The Direct Synthesis of Secondary Amides from Aldehydes; A Novel General Redox Procedure Mediated by Iodotrichlorosilane (ITCS)

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Iodotrichlorosilane, Aldehydes, Nitriles, sec-Amides

A unique, general redox process for the preparation of secondary amides by the interaction of aldehydes with nitriles in the presence of two equivalents of iodotrichlorosilane (ITCS) is described and possible pathways are discussed.

Iodotrichlorosilane (ITCS) [1] may be generated by the interaction of sodium iodide with tetrachlorosilane [2]. For reactions, the mixture of sodium iodide with tetrachlorosilane in solvents such as dichloromethane or acetonitrile may be used instead of isolated ITCS. So far, the organic chemistry of ITCS has received little attention, the only previously recorded reaction being that of ether cleavage [3]. We have recently shown [4] that acetals and ketals are efficiently cleaved by ITCS to yield the parent carbonyl compounds under anhydrous conditions. We have also shown that simple aldehydes react with simple aromatic and aliphatic nitriles to give secondary amides in a unique redox reaction [1]. The reaction takes a different course and gives unsaturated iminoaldehydes when acrylonitrile is used [5]. Simple ketones do not react in the usual conditions but α,β-unsaturated ketones either give allylic secondary amides or are reduced at the double bond [6].

We now report in detail on the production of secondary amides from aldehydes. We first came across this reaction when exploring the functionality that would withstand the ether cleavage. With this in mind, we subjected 4-methoxybenzaldehyde to reaction with ITCS in dichloromethane, using acetonitrile as a cosolvent. To our surprise, for demethylation with ITCS is a facile process [2], there was no 4-hydroxybenzaldehyde in the product but, instead, the reaction gave N-(4-methoxybenzyl)acetamide (II), in which the acetonitrile unit had been incorporated and the aldehyde reduced (Scheme 1).

Further investigation revealed that to obtain good yields of (II) from 4-methoxybenzaldehyde there was a requirement for two equivalents of ITCS. Overall, the reaction is summarized by equation (1), which represents a unique way of directly carrying out a fundamental transformation, that of aldehydes to secondary amides.

\[
R'\text{CHO} + R''\text{CN} + 2\text{ISiCl}_3 + 4\text{H}_2\text{O} \rightarrow R'\text{CH}_2\text{NHCO}R'' + \text{I}_2 + 2\text{SiO}_2 + 6\text{HCl} \quad (1)
\]

The introduction of the nitrogen atom to the aldehyde, together with reduction is, in a formal sense, similar to the well-known reductive aminations of aldehydes by amines in the presence of sodium cyanohydroborate [7] or pyridine-borane [8].

Using acetonitrile and benzonitrile as typical nitriles, we then investigated the scope of the reaction (Table I).

We first concentrated on aromatic aldehydes and showed that neither electron withdrawing nor electron donating groups inhibited the reaction, which also proceeds as well, or better, with benzonitrile as with acetonitrile. The reaction is subject to some steric interference (exp. 5) under our standard conditions (room temperature). The use of phenylacetalddehyde (exp. 6, 12) showed that the reaction is in no way confined to aromatic aldehydes. Cinnamaldehyde gave a mixture of 3-ido-3-phenylpropanal (1,4-addition of ITCS) and N-(1-phenyl-
Table I. The synthesis of amides according to eq. (1).

<table>
<thead>
<tr>
<th>Exp. no.</th>
<th>Aldehydes</th>
<th>Nitrile</th>
<th>Time (h)</th>
<th>Product</th>
<th>Yield (%)a,b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>C₆H₅CHO</td>
<td>CH₃CN</td>
<td>9</td>
<td>C₆H₅CH₂NHCOCH₃</td>
<td>77c</td>
</tr>
<tr>
<td>2</td>
<td>4-MeOC₆H₄CHO</td>
<td>CH₃CN</td>
<td>15</td>
<td>4-MeOC₆H₄CH₂NHCOCH₃</td>
<td>70c</td>
</tr>
<tr>
<td>3</td>
<td>2,3-(MeO)C₆H₅CHO</td>
<td>CH₃CN</td>
<td>11</td>
<td>2,3-(MeO)C₆H₅CH₂NHCOCH₃</td>
<td>64c</td>
</tr>
<tr>
<td>4</td>
<td>4-MeNC₆H₅CHO</td>
<td>CH₃CN</td>
<td>8</td>
<td>4-MeNC₆H₅CH₂NHCOCH₃</td>
<td>86c</td>
</tr>
<tr>
<td>5</td>
<td>α-Naphthaldehyde</td>
<td>CH₃CN</td>
<td>14</td>
<td>N-(α-naphthylmethyl)acetamide</td>
<td>43c</td>
</tr>
<tr>
<td>6</td>
<td>PhCH₂CHO</td>
<td>CH₂CN</td>
<td>10</td>
<td>PhCH₂CH₂NHCOCH₃</td>
<td>59c</td>
</tr>
<tr>
<td>7</td>
<td>PhCHO</td>
<td>PhCN</td>
<td>8</td>
<td>PhCH₂CH₂NHCOCH₃</td>
<td>80c</td>
</tr>
<tr>
<td>8</td>
<td>4-MeOC₆H₄CHO</td>
<td>PhCN</td>
<td>12</td>
<td>4-MeOC₆H₄CH₂NHCOCH₃</td>
<td>86d</td>
</tr>
<tr>
<td>9</td>
<td>4-ClC₆H₄CHO</td>
<td>PhCN</td>
<td>10</td>
<td>4-ClC₆H₄CH₂NHCOCH₃</td>
<td>81d</td>
</tr>
<tr>
<td>10</td>
<td>4-BrC₆H₄CHO</td>
<td>PhCN</td>
<td>10</td>
<td>4-BrC₆H₄CH₂NHCOCH₃</td>
<td>82d</td>
</tr>
<tr>
<td>11</td>
<td>4-O₂NC₆H₄CHO</td>
<td>PhCN</td>
<td>12</td>
<td>4-O₂NC₆H₄CH₂NHCOCH₃</td>
<td>60c</td>
</tr>
<tr>
<td>12</td>
<td>PhCH₂CHO</td>
<td>PhCN</td>
<td>8</td>
<td>PhCH₂CH₂NHCOCH₃</td>
<td>80c</td>
</tr>
</tbody>
</table>

a Reactions not optimized; b all yields are isolated, crystallized products, all products fully characterized; c CH₂Cl₂ as solvent; d CICH₂CH₂Cl as solvent.

1-propenyl)acetamide. Despite the fact that we adopted standard conditions and did not attempt to optimise any specific reaction, the yields of isolated recrystallized products are generally acceptable.

The detailed pathways of this multistep process is unknown, but we have some facts on which to base a working hypothesis. The first is that iodotrichlorosilane reacts with aldehydes, in a manner analogous to iodotrimethylsilane [9], to give the 1,2-addition products A, which we have isolated [2]. The second is that titration of the final reaction mixture with sodium thiosulphate shows that the production of iodine and secondary amide proceed in equal molar proportions. The third is that if the reaction is worked up with D₂O, then one atom of deuterium is incorporated into each of the benzyl and –NH– groups of the amide product. These findings are congruent with a working hypothesis based on Scheme 2.

The first step (eq. (2)) is the production of A, which would seem to have a particularly good leaving group, Cl₃SiO⁻. If the iodine were to leave instead, a somewhat similar but more complex pathway can be envisaged which, for simplicity, is not given here. Ionisation to give B as in equation (3) is then followed by a step similar to the well documented Ritter reaction [10], in which a nitrile adds to a carbonium ion. Indeed, in strong acid conditions nitriles which hydrolysed to amidic then add to aldehydes themselves (eq. (8)) to give 1,1-diamides [11, 12].

More recently [13] it has been shown that α,β-unsaturated ketones add iodotrimethylsilane to give a carbonium ion which adds acetonitrile to yield a further ion that is intercepted by cyclisation to give 4 H-1,3-oxazines [13] (eq. (9)).
The unique and the first irreversible step in Scheme 2 is shown in equation (6) which outlines the reaction of C with ITCS to give D plus iodine. The whole process is capable of being written, if required, as an initial dissociation, followed by one or two-electron attack by ITCS. Similarly, the intermediate D, may exist as an azirine, or a zwitterion for example. In any case, its reaction with water (eq. (7)) leads to the secondary amide E. We are currently investigating the ramifications of this Scheme and, in particular, we are testing the reactions of B with electron rich species other than nitriles.

Experimental

Infrared (IR) spectra were recorded on a JASCO IR. E spectrometer with only selected absorptions being recorded. Absorption maxima were recorded in cm⁻¹. Nuclear magnetic resonance (NMR) spectra were run at 200 MHz spectrometer and varian HA-100 D spectrometer. Spectra were taken using CDCl₃ as solvent with chemical shifts quoted in parts per million (δ ppm) using TMS as internal standard. The mass spectra were recorded on AE/MS-702 spectrometer.

Flask chromatography was performed on silica gel (Merck-Kieselgel 60 GF254 230-400 mesh). Preparative plate chromatography was carried out on glass plates (20 x 10 cm) coated with silica gel (Blend 41) and with a kieselgel band and were preeluted with dichloromethane before use. TLC was performed on aluminium sheets.

Tetrachlorosilane was used as obtained from commercial sources. The solvents were distilled before use. Acetonitrile and benzonitrile were dried by refluxing, over phosphorous pentaoxide and distilled. Dichloromethane and 1,2-dichloroethane were distilled over anhydrous calcium chloride.

General procedure

Tetrachlorosilane (2.4 ml, 20 mmol) in dichloromethane or 1,2-dichloroethane (10 ml) was added to a mixture of aldehyde (10 mmol) and sodium iodide (3 g, 20 mmol) in nitrile (10 ml). The heterogeneous mixture was stirred with exclusion of moisture at ambient temperature (25 °C). It was poured into water (50 ml) and extracted with dichloromethane (2 × 50 ml). The extracted were washed with sodium thiosulphate solution (5 ml 10%) to remove the colour of iodine, dried over anhydrous K₂CO₃, and the solvent removed under vacuum. The residue was purified by TLC on silica gel to give pure N-alkyl amide derivative.

**N-Benzylacetamide (I)**

The general procedure yielded compound I (1.147 g, 77%) from benzaldehyde (1.06 g, 10 mmol) after using chloroform-hexane as eluent for TLC on silica gel (m.p. 60 °C, lit[14], m.p. 59 °C).

**N-(p-Anisyl) acetamide (II)**

The general procedure and after using ethyl acetate-hexane as eluent for TLC on silica gel afforded the title compound (II) (1.25 g, 70%) from p-anisaldehyde (1.1 ml, 10 mmol) (m.p. 147 °C). IR (KBr plate): ν = 3400, 1650 cm⁻¹; ¹H NMR (CDCl₃); δ = 6.8 (m, 4H, Ar-H), 6.5 (br, 1H, NH), 4.2 (d, 2H, CH₂), 3.5 (s, 3H, OCH₃), 2.1 (s, 3H, CH₃); MS: Molecular ion at m/z = 179.

**N-(2,5-Dimethoxybenzyl) acetamide (III)**

The general procedure yielded III (1.335 g, 64%) from 2,5-dimethoxybenzaldehyde (1.66 g, 10 mmol). The product purified by TLC on silica gel using chloroform-hexane (m.p. 63 °C). IR (Neat): ν = 3330, 1660 cm⁻¹; ¹H NMR (CDCl₃); δ = 6.7 (q, 3H, Ar-H), 6.3 (br, 1H, NH), 3.8 (d, 2H, CH₂), 3.6 and 3.5 (two singlets, 6H, two OCH₃), 2.1 (s, 3H, CH₃); MS: Molecular ion at m/z = 209.

**N-[p-(N,N-Dimethylamino) benzyl] acetamide (IV)**

The general procedure yielded (IV) (1.65 g, 86%) from p-(N,N-dimethylamino) benzaldehyde (1.49 g, 10 mmol). The product was separated by TLC on silica gel using ethyl acetate-hexane (m.p. 70 °C). IR (KBr plate): ν = 3410, 1670 cm⁻¹; ¹H NMR (CDCl₃); δ = 7.4 (m, 4H, Ar-H), 6.9 (br, 1H, NH), 4.3 (d, 2H, CH₂), 3.1 (s, 6H, 2 CH₃), 2.1 (s, 3H, CH₃); MS: Molecular ion at m/z = 192.
N-(1-Naphthylmethyl) acetamide (V)

The general procedure yielded (V) (0.855 g, 43%) from a-naphthaldehyde (0.945 g, 10 mmol). The product was chromatographed using ethyl acetate-benzene (m.p. 133-135 °C, lit. [15], m.p. 134 °C). IR (KBr plate): $v = 3400$, 1680 cm$^{-1}$; $^1$H NMR (CDCl$_3$); $\delta = 7.4$ (m, 7 H, Ar-H), 6.8 (br, 1 H, NH), 4.4 (d, 2 H, CH$_2$), 2.0 (s, 3 H, CH$_3$); MS: Molecular ion $m/z =$ 199.

N-(2-Phenylethyl) acetamide (VI)

The general procedure yielded (VI) (0.962 g, 59%) from phenylacetaldehyde (1.2 g, 10 mmol). The product was purified by TLC on silica gel using ethyl acetate-benzene (m.p. 43 °C, lit. [16], m.p. 42-44 °C). IR (KBr plate): $v = 3400$, 1700 cm$^{-1}$; $^1$H NMR (CDCl$_3$); $\delta = 7.3 - 7.0$ (m, 5 H, Ar-H), 6.8 (br, 1 H, NH), 3.1 (t, 2 H, CH$_2$), 2.5 (t, 2 H, CH$_2$), 1.9 (s, 3 H, CH$_3$); MS: Molecular ion $m/z =$ 163.

N-Benzylbenzamide (VII)

The general procedure yielded the title compound (VII) (1.68 g, 80%) from freshly distilled benzaldehyde (1.01 ml, 10 mmol). The product was purified by TLC on silica gel using chloroform-hexane (m.p. 105 °C, lit. [17,18], m.p. 105-107 °C). IR (KBr plate): $v = 3300$, 2900-2820, 1640 cm$^{-1}$; $^1$H NMR (CDCl$_3$); $\delta =$ 7.7 (d, 2 H, O-protons on Ar-CO), 7.5-7.1 (m, 8 H, Ar-H), 7.3-7.1 (br, 1 H, NH), 4.5 (d, 2 H, CH$_2$); MS: Molecular ion $m/z =$ 211.

N-(P-Methoxybenzyl) benzamide (VIII)

The general yielded the title compound (VIII) (2.07 g, 86%) from 2-anisaldehyde (1.1 ml, 10 mmol). The product was purified by TLC on silica gel using ethyl acetate-hexane (m.p. 195 °C). IR (KBr plate): $v = 3400$, 2900-2830, 1650 cm$^{-1}$; $^1$H NMR (CDCl$_3$); $\delta = 7.6 - 7.0$ (m, 9 H, Ar-H), 7.2 (br, 1 H, NH), 4.6 (d, 2 H, CH$_2$), 3.8 (s, 2 H, OCH$_3$); MS: Molecular ion $m/z =$ 241.

(C$_{15}$H$_{15}$NO)
Calcd C 74.69 H 6.22 N 5.81% ,
Found C 74.96 H 6.43 N 5.61% .

N-(P-Chlorobenzyl) benzamide (IX)

The general procedure yielded the title compound (IX) (1.98 g, 81%) from P-chlorobenzaldehyde (1.4 g, 10 mmol). The product was purified by TLC on silica gel using ethyl acetate-benzene (m.p. 142-144 °C, lit. [19], m.p. 143 °C). IR (KBr plate): $v = 3300$, 2900-2820, 1640 cm$^{-1}$; $^1$H NMR (CDCl$_3$); $\delta = 7.6 - 7.3$ (m, 9 H, Ar-H), 7.1-7.0 (br, 1 H, NH), 4.5 (d, 2 H, CH$_2$); MS: Molecular ion $m/z =$ 245.5.

N-(P-Brombenzyl) benzamide (X)

The general procedure yielded the title compound (X) (2.38 g, 82%) from P-bromobenzaldehyde (1.85 g, 10 mmol). The product was purified by TLC on silica gel using ethyl acetate-benzene (m.p. 143 °C, lit. [19], m.p. 143 °C). IR (KBr plate): $v = 3300$, 2900-2820, 1640 cm$^{-1}$; $^1$H NMR (CDCl$_3$); $\delta = 7.7 - 7.3$ (m, 9 H, Ar-H), 7.2 (br, 1 H, NH), 4.6 (d, 2 H, CH$_2$); MS: Molecular ion $m/z =$ 290.

N-(P-Nitrobenzyl) benzamide (XI)

The general procedure yielded the title compound (XI) (1.54 g, 60%) from p-nitrobenzaldehyde (1.5 g, 10 mmol). The product was purified by TLC on silica gel using chloroform-hexane (m.p. 156 °C, lit. [20], 155-156 °C). IR (KBr plate): $v = 3300$, 2900-2825, 1680, 1570, 1365 cm$^{-1}$; $^1$H NMR (CDCl$_3$); $\delta =$ 8.1 - 7.7 (m, 9 H, Ar-H), 7.5 (br, 1 H, NH), 4.6 (d, 2 H, CH$_2$); MS: Molecular ion at $m/z =$ 256.

N-(2-Phenylethyl) benzamide (XII)

The general procedure yielded the title compound (XII) (1.46 g, 80%) from phenylacetaldehyde (1.2 g, 10 mmol). The product chromatographed using ethyl acetate-benzene (m.p. 112 °C); IR (KBr plate): $v = 3400$, 2980-2820, 1680 cm$^{-1}$; $^1$H NMR (CDCl$_3$); $\delta =$ 7.3 - 7.0 (m, 10 H, Ar-H), 6.9 (br, 1 H, NH), 3.1 (t, 2 H, CH$_2$), 2.7 (t, 2 H, CH$_2$); MS: Molecular ion at $m/z =$ 225.

(C$_{15}$H$_{15}$NO)
Calcd C 80.00 H 6.67 N 6.22% ,
Found C 79.81 H 6.79 N 6.08% .
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