Abstract
2-Oxo-substituted aryl azides such as 2-azidobenzene-carbaldehyde 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(10H)-acridinone 4a. On the other hand, 2-azidobenzene-carbonitrile 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., aryl nitrenes and aryl nitrenium ions respectively) continue to attract attention arising from synthetic, theoretical and biological interest. In the last decade, knowledge of the chemistry of N-aryl nitrenium ions has advanced significantly, but is still considerably less developed than that of carbenium ions, carbenes and nitrenes. 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. 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.

Previous studies using a number of substituted phenyl azides and BF$_3$·OEt$_2$ showed that the aryl nitrenium-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. 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. 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 phenyl nitrenium-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. 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. Recently we observed that similar dissociations with activated aryl azides and BF$_3$$\cdot$OEt$_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.

Here we investigate the related reactions of various 2-oxo aryl nitrenium-BF$_3$ ions generated from deactivated 2-oxoazidobenzenes, including 2-azidobenzene-carbaldehyde 1, 1-(2-azidophenyl)-1-ethanone 2, (2-azidophenyl) (phenyl)methanone 3, 2-azidobenzoic acid 4 and 2-azidobenzene-carbonitrile 5, with Lewis acid BF$_3$$\cdot$OEt$_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. 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.
Acridine and its 9-derivatives are biofluorescent stains\textsuperscript{12} and some 9-aminoacridines show antiseptic, analgesic and antitumor properties.\textsuperscript{13}

Results and Discussion

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

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Azide</th>
<th>Reactant</th>
<th>Reaction time (h)</th>
<th>Yield (%)</th>
<th>Yield (%)</th>
<th>Yield (%)</th>
<th>Other</th>
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<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>A</td>
<td>30</td>
<td>69</td>
<td>-</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>B</td>
<td>38</td>
<td>58</td>
<td>-</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>C</td>
<td>5</td>
<td>70</td>
<td>-</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>A</td>
<td>4</td>
<td>61</td>
<td>-</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>B</td>
<td>3</td>
<td>72</td>
<td>-</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>2</td>
<td>C</td>
<td>3</td>
<td>61</td>
<td>-</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>3</td>
<td>A</td>
<td>&gt;30</td>
<td>5</td>
<td>82</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>3</td>
<td>B</td>
<td>2</td>
<td>67</td>
<td>-</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>3</td>
<td>C</td>
<td>5</td>
<td>67</td>
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</tr>
<tr>
<td>10</td>
<td>4</td>
<td>A</td>
<td>&gt;30</td>
<td>5</td>
<td>80</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>4</td>
<td>B$^c$</td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>12</td>
<td>4</td>
<td>C</td>
<td>&gt;30</td>
<td>6</td>
<td>80</td>
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<tr>
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<tr>
<td>15</td>
<td>5</td>
<td>C</td>
<td>24</td>
<td>79</td>
<td>-</td>
<td>13</td>
<td></td>
</tr>
</tbody>
</table>

$^a$ 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-3H-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 1 - 3 with BF₃•OEt₂ 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 BF₃-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-BF₃ 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)

![Scheme 3](image)

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(10H)-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-BF₃ ion in this reaction was predominantly in the singlet state. The cyclo-dehydration process of 4b to acridinone 4a in concentrated H₂SO₄ 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-azidobenzene-carbonitrile 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 BF₃•OEt₂ were slower, with evidence of the formation of the stable 2-anilinobenzonitrile 5b. (Table 1, entry 13)
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 AlCl₃ (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 to those obtained using BF₃•OEt₂ 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. ¹H NMR and ¹³C 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, ², ³, ⁴, ⁵ 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\textsubscript{3}•OEt\textsubscript{2}. General procedure.** A mixture of the azide (1-5) (4.0 mmol) and BF\textsubscript{3}•OEt\textsubscript{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\textsubscript{2}Cl\textsubscript{2} (30 ml). The resulting suspension was neutralized (pH = 8-9) with aqueous sodium carbonate solution (20%) and then extracted twice with CH\textsubscript{2}Cl\textsubscript{2} (2x30 ml) and dried with CaCl\textsubscript{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\textsubscript{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\textsubscript{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\textsubscript{2}Cl\textsubscript{2} (30 ml). The resulting suspension was neutralized (pH = 8-9) with aqueous sodium carbonate solution (20%) and then extracted twice with CH\textsubscript{2}Cl\textsubscript{2} (2x30 ml) and dried with CaCl\textsubscript{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\textsubscript{2}Cl\textsubscript{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.
Acknowledgements

We gratefully acknowledge the financial support of Ministero della Istruzione, dell’Università e della Ricerca (MIUR) and partial support from the “Progetto di Finanziamento Triennale, Ateneo di Bologna”

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