Superelectrophilic Tscherniac Amidomethylation of Aromatics with N-Hydroxymethylphthalimide in Trifluoromethanesulfonic Acid

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N-Hydroxymethylphthalimide in trifluoromethanesulfonic acid (triflic acid) reacts readily at room temperature with benzene, halo-, polyhalo- and halonitrobenzenes to give high yields of the corresponding α-amidomethylated products. The scope of the α-amidomethylation reaction is substantially extended by the studied system, which is considered to involve diprotonated N-hydroxymethylphthalimide as the de facto superelectrophilic reagent.

Acid catalysed α-amidoalkylation of aromatics, considered a variation of the Mannich reaction in which the amine moiety is replaced by an amide functionality, has received considerable attention and has been extensively reviewed. A number of reagents have been developed for such reactions. Tscherniac’s original reagent was N-hydroxymethylphthalimide in sulfuric acid, whereas Einhorn extended the reaction to a series of N-hydroxymethylamides.

Generally, efficient α-amidoalkylation of benzenoid systems is limited to substrates that are more nucleophilic than benzene, i.e. those bearing OH, OMe or NMe₂ groups. Nitrobenzene and subsequently benzoic acid were, however, amidoalkylated in oleum. The reactions are invariably acid catalysed, and sulfuric acid is the most commonly used catalyst and reaction medium. However, side reactions such as sulfonation, disubstitution or rearrangement can lead to low yields. Acetic/sulfuric acid mixtures and trifluoroacetic acid have also been employed as reaction media.

The mechanism of the amidomethylation reaction was considered to involve carbimion ions, although the O-protonated N-hydroxymethylphthalimides themselves can be displaced in an Sₙ₂ fashion.

A ¹³C NMR spectrum of N-hydroxymethylphthalimide in fluorosulfonic acid (somewhat more acidic than triflic acid) was recorded at −70 °C. Both the methylene and carbonyl carbon nuclei were deshielded by about 5 ppm indicating protonation on both the hydroxyl and carbonyl functionalities. This doubly protonated species, analogous to 2a, would be more electrophilic towards deactivated aromatic substrates enabling α-amidomethylation to occur.

Readily available N-hydroxymethylphthalimide (3) was used as the α-amidoalkylating reagent as this reagent undergoes condensation with a series of nucleophilic aromatic substrates (the Tscherniac–Einhorn reaction). The reaction between 3 and aromatic substrates 4a–i in triflic acid on overnight stirring at room temperature gave the products 5a–k (Scheme). Chlorobenzene (4b) gave a mixture of ortho and para α-amidoalkylation products, 5b and 5c, in 67:33 ratio (GC). Similarly, fluorobenzene (4e) gave ortho and para isomers, 5d and 5e, in 78:22 ratio. In all cases, reaction workup was simple and yields high (Table). Arenes 5b and 5c have been prepared previously in 80 % yield by heating chlorobenzene with N-chlorophthalimide and zinc chloride at 100 °C. Similarly, nitrobenzene may be amidoalkylated, in 70 % yield, upon heating with N-chloromethylphthalimide and aluminum trichloride at 120–135 °C. Clearly our method requires less vigorous conditions for efficient amidomethylation. Systems as deactivated as 2,4-difluoronitrobenzene (4h) and 1,3,5-trifluoronitrobenzene (4g) were α-amidoalkylated in high yield at room temperature in this superacid solution, and even pentafluorobenzene gave a 69 % yield.

The structures of 5a–k follow directly from elemental analysis, NMR spectroscopy and mass spectrometry. ¹³C and ¹⁹F NMR data for 5a–k are collated in the Table. In summary, the scope of the α-amidoalkylation reaction can be extended to highly deactivated substrates by performing the reaction in superacidic trifluoromethanesulfonic acid solution. This solvent is very convenient.

Suitable π-donor aromatic nucleophiles react with these intermediate ions or their polarised precursors to give the desired products. However, with deactivated (less nucleophilic) aromatics the reaction generally fails.

Supercacids, such as trifluoromethanesulfonic acid, were observed to enhance the reactivity of the nitronion, NO₂⁺, by protosolvation to such an extent that 1,3,5-trifluorobenzene, 2,3,4-trifluorobenzene and 1,3-dinitrobenzene may be successfully nitrated by nitronium tetrafluoroborate in superacid solution. Similar activations in the Gattermann and Houben–Hoesch reactions were also observed.

In this paper we report the successful α-amidomethylation of benzene, halo-, polyhalo and halonitrobenzenes with N-hydroxymethylphthalimide in superacidic trifluoromethanesulfonic acid. The enhanced reactivity of the α-amidoalkylating reagent is considered to be due to protosolvation of the intermediate ion 5a or 1a to form superelectrophilic dications 2 or 2a, thus rendering α-amidomethylation of even deactivated systems highly efficient.
Table. Compounds 5 Prepared

<table>
<thead>
<tr>
<th>Product</th>
<th>Yield</th>
<th>mp (°C)</th>
<th>13C NMR (CDCl₃/TMS) δ, J (Hz)</th>
<th>MS (70 eV)</th>
<th>m/e (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5a</td>
<td>84</td>
<td>115–116</td>
<td>41.5, 123.2, 127.7, 128.5, 128.6, 132.0, 133.8, 136.3, 167.9</td>
<td>237 (100), 219 (38), 209 (14), 208 (22), 180 (10), 104 (35), 77 (17), 76 (14)</td>
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<tr>
<td>5b, 5c</td>
<td>89</td>
<td>39.3, 40.8, 123.4, 126.8, 128.5, 128.8, 129.6, 130.0, 131.9, 133.0, 133.3, 133.7, 134.1, 134.7, 167.9</td>
<td>5b: 236 (100), 130 (16)</td>
<td>5c: 273 (33), 271 (100), 253 (17), 242 (15), 237 (17), 236 (90), 208 (18), 138 (22), 130 (17), 105 (13), 77 (16)</td>
<td></td>
</tr>
<tr>
<td>5d, 5e</td>
<td>90</td>
<td>30.9, 115.5 (d, J = 21.2), 123.3, 130.5 (d, J = 8.6), 132.0, 132.2 (d, J = 3.0), 134.0, 162.3 (d, J = 245.8), 167.9</td>
<td>5d: 255 (100), 237 (22), 227 (16), 226 (19), 122 (29), 105 (11), 104 (10), 76 (12)</td>
<td>5e: 255 (100), 237 (26), 227 (18), 226 (24), 122 (28), 105 (11), 104 (10), 76 (12)</td>
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<tr>
<td>5f</td>
<td>92</td>
<td>152.5</td>
<td>35.0 (d, J = 4.3), 115.8 (dd, J = 20.2, J = 8.6), 116.2 (dd, J = 18.2, J = 8.6), 116.6 (dd, J = 18.2, J = 8.5), 123.5, 124.7 (dd, J = 17.6, J = 7.7), 131.9, 134.2, 156.4, (dd, J = 244.3, J = 2.4), 158.5 (dd, J = 242.9, J = 2.4), 167.7</td>
<td>273 (100), 255 (23), 245 (18), 244 (21), 140 (28), 105 (18), 104 (13), 77 (11), 76 (14)</td>
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<tr>
<td>5g</td>
<td>88</td>
<td>160.4</td>
<td>39.2, 123.6, 123.9, 130.7, 131.8, 134.6, 135.5, 140.0, 146.8, 167.8</td>
<td>281 (100), 267 (22), 130 (31), 104 (15), 102 (11), 76 (33)</td>
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<tr>
<td>5h</td>
<td>85</td>
<td>166.0</td>
<td>41.6, 123.1, 123.8, 124.0, 130.0, 131.8, 134.1, 134.5, 137.2, 147.4, 167.7</td>
<td>282 (17), 281 (100), 130 (28), 76 (6)</td>
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<tr>
<td>5i</td>
<td>80</td>
<td>123.4</td>
<td>29.7 (t, J = 3.8), 100.9 (dd, J = 26.5, J = 2.9), 108.2 (dd, J = 20.6, J = 4.9), 123.5, 132.1, 134.1, 161.8 (dd, J = 251.8, J = 14.8, J = 10.0), 162.7 (dt, J = 265.2, J = 15.2), 167.4</td>
<td>291 (100), 263 (16), 262 (15), 207 (13), 158 (38), 145 (15), 105 (19), 104 (13), 89 (13), 77 (10), 76 (14)</td>
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<tr>
<td>5j</td>
<td>70</td>
<td>141.4</td>
<td>34.3 (d, J = 3.6), 106.8 (dd, J = 26.7, 24.3), 120.8 (dd, J = 16.7, J = 4.0), 123.7, 128.4 (m, J = 5.1), 131.7, 133.8, 134.5, 156.0 (dd, J = 267.1, J = 12.5), 163.3 (J = 261.0, J = 10.9), 167.5</td>
<td>318 (15), 302 (21), 301 (100), 272 (18), 271 (99), 130 (20), 105 (12), 77 (10), 76 (13)</td>
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<tr>
<td>5k</td>
<td>69</td>
<td>109.0</td>
<td>34.3 (d, J = 3.6), 106.8 (dd, J = 26.7, 24.3), 120.8 (dd, J = 16.7, J = 4.0), 123.7, 128.4 (m, J = 5.1), 131.7, 133.8, 134.5, 156.0 (dd, J = 267.1, J = 12.5), 163.3 (J = 261.0, J = 10.9), 167.5</td>
<td>327 (100), 299 (14), 298 (12), 194 (14), 181 (14), 105 (36), 104 (19), 77 (25)</td>
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</table>

a Yield of isolated product. For new compounds satisfactory microanalyses obtained: C ± 0.39, H ± 0.38, N ± 0.44.
b Lit. mp 110–114°C.
c Mixture of isomers.
d 19F NMR (CDCl₃/FCl₃), δ: 5d, -118.9; 5e, -115.0; 5f, -119.9; -123.9; 5i, -108.0, -110.9; 5j, -101.4, -112.4; 5k, -101.8, -115.4, -117.4.
e 13C NMR shows many overlapping peaks in the aromatic region due to extensive C-F coupling rendering a full assignment of the spectrum difficult. The structure of 5k follows from the other available data.

Since in contrast to sulfuric acid, it does not sulfonate or oxidise aromatics. Protosolvation of N-hydroxybenzylphthalimide, giving a superelectrophilic, highly reactive reagent, can be used to explain the enhanced reactivity of the z-amidoalkylating agent.

Melting points were measured on a Mettler FP1 apparatus and are uncorrected. NMR spectra were recorded in CDCl₃ solution on a Varian VXR-200 spectrometer with TMS and CFC₃ as internal standards. Mass spectra were recorded on a Hewlett-Packard 5971 mass spectrometer. Elemental analyses were performed by Gaithersburg Laboratories, Inc., Knoxville, TN, USA.

**Amidoalkylation of Aromatics: General Procedure:**
N-Hydroxybenzylphthalimide (3; 1.0 g, 5.6 mmol) was dissolved in triflic acid (10 mL) with stirring at 0°C. Excess of the aromatic 4 (12 mmol) was added in one portion and the mixture was stirred at r.t. overnight, poured onto ice/water and extracted with CH₂Cl₂. The organic layer was washed with NaHCO₃ solution, dried (MgSO₄) and evaporated. The residue was recrystallised from EtOH. Data for products 5a–k are summarised in the Table.

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Scheme
(2) Tramontini, M. Synthesis 1973, 703.