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A novel DMSO-assisted regioselective iodination of aniline analogues

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ABSTRACT

A metal- and oxidant-free electrophilic iodination of aniline analogues was achieved in high to excellent yields at room temperature in MTBE with 0 or 3.5 equivalents of DMSO. Examined substituents include *N*-alkyl, *N*,*N*-dialkyl, *N*-morpholinyl and *N*-piperazinyl as well as methyl, Br, CN and CO_2CH_3 aryl ring substitutions.

Iodoanilines are important intermediates in the syntheses of anti-inflamatory [1] and antimicrobial compounds [2]. They also serve as intermediates of organic dyes used in non-linear optics [3], and of *N*-heterocyclic carbene ligands employed in a variety of organometallic complexes, which include the second and third generation Grubbs olefin metathesis catalysts [4]. The superior reactivity of iodoanilines over bromo and chloro analogues makes them ideal for the palladium-catalysed Stille, Suzuki, and Heck cross-coupling reactions [5].

Although iodine and iodide are inexpensive and environmentally friendly sources of iodonium ions, both are hampered by the need to employ potentially toxic and expensive co-reagents. Numerous methodologies are available for the iodination of aniline, which typically require a combination of iodine or iodide with a co-oxidant [6]. These include oleum [7a], $KMnO_4$ [7b], $KClO_3$/HCl [7c], KIO_3/HCl [7d], H_2O_2 [7e], $Fe(NO_3)_3$ [7f], H_5IO_6 [7g], F-TEDA-BF_4 [7h], SPC [7i], and catalytic $H_5PV_2Mo_{10}O_{40}$ with O_2 [7j].

An alternative, non-oxidative method involving $HgCl_2$ and iodine was also used to iodinate aniline; the active iodonium ion came from the exchange reaction of iodide for the chloride of Hg (II) [8a]. Interhalogens, such as ICl and IBr, in conjunction with the Lewis acid catalyst $In(OTf)_3$ were also reported to be effective in the iodination of aniline and its analogues (Scheme 1a) [8b]. Furthermore, the iodination of *N*-alkyl and *N*,*N*-dialkyl aniline derivatives was reported using four equivalents of iodine in a 1:1 mixture of pyridine and 1,4-dioxane (Scheme 1b) [9].

Previous reports of the iodination of anilines have featured two types of aniline analogues, namely aniline itself, as well as *N*-alkyl- and *N*,*N*-dialkylanilines. To the best of our knowledge, the direct iodination of aniline analogues containing various electron-donating and withdrawing substituents has not been reported. A general methodology covering these substituents as well as those with *N*-alkyl-, *N*,*N*-dialkyl- and heterocyclic aliphatic rings, such as morpholine and piperazine - extending from the nitrogen of aniline, would be highly desirable. Furthermore, any elimination of oxidants, especially those that are metal-based or the employment of heavy metal salts in neutralisation of the HI by-product, and a reduction in the amounts of elemental iodine employed would also be beneficial. As such, we report herein a metal- and oxidant-free methodology for the iodination of aniline analogues using 1.5 to 2.6 equivalents of elemental iodine with 0 or 3.5 equivalents of DMSO as an additive at room temperature in MTBE (Scheme 1c).

Among the solvents studied for the model iodination of methyl 2-aminobenzoate **11** with 1.5 equivalents of iodine at room temperature, MTBE, acetonitrile, diethyl ether and DMSO all gave excellent *para*-selectivity for methyl 2-amino-5-iodobenzoate **11a** (Table 1, entries 4, 7, 11 and 13). Other solvents, including methanol, ethanol, chlorinated solvents, alkanes, 1,4-dioxane and THF showed lower selectivity for **11a**.

During our solvent study, we observed that DMSO was more effective than DMF but the associated difficulties in work-up and product isolation renders it unfavorable. We also observed that

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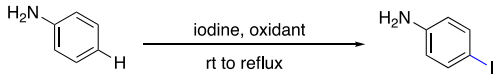
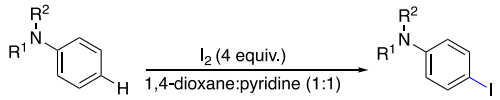
0040-4039/

a) Previous iodination of aniline:[7,8]

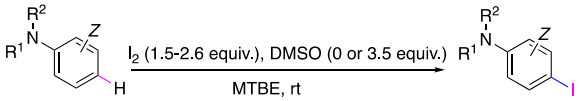


b) Previous iodination of *N*-alkyl and *N*,*N*-alkylanilines:[9]



$R^1 = R^2 = CH_3$, n-hexyl, C_2H_4OH; R^1 = Et, $R^2 = C_2H_4OH$

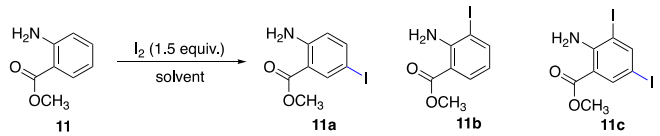
c) This work: I_2 with or without DMSO at room temperature in *t*-butyl methyl ether (MTBE):



R^1 = H, R^2 = Me, Et; R^1, R^2 = Me, Et, morpholine, piperazine
R1, R^2 = H, *Z* = Me, Br, CO_2CH_3, CN

Scheme 1. Selected iodination reactions of aniline and its derivatives.

Table 1
Solvent optimization for the iodination of methyl 2-aminobenzoate.[a]



Entry	Solvent	**11** (%)	**11a** (%)	***para*-Selectivity (%)**
1	CH_3CH_2OH	46	54	99
2	CH_3OH	43	56	99
3	EtOAc	48	52	99
4	CH_3CN	40	60	100
5	Formamide	29	70	98
6	DMF	27	68	93
7	DMSO	24	76	100
8	CH_2Cl_2	49	49	97
9	$CHCl_3$	66	33	98
10	Cyclohexane	46	53	97
11	$(CH_3CH_2)_2O$	52	47	100
12	THF	50	49	99
13	MTBE	54	46	100

[a] Reagents and conditions: iodine (1.5 mmol) was added to a solution of methyl 2-aminobenzoate **11** (1.0 mmol) in solvent (2 mL). The resulting mixture was stirred at room temperature for 1 h, then diluted with diethyl ether (15 mL) and quenched with 10% aqueous $Na_2S_2O_3$ (2 mL). The yield was determined by GC/ MS.

when MTBE was mixed with DMSO, higher yields of the iodinated aniline derivatives were obtained. Subsequently, a study of different DMSO proportions in MTBE was conducted where 3.5 equivalents of DMSO was found to be optimum (Table 2, entry 5). To further ensure that MTBE was the optimum solvent with DMSO, the iodination of **11** was conducted in other solvents that also gave excellent *para*-selectivity. Iodination in acetonitrile and diethyl ether gave **11a** in 65% and 77% yield, respectively (Table 2, entries 6 and 7). The lower yield in acetonitrile rendered it unsuitable and, due to our tropical climate, diethyl ether is also unsuitable despite its slightly higher yield. Based on these findings, the reaction conditions consisting of MTBE as the solvent and 3.5 equivalents of DMSO were adopted in the ensuing study of other aniline analogues.

The results of the room temperature iodination of aniline derivatives are shown in Table 3. The enhancing effect of DMSO toward iodination was not uniform among the highly activated

Table 2
DMSO optimization for the iodination of methyl 2-aminobenzoate **11**.[a]

Entry	Additive	Amount (mmol)	**11** (%)	**11a** (%)
1	DMSO	None	54	46
2	DMSO	1.0	41	59
3	DMSO	2.0	35	65
4	DMSO	3.0	31	69
5	DMSO	3.5	25	75
6	DMSO[b]	3.5	35	65
7	DMSO[c]	3.5	23	77
8	DMSO	4.0	27	73
9	DMSO	5.0	25	75
10	DMF	3.5	44	56
11	Formamide	3.5	37	63

[a] Reagents and conditions: iodine (1.5 mmol) was added to a solution of methyl 2-aminobenzoate **11** (1.0 mmol) and DMSO (1–5 mmol) or DMF or formamide (3.5 mmol each) in MTBE (2 mL). The resulting mixture was stirred at room temperature for 1 h, then diluted with diethyl ether (15 mL) and quenched with 10% aqueous $Na_2S_2O_3$ (2 mL). The yield was determined by GC/ MS.
[b] In acetonitrile (2 mL).
[c] In diethyl ether (2 mL).

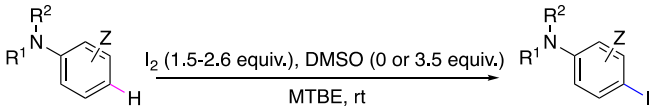
aniline analogues: *N*-methylaniline (**1**), *N*-ethylaniline (**2**), *N*,*N*-dimethylaniline (**3**), *N*,*N*-diethylaniline (**4**), *o*-toluidine (**5**), and *m*-toluidine (**6**), *p*-toluidine (**7**), and aniline (**8**). Except for compounds **4** and **7**, which showed significant enhancement with DMSO, substrates **1**–**3**, **5**, **6** and **8** showed either no enhancement or only a slight enhancement with DMSO (Table 3, entries 1–16). In fact, higher yields of **1a**, **2a**, **6a** and **8a** were obtained without DMSO and interestingly, in the case of **2**, a 30-minute reaction time extension increased the yield from 65% to 78% (Table 3, entry 3). A slightly increased yield was observed in the DMSO-assisted iodination of **3** and **5** (Table 3, entries 5–6 and 9–10). On the other hand, notable enhancement was observed with DMSO for the iodination of **4** and **7**, which gave **4a** and **7a** in 85% and 77% yield, respectively, compared to 70% and 45% yield, respectively, without DMSO (Table 3, entries 7–8 and 13–14). DMSO assistance in the iodination of highly activated aniline systems (**1**–**8**) was not consistent. Nevertheless, the iodination in MTBE without DMSO using 1.5 equivalents of iodine represents a suitable method for obtaining high yields of the iodinated products.

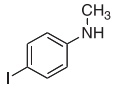
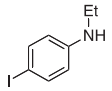
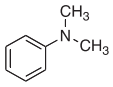
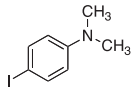
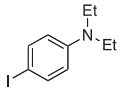
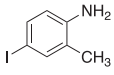
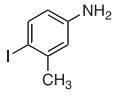
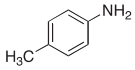
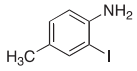
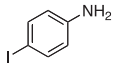
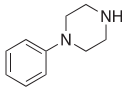
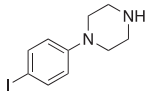
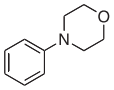
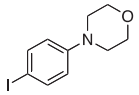
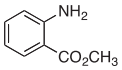
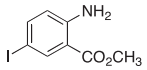
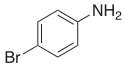
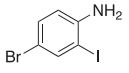
The effect of DMSO enhancement is significant with aniline analogues containing morpholinyl and piperazinyl rings, as well as electron-withdrawing substituents. The iodinations of *N*-phenylpiperazine (**9**) and *N*-phenylmorpholine (**10**) are both enhanced by the addition of DMSO, resulting in the yields of **9a** and **10a** increasing from 61% to 82% and 63% to 91%, respectively (Table 3 entries 17–20). The iodination of electron-withdrawing group containing anilines, such as 2-methyl carboxylate (**11**), 4-bromo (**12**) and 4-cyano (**13**), 2-cyano (**14**) and 3-cyanoanilines (**15**), were best with DMSO, affording **11a**-**15a** in 71–96% yield (Table 3, entries 21–30).

A mechanism for the interaction of DMSO and iodine is proposed in Scheme 2. A halogen bond (HB) is envisaged between the HB-accepting oxygen of DMSO and the sigma hole of iodine (HB-donor). Such an interaction has been demonstrated in the study of the reaction mechanism of iodine-catalysed Michael addition [10], and in the UV–visible spectroscopic study of DMSO and iodine in carbon tetrachloride [11]. The interaction between the oxygen of DMSO and iodine is thought to lead to heterolytic cleavage of the diiodine bond, resulting in an iodonium ion coordinated to the oxygen of DMSO (complex **I**).

In the iodination reactions without DMSO, we postulate that it is the nitrogen of the aniline analogue that coordinates with iodine through a halogen bond between the nitrogen lone pair and the sigma-hole of iodine (complex **II**, Scheme 3). A halogen bond between the oxygen lone pair of MTBE and iodine is also possible;

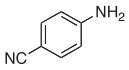
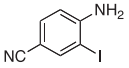
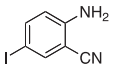
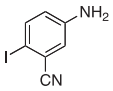
Table 3
Iodination of selected aniline analogues.



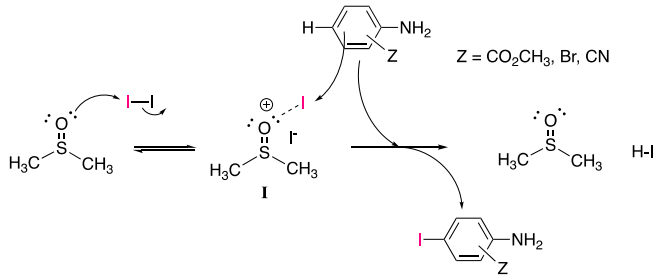
Entry	Substrate	Iodine (mmol)	DMSO (mmol)	Time (h)	Product[a]	Isolated yield (%)
1	 **1**	1.5	0	20 min	 **1a**	74
2	**1**	1.5	3.5	20 min	**1a**	62
3	 **2**	1.5	0	1	 **2a**	78
4	**2**	1.5	3.5	30 min	**2a**	77
5	 **3**	1.5	0	30 min	 **3a**	79
6	**3**	1.5	3.5	30 min	**3a**	81
7	 **4**	1.5	0	30 min	 **4a**	70
8	**4**	1.5	3.5	30 min	**4a**	85
9	 **5**	1.5	0	1	 **5a**	80
10	**5**	1.5	3.5	1	**5a**	83
11	 **6**	1.5	0	30 min	 **6a**	86
12	**6**	1.5	3.5	30 min	**6a**	69
13	 **7**	1.5	0	30 min	 **7a**	45
14	**7**	1.5	3.5	30 min	**7a**	77
15	 **8**	1.8	0	30 min	 **8a**	76
16	**8**	1.8	1.0	30 min	**8a**	62
17	 **9**	2.0	0	3	 **9a**	61
18	**9**	1.8	3.5	3	**9a**	82
19	 **10**	2.0	0	3	 **10a**	63
20	**10**	2.0	3.5	3	**10a**	91
21	 **11**	2.0	0	2	 **11a**	51
22	**11**	2.0	3.5	2	**11a**	81
23	 **12**	2.6	0	2.5	 **12a**	50

(*continued on next page*)

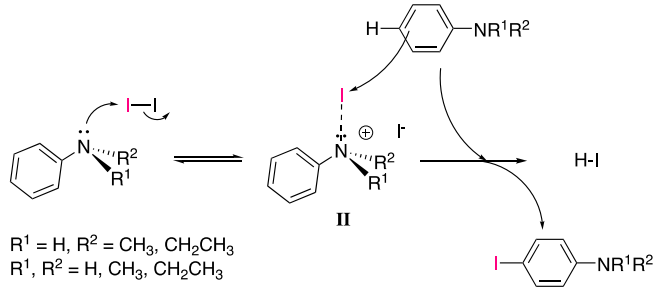
Table 3 (*continued*)

Entry	Substrate	Iodine (mmol)	DMSO (mmol)	Time (h)	Product[a]	Isolated yield (%)
24	**12**	2.6	3.5	2.5	**12a**	71
25	 **13**	2.4	0	5	 **13a**	17
26	**13**	2.4	3.5	3	**13a**	72
27	 **14**	2.2	0	19	 **14a**	10
28	**14**	2.2	3.5	7	**14a**	80
29	 **15**	2.0	0	5	 **15a**	36
30	**15**	2.0	3.5	3	**15a**	96

[a] Reagents and conditions: iodine (1.5 to 2.6 mmol) was added to a solution of the aniline derivative **1**–**15** (1.0 mmol) and DMSO (3.5 mmol) in MTBE (2 mL). The resulting mixture was stirred at room temperature for the time specified. The solution was diluted with diethyl ether (15 mL) and quenched with 10% aqueous $Na_2S_2O_3$ (2 mL). The reactions without DMSO were conducted in the same manner as those with DMSO.



Scheme 2. Proposed interaction of DMSO and iodine during iodination.



Scheme 3. Proposed interaction during iodination without DMSO.

however, this interaction is likely to be less effective due to the steric hindrance imposed by the large *t*-butyl and methyl groups sandwiching the oxygen which would prevent a tight bonding with the bulky iodine.

In conclusion, we have shown that our iodination method is effective on a variety of aniline systems; substituents include alkyl groups on the nitrogen or on the ring, as well as morpholinyl and piperazinyl rings, and various electron-withdrawing groups such as CO_2CH_3, Br and CN. Furthermore, the reactions with DMSO gave higher yields with aniline systems containing electron-withdrawing groups, piperazine and morpholine rings. The mechanistic implication of the DMSO and iodine interaction is intriguing and further studies will examine the nature of this interaction and its implication in other aromatic systems. The results of these studies shall be reported in due course.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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