Regioselective Dealkylation of 2-Alkoxybenzoic Acid and Its Amide Derivatives with Aliphatic Amines

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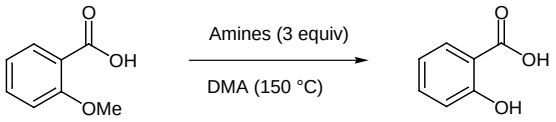
Abstract: The methoxy group of *o*-anisic acid was cleaved with aliphatic amines in aprotic dipolar solvents. This cleavage reaction was especially smooth when piperazine in dimethylacetamide was used. This method was applicable to a variety of dealkylations of *o*-alkoxybenzoic acid and ist amide derivatives with high regioselectivity.

Key words: amides, carboxylic acids, cleavage, ethers, regioselectivity, *o*-anisic acid

For the demethylation of *o*-anisic acid (*o*-methoxybenzoic acid) and amide derivatives, dealkylation methods used for the *O*-alkyl protective group of phenols[1] can generally be applied. A number of methods have been reported using reagents such as Brønsted acid,[2] Lewis acid,[3–7] alkali metals or organic metals.[8–12] However, the use of aliphatic amines as a nucleophile has not been reported in the dealkylation of the *O*-alkyl protective group of phenols.

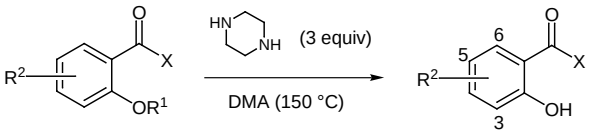
Buchanan and coworkers have succeeded in the specific demethylation of *o*-anisic acid using lithium iodide or pyridinium hydroiodide in boiling pyridine.[14,15] The reaction was explained in terms of nucleophilic attack of the iodide ion on the methyl group with activation of the ether oxygen by intramolecular hydrogen bonding.[16,17]

In a preliminary investigation, we found that heating *o*-anisic acid and hexylamine in 2-methoxyethyl ether at 150°C led to a 30% of salicylic acid accompanied by 28% of *N*-hexyl-*o*-anisamide. In order to systematically investigate this interesting cleavage of the methoxy group, we attempted to find the optimal reaction conditions and to clarify the scope and limitations of this useful method for the dealkylation of *o*-alkoxybenzoic acid and amide derivatives.



Scheme 1

Table 1 shows the results of the reaction of *o*-anisic acid with various amines and solvents. In using hexylamine, the cleavage reaction proceeded predominantly in DMSO, DMF and dimethylacetamide (DMA) (Entries 1–3) although the amide formation was only observed in cumene (Entry 4). The results of various amines in DMA revealed that the use of secondary or tertiary amines was superior to that of primary amines in terms of yield and reaction time (Entries 3, 8, 9). Furthermore, diacidic bases (ethylenediamines) shortened the reaction time (Entries 13, 14) and cyclic amines (piperidine, morpholine) gave higher yields (Entries 15, 16). Consequently, the optimal condition was obtained using piperazine as a diacidic cyclic base in DMA at 150°C (Entry 17).



Scheme 2

Table 2 shows the results of the reaction of various alkoxybenzoic acids and amides with piperazine in DMA. The amide derivatives required a longer time for completion of this demethylation in comparison with acids. The benzyloxy, methoxymethoxy or even ethoxy group was cleaved at the *ortho* position, but the isopropoxy group was inactive (Entries 8–11). In addition, *o*-anisic acid or amide derivatives including a *meta*- or *para*-alkoxy group underwent the selective cleavage of the *ortho*-alkoxy group without affecting other substituents (Entries 12–14, 17–20). However, 2,6-dimethoxybenzoic acid failed to demethylate, and 6-methyl-*o*-anisic acid required a longer reaction time for completion (Entries 15, 16).

Ethyl ester or dimethylamide of *o*-anisic derivatives and the *m*- or *p*-anisic acid were not cleaved under these reaction conditions. The sodium salt of *o*-anisic acid was hardly cleaved (Entries 2, 3, 6, 21, 22). The presence of acidic proton was necessary at the heteroatom adjacent to the *ortho*-carbonyl group to cleave the methoxy group.

This cleavage reaction is considered to occur through nucleophilic attack by amines, since *N*-alkylated amine was isolated from the reaction mixture (Table 1, Entries 8, 11). The necessity of the neighboring acidic proton is strongly suggested to activate the ether oxygen by an internal hydrogen bonding (IHB) during this process. The degree of IHB may be enough to activate the ether oxygen, even though the IHB of *o*-anisic acid is quite small in aprotic dipolar solvents.[16]

The coplanarity between the phenyl ring and carbonyl group is essential for the creation of IHB,[16] and the presence of 6-methyl or methoxy group in the phenyl ring prevents coplanarity through steric hindrance with the carbonyl group[27]. Therefore, the low reactivity of 6-methoxy- or 6-methyl-*o*-anisic acid was caused by the formative difficulty of IHB.

In summary, we have found that the methoxy group of *o*-anisic acid can be cleaved with aliphatic amines in aprotic dipolar solvents. To optimize the reaction conditions, a novel method using piperazine in DMA at 150°C was applied to the *ortho*-selective cleavage of the alkoxy group substituted at benzoic acid or amide derivatives. The present reaction will be particularly useful for large scale synthesis of salicylic acid and amide derivatives that have been used as drug intermediates, because no toxic gases such as methyl halide or methane thiol are generated in this process.

Melting points were measured with Büchi MeltingPoint B-545 apparatus. FT-IR were recorded on Shimadzu FTIR-8100 spectrometer. ^{1}H NMR spectra were recorded at 270 MHz on JEOL JNM-GSX-270 spectrometer and were referenced to TMS. Electron ionization mass spectral (EI-MS) data was recorded on Shimadzu QP-2000 spectrometer. Elemental analysis were carried out on Perkin-Elmer CHN Elemental Analyzer 2700.

4-Methoxymethoxy-2-methoxybenzoic Acid (Table 2, Entry 19)

To a solution of methyl 4-methoxymethoxysalicylate[34] (2.12 g, 10 mmol) in DMF was added NaH (60% oil suspension, 0.44 g, 11 mmol) in portions at 0°C, and the mixture was stirred for 1 h. MeI (1.84 g, 13 mmol) was added to the mixture, and heated at 60°C for 1 h. The mixture was poured into ice-water, and extracted twice with EtOAc. The combined extracts were concentrated in vacuo. The obtained residue was heated with 15% NaOH (20 mL) and EtOH (20 mL) at 60°C for 30 min. After cooling, ice-water (50 mL) and $KHSO_4$ (13 g) were added, and resulting precipitate was collected by filtration. Recrystallization from EtOAc/*i*-Pr_2O gave the title compound as colorless prisms; yield: 3.20 g (70%); mp 77°C.

MS: *m*/*z* = 212 (M^+), 150 (M − 62).

^{1}H NMR ($CDCl_3$): δ = 3.50 (s, 3 H, 2-OCH_3), 4.06 (s, 3 H, CH_2CH_3), 5.24 (s, 2 H, OCH_2O), 6.70 (d, 1 H, *J* = 2 Hz, H-3), 6.80 (dd, 1 H, *J* = 2 Hz, 9 Hz, H-5), 8.12 (d, 1 H, *J* = 9 Hz, H-6), 10.48 (br, 1 H, OH).

IR (KBr): ν = 2995, 1705, 1663, 1614, 1574, 1412, 1157, 1012 cm^{-1}.

Ethyl 4-(2,4-Dimethoxybenzoylamino)benzoate (Table 2, Entry 20)

A mixture of 2,4-dimethoxybenzoylchloride (2.21 g, 11 mmol) and ethyl 4-aminobenzoate (1.82 g, 11 mmol) in 1,2-dichloroethane (40 mL) was heated to reflux for 6 h. After cooling, the mixture was washed with 1 N HCl, satd aq $NaHCO_3$ solution and brine. The organic extract was dried ($MgSO_4$), and the solvent was removed in vacuo. Recrystallization from EtOAc gave the title compound as colorless needles; yield: 3.20 g (88%); mp 132°C.

MS: *m*/*z* = 329 (M^+), 284 (M − 45), 165 (M − 164).

^{1}H NMR (DMSO-d_6): δ = 1.32 (t, 3 H, *J* = 7 Hz, OCH_2CH_3), 3.85 (s, 3 H, OCH_3), 3.95 (s, 3 H, OCH_3), 4.30 (q, 2 H, *J* = 7 Hz, OCH_2CH_3), 6.68 (dd, 1 H, *J* = 2 Hz, 8 Hz, H-5), 6.71 (d, 1 H, *J* = 2 Hz, H-3), 7.74 (d, 1 H, *J* = 8 Hz, H 6), 7.86−7.96 (m, 4 H_{arom}), 10.21 (br s, 1 H, NH).

Table 1 Cleavage of *o*-Anisic Acid with Various Amines and Solvents (Scheme 1)

Entry	Solvent	Amine	Reaction Time (h)	Yield (%)[a,b]
1	DMSO	$C_6H_{11}NH_2$	5	30
2	DMF	$C_6H_{11}NH_2$	6	51
3	Dimethylacetamide (DMA)	$C_6H_{11}NH_2$	6	55
4	Cumene	$C_6H_{11}NH_2$	24	0[c]
5	1,1,2,2-Tetrachloroethane	$C_6H_{11}NH_2$	24	8
6	Ethyleneglycol	$C_6H_{11}NH_2$	24	0[d]
7	2-Methoxyethyl ether	$C_6H_{11}NH_2$	24	30[e]
8	DMA	$C_6H_{11}NHMe$	3	72[f]
9	DMA	$C_6H_{11}NMe_2$	3	73
10	DMA	*sec*- Bu_2NH	16	35[g]
11	DMA	Bzl_2NH	4	62[h]
12	DMA	$C_6H_5NH_2$	24	0[d]
13	DMA	$MeNHCH_2CH_2NHMe$	1	78
14	DMA	$Me_2NCH_2CH_2NMe_2$	2	77
15	DMA	Piperidine	4	86
16	DMA	Morpholine	3	80
17	DMA	Piperazine	1	84
18	DMA (130 °C)	Piperazine	3	74

[a] Yield of isolated product.
[b] All compounds were identified with authentic samples by ^{1}H NMR spectroscopy and melting points.
[c] *N*-hexyl-*o*-anisamide was isolated in 40% yield.
[d] A complex mixture was obtained.
[e] *N*-hexyl-*o*-anisamide was isolated in 28% yield.
[f] *N*,*N*-Dimethylhexylamine was isolated in 63% yield.
[g] Methyl *o*-anisate was isolated in 12% yield.[18]
[h] Dibenzylmethylamine was isolated in 60% yield.

Table 2 Cleavage of Anisic Acid and Amide Derivatives with Piperazine in Dimethylacetamide (Scheme 2)

Entry	Anisic Acid and Anisamide Derivatives			Reaction Time (h)	Yield (%)[a]	mp (°C)	
	X	R^1	R^2			found	reported
1	OH	Me	H	1	84	160	160[19]
2	ONa	Me	H	24	12[b]	159	–
3	OEt	Me	H	24	0[c]	–	–
4	NH_2	Me	H	8	74	142	144[20]
5[21]	NHMe	Me	H	13	67	88	88[22]
6[23]	NMe_2	Me	H	24	0[c]	–	–
7[24]	NHPh	Me	H	5	95	135	135[25]
8	OH	Et	H	12	74	159	160[19]
9	OH	*i*-Pr	H	24	0[c]	–	–
10[26]	OH	MOM[d]	H	0.5	93	160	160[19]
11	OH	Bzl	H	1	91	159	160[19]
12	OH	Me	3-MeO	0.2	94	150	152[27]
13	OH	Me	4-MeO	0.2	89	161	161[28]
14	OH	Me	5-MeO	1	93	142	141[29]
15	OH	Me	6-MeO	18	0[e]	–	–
16[30]	OH	Me	6-Me	10	52	172	172[31]
17[32]	OH	Me	4-BzlO	0.2	93	183	182[32]
18[33]	OH	Bzl	4-BzlO	0.5	95	183	182[32]
19	OH	Me	4-MOMO	0.5	93[f]	143	–
20	*p*-NHPhCO_2Et	Me	4-MeO	4	96[g]	193	–
21		*m*-anisic acid		24	0[c]	–	–
22		*p*-anisic acid		24	0[c]	–	–

[a] Yield of isolated product.
[b] Starting material was recovered in 81% yield as a free acid. The product and the starting material were separated by column chromatography (silica gel, $CHCl_3$ /MeOH, 9:1).
[c] Starting material was recovered.
[d] MOM: methoxymethyl.
[e] Complex mixture was obtained, and the starting material was recovered in 5% yield.
[f] MS: *m/z* = 198 (M^+), 180 (M − 18), 150 (M − 48).
^{1}H NMR ($CDCl_3$): δ = 3.49 (s, 3 H, OCH_3), 5.22 (s, 2 H, OCH_2O), 6.60 (dd, 1 H, *J* = 2 Hz, 9 Hz, H-5), 6.64 (d, 1 H, *J* = 2 Hz, H-3), 7.72 (d, 1 H, *J* = 9 Hz, H-6). The methylene signal at δ = 5.22 showed NOE correlation to H-3 at δ = 6.64 and H-5 at δ = 6.60, respectively.
IR (KBr): ν = 2995, 1661, 1622, 1456, 1260, 1146, 1073, 994 cm^{-1}.
Anal. Calcd for C, 54.55; H, 5.09. Found: C, 54.33; H, 5.03.
[g] MS: *m/z* = 315 (M^+), 270(M − 45), 165(M − 150), 151(M − 164).
1H NMR (DMSO-d_6): δ = 1.33 (t, 3 H, *J* = 7 Hz, OCH_2CH_3), 3.81 (s, 3 H, OCH_3), 4.30 (q, 2 H, *J* = 7 Hz, OCH_2CH_3), 6.53 (d, 1 H, *J* = 2 Hz, H-3), 6.58 (dd, 1 H, *J* = 2 Hz, 9 Hz, H-5), 7.98 (d, 1 H, *J* = 9 Hz, H-6), 7.85−7.98 (m, 4 H_{arom}), 10.46 (br, 1 H, NH), 12.14 (br, 1 H, OH). The methyl signal at δ = 3.81 showed NOE correlation to H-3 at δ = 6.53 and H-5 at δ = 6.58, respectively.
IR (KBr): ν = 3316, 2995, 1713, 1615, 1541, 1516, 1254, 1175, 1105, 1030 cm^{-1}.
Anal. Calcd for C, 69.12; H, 5.39. Found: C, 69.02; H, 5.55; N, 5.45.

IR (KBr): ν = 3349, 1713, 1659, 1595, 1541, 1291, 1250, 1123 cm^{-1}.

Dealkylation of 2-Alkylsubstituted o-Anisic Acids; General Procedure

A mixture of the starting material (1 equiv) and piperazine (3 equiv) in DMA (1 mL/mmol) was heated at 150°C under argon. When the starting material had disappeared (TLC monitoring), the solvent was removed in vacuo, and the residue was acidified with 1 N HCl at 0°C. The resulting precipitate was collected by filtration, washed with H_2O and dried in vacuo.

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