2-azidobenzoic acid **4** gives mainly 2-anilinobenzoic acid **4b** together with trace amounts of the 9(10*H*)-acridinone **4a**. On the other hand, 2-azidobenzenecarbonitrile **5** gives the 9-amino acridine **5a** via a conjugated imine, which undergoes intramolecular cyclization. The BF_3•OEt_2 promoted dissociation of aryl azides to aryl nitrenium ions is compared with those promoted by $AlCl_3$ or a strong protic acid (TFA/TFSA mixture).

Keywords: Nitrenium ions, acridines, arylazides, reactivity, BF_3·OEt_2, cyclo-dehydration

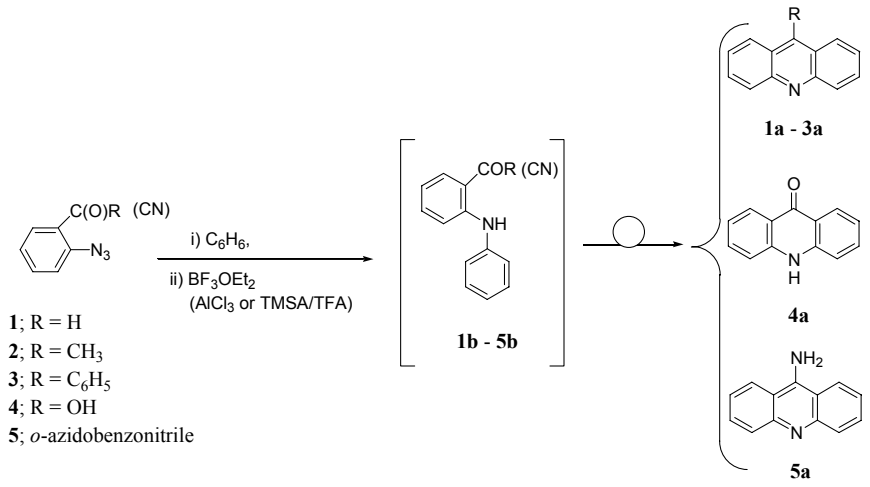
Introduction

Reactive species resulting from photo/thermal or chemical dissociation of aryl azides (i.e., arylnitrenes and arylnitrenium ions respectively) continue to attract attention arising from synthetic,[1] theoretical[2] and biological interest.[3] In the last decade, knowledge of the chemistry of *N*-arylnitrenium ions has advanced significantly, but is still considerably less developed than that of carbenium ions, carbenes and nitrenes.[4] It is now over a century since the discovery that the azido group is the best starting functional group in a great variety of reactions, including the generation of nitrenes and nitrenium ions.[5] Interest in this group has constantly grown as researchers have overcome their awe of the hazard posed by the handling of organic azides and have achieved a better understanding of the toxic and explosive properties of these compounds.[6]

Previous studies using a number of substituted phenyl azides and BF_3•OEt_2 showed that the arylnitrenium-BF_3 ions generated in presence of methylated benzenes led preferentially to *N*-

benzylanilines or diarylamines, where the product formed depended greatly on the electronic nature of the phenyl azide substituent and the nucleophilicity of the solvent.[7] The chemical trend exhibited by these aryl nitrenium-BF_3 ions was not consistent with that shown by aryl nitrenium ions generated from aryl azides and strong protic acid (TFSA or TFA), whose selectivity for *N*- or *C*-attack has been found to depend on the electronic character of the substituent.[8] In the systems we have previously studied, the exclusive regiospecific *N*-attack observed for phenyl nitrenium-BF_3 ion could be explained in terms of a disfavoring of delocalization of the positive charge over the phenyl ring due to the presence of strong opposite charges on the adjacent nitrogen and boron atoms. Incidentally, this hypothesis was supported by the reactivity value of the phenylnitrenium-BF_3 ion, determined by the Hammett $\sigma\rho$ relationship: the exhibited value of $\rho = -6.69$ was in the range expected for reactions with large positive charge generated at the reaction center in the transition state.[9] Although full elucidation of the effect of the substituent on the actual electronic states of the intermediate aryl nitrenium ions would require more careful investigation, there is a body of evidence indicating that the diarylamines are mainly formed from deactivated aryl azides via aromatic *N*-substitution by singlet nitrenium ions, whereas *N*-benzylanilines obtained from activated aryl azides are believed to be products of the side-chain C-H insertion of the triplet state.[7,8] Recently we observed that similar dissociations with activated aryl azides and BF_3•OEt_2 carried out in the absence of a trapping nucleophile normally afford products derived via nitrenium-BF_3 ions in the triplet state, specifically symmetric azobenzenes and anilines (hydrogen-abstraction product) in variable ratios.[10]

Here we investigate the related reactions of various 2-oxo arylnitrenium-BF_3 ions generated from deactivated 2-oxoazidobenzenes, including 2-azidobenzenecarbaldehyde **1**, 1-(2-azidophenyl)-1-ethanone **2**, (2-azidophenyl) (phenyl)methanone **3**, 2-azidobenzoic acid **4** and 2-azidobenzenecarbonitrile **5**, with Lewis acid BF_3•OEt_2 in the presence of benzene, as a possible source of 2-anilino-oxobenzenes **1b**–**5b** and/or acridines **1a**–**5a**. (Scheme 1) Simple acridine or 9-substituted acridines have been conveniently prepared by cyclization of 2-anilino-oxobenzenes (aldehydes, ketones, and carboxylic acids) in protic acids, through carbonyl group oxygen-protonation followed by intramolecular cyclo-dehydration at the activated carbonyl group.[11] (Scheme 1). A comparison with the similar dissociation promoted by $AlCl_3$ (B) or a strong protic trifluoromethanesulfonic and triflic acid mixture (TFSA/TFA, C) was also carried out.

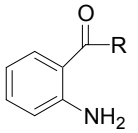


Scheme 1

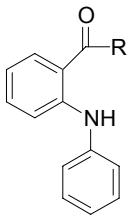
Acridine and its 9-derivatives are biofluorescent stains[12] and some 9-aminoacridines show antiseptic, analgesic and antitumor properties.[13]

Results and Discussion

All the azides **1**[14], **2**[15], **3**[16], **4**[17], **5**[18] were prepared by known literature methods, and had physical and spectral data identical to those already published. Heating the 2-azidobenzenecarbaldehyde **1** at 65 °C in benzene in the presence of a two-fold molar excess of $BF_3{\cdot}OEt_2$ under nitrogen pressure in a heavy-walled tube sealed with a Teflon septum inlet led to the complete disappearance of the starting azide **1** within about 30 h. Then, after hydrolysis and neutralization of the reaction mixture, chromatographic separation gave mainly the acridine **1a** (69% yield) and trace amounts of the corresponding 2-aminobenzenecarbaldehyde **1c** (9%) (Scheme 2). The latter product can be ascribed to hydrogen-abstraction by the minor triplet arylnitrenium intermediate (Table 1, entry 1).



1c; R = H
2c; R = CH_3
3c; R = C_6H_5
4c; R = OH



1b; R = H
2b; R = CH_3
3b; R = C_6H_5
4b; R = OH

Scheme 2

Table 1. Reaction of 2-oxo azidobenzenes (**1**–**5**) in benzene in the presence of BF_3·OEt_2 (A), $AlCl_3$ (B) or TFSA/TFA (C) at 65 °C

Entry	Azide	Reactant	Reaction time (h)	Yield (%) **1a-5a**	Yield (%) **1b-5b**	Yield (%) **1c-5c**	Other
1	**1**	A	30	69	-	9	[a]
2		B	38	58	-	8	
3		C	5	70	-	8	
4	**2**	A	4	61	-	6	
5		B	3	72	-	4	
6		C	3	61	-	6	
7	**3**	A	2	64	-	9	[b]
8		B	2	67	-	8	
9		C	5	67	-	8	
10	**4**	A	>30	5	82	5	
11		B [c]					
12		C	>30	6	80	5	
13	**5**	A	80	69	12	6	
14		B [c]					
15		C	24	79	-	13	

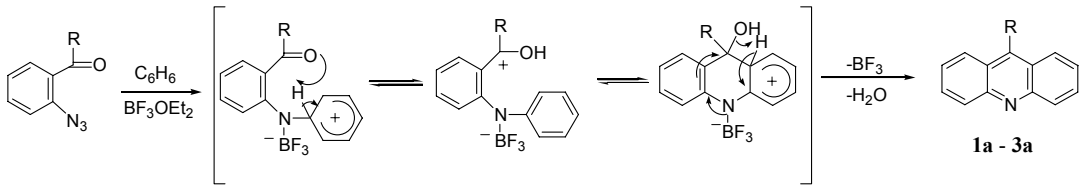
[a] Plus 7-azabicyclo[4.2.0]octa-1,3,5-trien-8-one (12%) detected by GC-MS analysis (*m*/*z* = 119, 74%, 92 M-27, 100%); [b] plus 1,2-dihydro-3*H*-indol-3-one (5%) detected by GC-MS analysis (*m*/*z* = 133, 100%, 104 M-29, 84%); [c] not carried out.

GC-MS analysis performed before chromatographing the reaction mixture of the azide **1**, showed that together with the acridine **1a** (*m/z* 179), additional small amounts of 2-aminobenzaldehyde **1c** (*m/z* 121, 6%) and 7-azabicyclo[4.2.0]octa-1,3,5-trien-8-one (*m/z* 119, 12%) were obtained. The latter species, which were not isolated by chromatography, are likely by-products of an intramolecular [-C(O)H] hydrogen-insertion by the arylnitrenium triplet.

Analogous treatment of the azides **2** and **3** afforded mainly the corresponding substituted acridines 9-Me **2a** and 9-Ph **3a**, but with a remarkably increased dissociation rate (4 and 2 h. respectively). (Table 1, entry 4 and 7) The MS-GC analyses for **2** and **3** revealed the fundamental peaks of the appropriate acridines **2a** (*m/z* 193) and **3a** (*m/z* 255) together with small amounts of

2-aminoacetophenone **2c** (*m/z* 135, 6%) and 2-aminobenzophenone **3c** (*m/z* 197, 9%), respectively. Moreover, in the case of the azide **2**, the MS-GC analysis revealed the presence of 1,2-dihydro-3*H*-indol-3-one (*m/z* 133, 5%), the formation of which can be ascribed to internal nitrenium triplet hydrogen-insertion on the methyl group. Interestingly, no evidence was observed of the 2-oxodiarylamines **1b**, **2b** and **3b** (Scheme 2).

The experiments established that the reaction in benzene of the 2-oxo azidobenzenes **l - 3** with BF_3·OEt_2 leads to the appropriate acridines **1a**–**3a** as the major product via an extensive two-step mechanism that begins with the expected formation of 2-anilino-oxobenzene BF_3-complexes **I**. Our proposed mechanism for the Lewis acid promoted formation of the acridines **1a**–**3a** is shown in Scheme 3. The *N*-substitution by the powerful electrophilic arylnitrenium-BF_3 ions on the nucleophile benzene clearly proceeds via the zwitterionic intermediate **I**, which is rapidly converted into acridines via an intramolecular cyclization and dehydration at the activated carbonyl group. (Scheme 3)



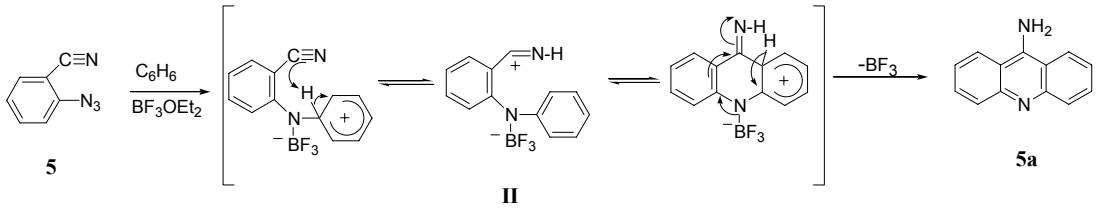
1; R = H
2; R = CH_3
3; R = C_6H5

I

Scheme 3

The chemical behavior observed with the 2-azidobenzoic acid **4** is an exception that makes clear the general protocol. In this instance, under the same reaction conditions, 2-anilinobenzene carboxylic acid **4b** (*m/z* 213, 82% yield) was the main product obtained, together with trace amounts of the 9(10*H*)-acridinone **4a** (*m/z* 195, 5%) and 2-aminobenzoic acid **4c** (*m/z* 137, 5%). (Table 1, entry 19) Despite the failure to directly obtain the acridine **4a**, the high yield of **4b** confirms that the nitrenium-BF_3 ion in this reaction was predominantly in the singlet state. The cyclo-dehydration process of **4b** to acridinone **4a** in concentrated H_2SO_4 represents a well-known protocol, but the reaction conditions are very critical.[19]

Another candidate molecule that could potentially conform to the proposed protocol is 2-azidobenzenecarbonitrile **5**. We found that, under the same conditions as above, **5** afforded the 9-amino acridine **5a** in fairly good yield (*m/z* 194, 69%) along with 2-anilinobenzonitrile **5b** (*m/z* 194, 12%). Both chromatography and GC-MS additionally confirmed the minor formation of the 2-aminobenzonitrile **5c** (*m/z* 118, 6%). A plausible mechanism for the formation of **5a** is that it is produced via the intermediate **II** that involves an imine form, which rapidly tautomerizes.[20] (Scheme 4) It is noteworthy that, compared to the reaction of **1**-**3**, the reactions carried out in BF_3·OEt_2 were slower, with evidence of the formation of the stable 2-anilinobenzonitrile **5b**. (Table 1, entry 13)



Scheme 4

To test the similarity of the here considered method with other such ones, we tried two other known procedures for the dissociation of aryl azides to aryl nitrenium ions: by using $AlCl_3$ (B) or a mixture of trifluoromethanesulfonic acid and triflic acid (TFSA/TFA, 4:5 v/v) (C).[21] We observed that these two reagents gave outcomes similar than those obtained using BF_3•OEt_2 within the limits of the different work-up required. Ratios of singlet *N*-substitution (**a** and **b**) vs triplet hydrogen-abstraction (**c** or other) products in protic TFSA/TFA are comparable with that previously reported for analogous dissociation of the phenyl azide in benzene.[22] The results are listed in Table 1, entries 2, 5 ,8 and 3, 6, 9, 12, 15.

Conclusions

The present work represents an experimental evaluation of the singlet/triplet rectivities of aryl nitrenium ions generated by dissociation of the corresponding deactivated aryl azides with a Lewis acid or a strong protic acid. The resulting aryl nitrenium-Lewis acid (or protic) ions are mainly in the singlet state. The singlet state ions react with benzene to yield mostly acridines via 2-anilino oxobenzene complexes, whereas the reaction of the minor triplet species yields products of hydrogen-abstraction (2-oxoarylamines) or occasionally C-H insertion reactions.

Experimental Section

Genera Procedures. Melting points were determined on a Büchi apparatus and are uncorrected. IR spectra were measured from films on a Perkin-Elmer Spectrum 2000 FT-IR spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Gemini 200 (200 and 50 MHz, respectively) or 300 (300 and 75 MHz, respectively). GC/Mass spectra were recorded on VG7070E instruments using electron impact ionization.

Materials. Starting 2-oxo arylazides **2**–**5** and 2-azidobenzylalcohol were prepared from the corresponding amines by diazotization followed by treatment with sodium azide according to the Smith protocol,[23] whereas the 2-azidobenzaldehyde **1** has been prepared by oxidation of the 2-azidobenzylalcohol.[14a] All the isolated azides **1**[14], **2**[15], **3**[16], **4**[17], **5**[18] had physical and spectral data identical to those already published. The Lewis and protic acids were purchased from Aldrich

Chimica Italiana and the anhydrous benzene was degassed with nitrogen before the use. Authentic samples of the acridines **1a**, **2a** and **5a**, the aryl amines (**1c**–**5c**) and the anilide **4b** were obtained from the same commercial sources, and their physical and spectral data were compared to the ones of the obtained corresponding products, while **3b**,[24] **3a** and **4a**[25] were prepared according to the procedure described.

Decomposition of the 2-oxo arylazides (1-5) with BF_3•OEt_2. General procedure. A mixture of the azide (**1-5**) (4.0 mmol) and BF_3•OEt_2 (8.0 mmol) in benzene (30 ml) was heated at 60 °C until nitrogen evolution ceased (1-80 h). The excess of solvent was then eliminated *in vacuo* and replaced with CH_2Cl_2 (30 ml). The resulting suspension was neutralized (pH = 8-9) with aqueous sodium carbonate solution (20%) and then extracted twice with CH_2Cl_2 (2x30 ml) and dried with $CaCl_2$, after which the solvent was eliminated *in vacuo*. The acridines (**1a**–**5a**) and any by-products were separated by elution on a Brockmann grade I aluminum oxide column with petroleum ether (bp 40 to 60 °C) with increasing amounts of diethyl ether (up to 100%). Product yields are listed in Table 1, entries 1a-5a. All the isolated acridines **1a**–**5a** display physical and IR, NMR, and MS spectral data consistent with those commercially available (**1a**, **2a** and **5a**) or reported (**3a**, **4a**) in the literature.

Decomposition of the 2-oxo arylazides (1 - 3) in $AlCl_3$. General procedure. A solution of the azide (**1 - 3**) (4.0 mmol) in dry benzene (10 ml) was added to a stirred suspension of $AlCl_3$ (6.0 mmol) in benzene (20 ml). The resulting mixture was maintained at 65 °C until nitrogen evolution ceased (2-38 h). The excess of solvent was eliminated *in vacuo* and replaced with CH_2Cl_2 (30 ml). The resulting suspension was neutralized (pH = 8-9) with aqueous sodium carbonate solution (20%) and then extracted twice with CH_2Cl_2 (2x30 ml) and dried with $CaCl_2$, after which the solvent was eliminated *in vacuo*. The acridines (**1a** – **3a**) and any by-products were separated by elution on a Brockmann grade I aluminum oxide column with petroleum ether (bp 40-60 °C) with increasing amounts of diethyl ether (up to 100%).

Product yields are listed in Table 1, entries 1b-3b.

Decomposition of the 2-oxo arylazides (1 - 5) in TFA/TFSA. General procedure. A solution of the azide (**1 - 5**) (4.0 mmol) in benzene (20 ml) was added drop-wise to a mixture of TFMSA (4 ml) and TFA (5 ml) at 0 °C and stirred at the same temperature for 15 min. The reaction mixture was maintained at 65 °C until TLC showed that no starting material remained, then cooled and neutralized with aqueous sodium hydroxide solution (10%) and extracted twice with CH_2Cl_2 (2x30 ml). The acridines (**1a** – **5a**) and any by-products were separated by elution on a Brockmann grade I aluminum oxide column with petroleum ether (bp 40-60 °C) with increasing amounts of diethyl ether (up to 100%). Product yields are listed in Table 1, entries 1c-5c.

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