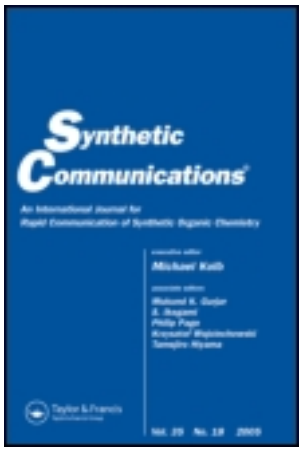

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IMPROVED METHOD FOR DEMETHYLATION OF NITRO-CATECHOL METHYL ETHERS

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IMPROVED METHOD FOR DEMETHYLATION OF NITRO-CATECHOL METHYL ETHERS

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ABSTRACT

Several nitro-catechol compounds, useful as inhibitors of COMT were obtained in excellent yield and purity via an improved procedure for demethylation of the corresponding methyl ethers using aluminium chloride and pyridine in ethyl acetate.

BIA 3-202, [1-(3,4-Dihydroxy-5-nitrophenyl)-2-phenyl-ethanone] (**1**), is a potent and highly selective inhibitor of the enzyme catechol-*O*-methyl-transferase which is currently under clinical development for the treatment of Parkinson's disease.[1] These clinical studies have necessitated the production of multi-kilogramme quantities of BIA 3-202 of sufficient chemical purity to be tested in human patients.

The original five-step synthesis starting from 4-*O*-benzyl vanillin (**2**) is shown in Scheme 1.

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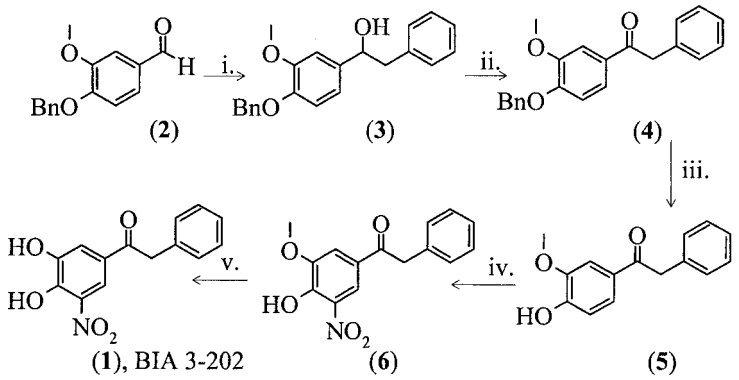

Reagents: i. a) $ArCH_2Cl$, Mg, Et_2O/THF b) H_3O^+, (95%); ii. $Na_2Cr_2O_7$, H_2SO_4, CH_2Cl_2, H_2O, $Bu_4N^+Br^-$, (96%); iii. 30% HBr in AcOH, CH_2Cl_2, (91%); iv. 70% HNO_3, AcOH (72%); v. 48% HBr/AcOH (68%).

Scheme 1. Original synthesis of BIA 3-202.

While efficient, economical and environmentally acceptable alternative procedures for steps ii–iv were subsequently developed for scale-up and synthesis of multi-kilogramme (1–50 kg) batches of BIA 3-202, step v., involving cleavage of the 3-*O*-methyl group of the nitro-catechol methyl ether (**6**) was a principal cause of concern, primarily due to the use of large volumes of corrosive hydrobromic acid, harsh conditions and the relatively low reaction yield. An operationally simple, scaleable, cheap and high-yielding procedure for the demethylation of (**6**) was sought.

The cleavage of aryl methyl ethers to liberate the corresponding phenolic compounds has been reviewed in the literature.[2–4] The apparent simplicity of this commonly found protecting group belies its sheer ruggedness and organic chemists over many decades have been challenged to develop improved methods for its removal. However, the presence of the relatively sensitive nitro-group of the nitro catechol methyl ether (**6**) precludes the use of many of the routine reagents for this transformation and surprisingly, few methods were considered both suitably mild and appropriate for large-scale demethylation of (**6**). In fact complex reaction mixtures were obtained from the attempted demethylation of (**6**) with pyridinium hydrochloride,[5] boron tribromide,[6] sodium cyanide/DMSO[7] or thiophenolate anion.[8]

Notwithstanding, the successful cleavage of aromatic methyl ethers with aluminium chloride alone[9] and some alkyl ortho-hydroxyphenyl

ethers such as vanillin using an aluminium chloride-pyridine mixture have been reported.[10] However, the latter reactions were usually run in dichloromethane and required refluxing for 24 h to achieve good conversion and product yields. Alternative solvents utilised such as benzene, carbon tetrachloride, ethylene chloride and ethyl bromide must be considered unsuitable for the production of pharmaceutical products intended for human use (residual levels of Class 1 solvents in medicinal products are severely limited[11] at $\leq$5 ppm). Of course, even for routine applications, it would be preferable to avoid such toxic solvents.

We therefore undertook a reinvestigation of this reaction with respect to its suitability for the large-scale demethylation of the nitro-catechol methyl ether (**6**) and now report on its general utility for the demethylation of related compounds.

Table 1 summarises the results from these experiments. Using initially chlorinated solvents, it was found that temperature had a profound effect on reaction rate. Whereas the reaction was incomplete in dichloromethane (b.p. 40°C) after reflux over 24 h, the use of either 1,2-dichloroethane at reflux (b.p. 83°C) or 1,1,2,2-tetrachloroethane at 100°C (b.p. 147°C) provided complete conversion of (**6**) to BIA 3-202 in 2 h (no significant by-products or even starting material was found in the crude product by HPLC analysis in each case indicating the 'clean' nature of the reaction). The molar ratio of reactants to reagents was thereafter investigated, and although the ratio 4 : 1.2 : 1 (pyridine : aluminium chloride : (**6**)) was routinely employed, pyridine could be satisfactorily reduced to under three molar equivalents without deleterious effect on

Table 1. Demethylation of Nitro-Catechol Ether (**6**) to BIA 3-202

Run	Solvent	B.P. (°C)	Time (h)	Isolated Yield (%)	Purity BIA 3-202 % (HPLC)[a]
1	Dichloromethane	40	24	79	94
2	1,2-Dichloroethane	83	2	87	>99
3	1,1,2,2-Tetrachloroethane	147	2	85	>99
4	Pyridine	115	0.5	79	>98
5	Methyl ethyl ketone	80	3.5	78	>98
6	Acetone	56	5	72	>98
7	1,4-Dioxan	100	2	70	>97
8	Ethyl acetate	77	1.5	99	>99

[a]See Experimental section.

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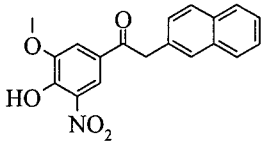
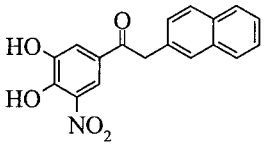
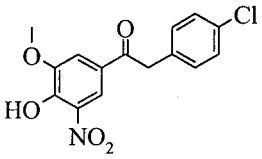
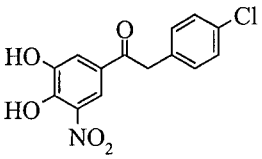
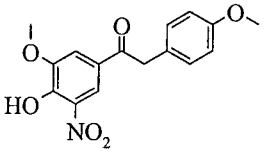
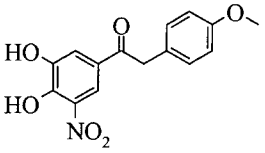
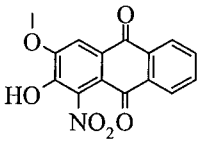
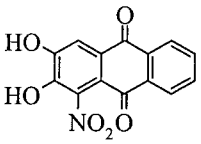
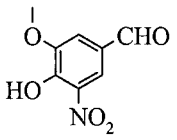
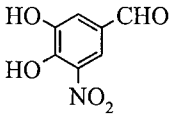
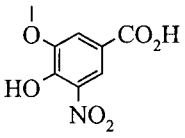
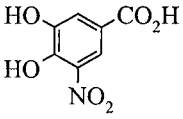
Table 2. Demethylation of Nitro-Catechol Methyl Ethers

Entry	Nitro- Catechol Methyl Ether	Time (h)	Nitro- Catechol Product	Yield (%)
1		2		95
2		2		94
3		2		91[a]
4		2		96
5		2		75
6		3		70

[a]Converted to the 3,4-diacetoxy-5-nitro-derivative (Ac_2O, py, CH_2Cl_2) and purified by recrystallisation.

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product yield. A slight excess of aluminium chloride (1.2 equivalents) was found advantageous.

Interestingly, the reaction could be run in pyridine (Class 2) alone without organic solvent (Run 4). Although the reaction was observed to be complete within 30 min and a reasonable yield of product was obtained, the viscosity of the reaction mixture complicated work-up. The use of 1,4-dioxan (also Class 2) (Run 7) avoided this problem and although there was good conversion after only 2 h, the product yield diminished slightly (70%). Subsequently, we were pleasantly surprised to discover that cheap and readily available, low risk (Class 3) solvents such as methyl ethyl ketone and acetone were also suitable for the reaction, although reaction times were slightly increased. In particular, ethyl acetate was outstanding, affording excellent yields of BIA 3-202 of high purity in relatively short reaction times.

These same reaction conditions were then applied to the demethylation of other nitro-catechol methyl ethers to ascertain its generality. The results are summarised in Table 2. Entry 3 serves to display a further previously unreported advantage of this demethylation procedure; isolated methoxy groups without ortho-hydroxy substituents which would be otherwise cleaved by conventional reagents are unaffected by the aluminium chloride-pyridine reagent. This selectivity therefore allows facile preparation of nitro-catechol compounds containing other isolated methoxy-substituents.

CONCLUSIONS

A simple, economical, selective and high-yielding procedure for the rapid demethylation of nitro-catechol methyl ethers has been developed using reagents and solvents suitable for production of medicinal products. This procedure is superior to other demethylation methodologies especially for larger-scale operations and has been successfully applied to the synthesis of BIA 3-202, a potent inhibitor of catechol-*O*-methyltransferase. The method should prove generally useful for the rapid demethylation of ortho-hydroxy arylmethyl ethers.

EXPERIMENTAL SECTION

Melting points were measured in open capillary tubes on an Electrothermal Model 9100 hot stage apparatus and are uncorrected. NMR spectra were recorded on a Bruker Avance DPX (400 MHz) Spectrometer with solvent used as internal standard, and data are reported

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in the order: chemical shift (ppm), multiplicity (s, singlet; d, doublet; t, triplet; m, multiplet; br, broad), number of protons, approximate coupling constant in Hertz and assignment of a signal. IR spectra were measured with a Bomem Hartmann & Braun MB Series FTIR spectrometer using KBr tablets. Analytical HPLC was performed on a Gilson System equipped with a Model 305 pump and 117 UV detector, LiChrospher 100 RP-18 EcoCART 125-3 Cartridges (Merck) in combination with acetonitrile/water mixtures. Analytical TLC was performed on precoated silica gel plates (Merck 60 Kieselgel F 254) and visualised with UV light. Preparative chromatography was done on Merck 60 Kieselgel (0.063–0.2 mm). Elemental analyses were performed on a Fisons EA 1110 CHNS instrument and all analyses are consistent with theoretical values to be within ±0.4% unless indicated. Solvents and reagents were purchased from Aldrich, Fluka, E. Merck or local sources and used as received.

A typical experimental procedure for the demethylation of the nitro-catechol methyl ethers is exemplified by the following example.

1-(3,4-Dihydroxy-5-nitrophenyl)-2-phenyl-ethanone (1)

To a stirred yellow suspension of 1-(4-hydroxy-3-methoxy-5-nitrophenyl)-2-phenyl-ethanone ((**6**), 50.0 g, 174 mmol) in ethyl acetate (500 ml) at room temperature was added aluminium chloride (27.84 g, 209 mmol) in one portion. To the resulting orange/red suspension was added dropwise pyridine (55.1 g, 56.2 ml, 696 mmol) causing the internal temperature to rise to 45°C. The orange solution was then heated at reflux (77°C) for 2 h and then allowed to cool to 60°C whereupon the reaction mixture was carefully added to a mixture of ice/concentrated hydrochloric acid (200 ml). After stirring at 50°C for 1 h, the mixture was cooled in an ice/water bath for 1 h and then filtered. The filter cake was washed by water and the product then dried (70°C, 0.02 mmHg, 5 h) to afford the title product as a yellow solid, 47.21 g, (99.4%) of m.p. 177.6–178.8°C.

^{1}H NMR (DMSO) δ 10.9 (br s, 2H, 2 × Ar-OH), 8.1 (d, 1H, $J = 2.1$ Hz, Ar-H), 7.6 (d, 1H, $J = 2.1$ Hz, Ar-H), 7.35–7.2 (m, 5H, Ar-H), 4.3 (s, 2H, CH_2).

^{13}C NMR (DMSO) δ 196 (CO), 148.7 (ArC-OH), 146.7 (ArC-OH), 138.2 (ArC-NO_2), 136.0 (quaternary C), 130.7, 129.3, 127.7 (quaternary C), 127.5, 118.4, 117.5, 45.2 (CH_2).

I.R (KBr) 3352 (OH), 1669 (C=O), 1539 (NO_2).

Found: C, 61.63; H, 4.05; N, 5.20%. $C_{14}H_{11}NO_5$ requires: C, 61.54; H, 4.06; N, 5.13%.

HPLC analysis indicated purity >99.9%.

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1-(3,4-Dihydroxy-5-nitrophenyl)-2-(2-naphthyl)-ethanone (Entry 1)

Yellow crystals, m.p. 190–192°C.

^{1}H NMR (DMSO) δ 10.8 (br s, 2H, 2 × Ar-OH), 8.15 (d, 1H, $J = 1.9$ Hz, Ar-H), 7.65 (d, 1H, $J = 1.9$ Hz, Ar-H), 7.75 (s, 1H, Ar-H), 7.4 (dd, 1H, $J = 8.4$, 1.2 Hz, Ar-H), 7.85–7.8 (m, 3H, Ar-H), 7.5–7.45 (m, 2H, Ar-H), 4.5 (s, 2H, CH_2).

^{13}C NMR (DMSO) δ 196.2 (C=O), 148.7 (ArC-OH), 146.9 (ArC-OH), 138.2 (ArC-NO_2), 134.0 (quaternary C), 133.8 (quaternary C), 132.8 (quaternary C), 129.3, 129.1, 128.7, 128.4, 128.5, 127.1, 126.7, 126.6 (quaternary C), 118.3, 117.6, 45.3 (CH_2).

I.R. (KBr) 3398 (OH), 1684 (C=O), 1548 (NO_2).

Found: C, 66.83; H, 4.06; N, 4.22%. $C_{18}H_{13}NO_5$ requires: C, 66.87; H, 4.05; N, 4.33%.

HPLC analysis indicated purity 98.7%.

1-(3,4-Dihydroxy-5-nitrophenyl)-2-(4-chlorophenyl)-ethanone (Entry 2)

Yellow crystals, m.p. 162–164°C.

^{1}H NMR (DMSO) δ 10.9 (br s, 2H, 2 × Ar-OH), 8.1 (d, 1H $J = 1.9$ Hz, Ar-H), 7.6 (d, 1H, $J = 1.9$ Hz, Ar-H), 7.4 (d, 2H, $J = 8.3$ Hz, Ar-H), 7.3 (d, 2H, $J = 8.3$ Hz, Ar-H), 4.4 (s, 2H, CH_2).

^{13}C NMR (DMSO) δ 195.8 (C=O), 148.7 (ArC-OH), 146.8 (ArC-OH), 138.2 (ArC-NO_2), 135.1 (quaternary C), 132.3 (ArC-Cl), 130.2, 129.2, 127.6 (quaternary C), 118.2, 117.5, 44.3 (CH_2).

I.R. (KBr) 3374 (OH), 1670 (C=O), 1539 (NO_2).

Found: C, 54.91; H, 3.27; N, 4.45%. $C_{14}H_{10}ClNO_5$ requires: C, 54.65; H, 3.28; N, 4.55%.

HPLC analysis indicated purity 99.6%.

1-(3,4-Diacetoxy-5-nitrophenyl)-2-(4-methoxyphenyl)-ethanone (Entry 3)

White crystals, m.p. 88–89°C.

^{1}H NMR ($CDCl_3$) δ 8.6 (d, 1H, $J = 2$ Hz, Ar-H), 8.1 (d, 1H, $J = 2$ Hz, Ar-H), 7.2 (d, 2H, $J = 8.6$ Hz, Ar-H), 6.9 (d, 2H, $J = 8.6$ Hz, Ar-H), 4.25 (s, 2H, CH_2), 3.8 (s, 3H, Ar-OCH_3), 2.4 (s, 3H, -$COCH_3$), 2.35 (s, 3H, -OCH_3).

^{13}C NMR ($CDCl_3$) δ 194.3 (C=O), 168.1 (-OCO-), 167.3 (-OCO-), 159.5 (ArC-OMe), 145.2 (ArC-OAc), 141.0 (ArC-OAc), 134.7 (quaternary C),

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131.0, 125.3 (quaternary C), 123.5, 115.0, 55.8 (Ar-OCH_3), 45.2 (CH_2), 21.1 (CH_3CO_2-), 21.0 (CH_3CO_2-).

I.R. (KBr) 1779 (C=O, acetate), 1687 (C=O), 1539 (NO_2).

Found: C, 58.51; H, 4.40; N, 3.53%. $C_{19}H_{17}NO_8$ requires: C, 56.96; H, 2.39; N, 4.74%.

HPLC analysis indicated purity 99.4%.

2,3-Dihydroxy-1-nitro-9,10-anthraquinone (Entry 4)

Orange crystals, m.p. decomposes above 255°C.

^{1}H NMR (DMSO) δ 11.6 (br s, 2H, 2 × Ar-OH), 8.15 (m, 1H, Ar-H), 8.1 (m, 1H, Ar-H), 7.9 (m, 2H, Ar-H), 7.7 (s, 1H, Ar-H).

^{13}C NMR (DMSO) δ 181.5 (C=O), 180.2 (C=O), 153.6 (ArC-OH), 144.6 (ArC-OH), 138.7 (ArC-NO_2), 135.4, 135.3, 133.7 (quaternary C), 133.3 (quaternary C), 127.4, 127.3, 126.7 (quaternary C), 117.6 (quaternary C), 113.6.

I.R. (KBr) 3384, 3307 (OH), 1672 (C=O), 1543 (NO_2).

Found: C, 56.84; H, 2.76; N, 4.40%. $C_{14}H_7NO_6.0.5H_2O$ requires: C, 56.96; H, 2.39; N, 4.74%.

HPLC analysis indicated purity 99.9%.

3,4-Dihydroxy-5-nitrobenzaldehyde (Entry 5)

Yellow-orange crystals, m.p. 142–143°C (lit[12] m.p. 145–146°C).

^{1}H NMR (DMSO) δ 10.9 (br s, 2H, 2 × Ar-OH), 9.8 (s, 1H, -CHO), 8.0 (d, 1H, $J = 2$ Hz, ArH), 7.5 (d, 1H, $J = 2$ Hz, ArH).

I.R. (KBr) 3223 (OH), 1680 (C=O), 1545 (NO_2).

HPLC analysis indicated purity 99.2%.

3,4-Dihydroxy-5-nitrobenzoic Acid (Entry 6)

Orange crystals, m.p. 222–224°C (lit[13]. m.p. 224–226°C).

^{1}H NMR (DMSO) δ 13.7 (br s, 1H, -CO_2H), 10.9 (br s, 2H, 2 × Ar-OH), 8.5 (d, 1H, $J = 2.1$ Hz), 8.2 (d, 1H, J=2.1 Hz).

I.R. (KBr) 3450 (OH), 1710 (C=O), 1546 (NO_2).

HPLC analysis indicated purity 98.9%.

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