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A facile preparation of *N*-protected indolaldehydes using a modified Hass procedure

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Abstract—The preparation of a variety of *N*-protected indolaldehydes is reported via the reaction of *N*-protected bromomethylindoles with 2-nitropropane using NaH/DMF.

Indolaldehydes are crucial intermediates for the synthesis of several indole alkaloids.[1] While indole-3-carboxaldehyde can be prepared easily under conventional Vilsmeier formylation conditions, aldehydes at other positions of the indole ring are not easily accessible. Several methods have been developed for the synthesis of indolaldehydes and most are not scalable to any reasonable extent.

Traditionally, indolaldehydes have been prepared from the corresponding indolylmethanol via MnO_2 oxidation.[2] Nagarathnam reported a synthesis of *N*-phenylsulfonylindole-3-carboxaldehyde[3] via hydrolysis of the corresponding dibromomethylindole. Li et al. observed a facile preparation of 1,3-disubstituted indole-2-carboxaldehydes[4] by the reactions of the corresponding dibromomethylindole with DMSO. In that article, the spectral data of the reported indolaldehyde was not given nor was the reaction extended to the synthesis of any other indolaldehydes. However, the methodology has been well exploited for the synthesis of several benzaldehydes.

The synthesis of the highly expensive indole-7-carboxaldehyde was realized through the Bartoli protocol.[5] Srinivasan and co-workers recently observed the synthesis of *N*-protected indolaldehydes through the reactions of bromomethylindole[6a] with tetrabutylammonium dichromate.[6b] A simple synthesis of *N*-tosylindole-4-carboxaldehyde[7] was realized through the reactions of the corresponding bromomethylindole with DMSO in the presence of $NaHCO_3$. Our recent studies on the preparation of indolaldehydes using enamine methodology led us to the synthesis of carbazoles.[8]

Hass and co-workers[9] transformed a variety of substituted benzyl halides into the corresponding benzaldehydes using sodium-2-propane nitronate in ethanol. Later, the methodology was extended to the synthesis of heterocyclic and other carboxaldehydes[10] except for indolaldehydes.

Even though several methods have been introduced for the conversion of benzyl halides into the corresponding aldehydes most have yet to be explored for the indole system. The synthetic utility of indolaldehydes and also the availability of bromomethylindoles prompted us to explore a viable procedure for the smooth transformation of bromomethylindoles into the respective aldehydes.

Initially, the bromo compound **1a′** was reacted with $NaHCO_3$ in dry DMSO at 60 °C for 2 h. The usual workup followed by mass spectral analysis of the crude product indicated the formation of aldehyde **2a** [M^+, 299] and alcohol **3** [M^+, 301] as a mixture (Scheme 1).

All the conditions tried for the oxidation of bromomethylindole **1a′** using dry DMSO in the presence of $NaHCO_3$ yielded the corresponding indolylmethanol **3** as a side product. Hence we decided to explore the sodium-2-propane nitronate technique for the oxidation of *N*-phenylsulfonyl-3-methyl-2-bromomethylindole.

Keywords: Bromomethylindoles; Sodium-2-propane nitronate; Indolaldehydes.
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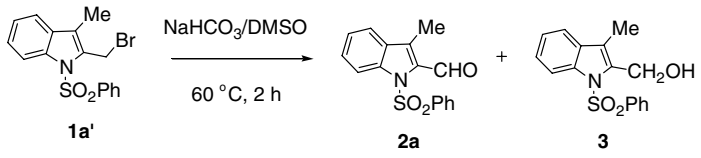
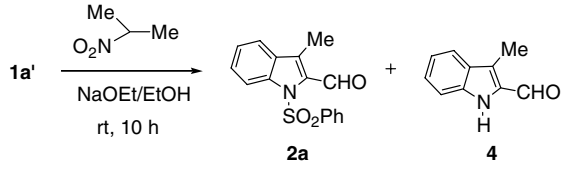
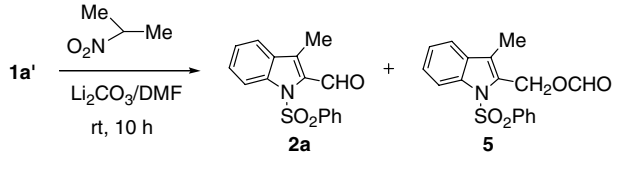
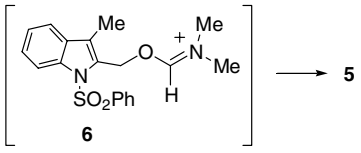


Scheme 1.



Scheme 2.





Scheme 3.

The reaction of the bromo compound **1a**′ with sodium-2-propane nitronate in ethanol at room temperature for 10 h led to the formation of a mixture of the *N*-protected and free aldehydes **2a** and **4** in 40% and 25% yields, respectively (Scheme 2).

In particular, NaOEt being nucleophilic, had cleaved the *N*-phenylsulfonyl unit. Additionally, in the ethanol solvent, the reaction was found to be slow. Hence, we decided to modify the reported Hass conditions by changing the solvent/base.

The reaction of the bromo compound **1a**′ with 2-nitropropane using Li_2CO_3 in DMF at room temperature led to the isolation of the formate ester **5** in 56% yield along with a minor amount of expected aldehyde **2a** (Scheme 3). The formation of compound **5** can be explained via nucleophilic displacement of the bromo compound by the DMF to form the intermediate **6**. The latter on aqueous workup could lead to compound **5**. However, the reaction of 2-nitropropane with Li_2CO_3 in DMF at 60 °C for 2 h, followed by the addition of bromo compound **1a**′ led to the formation of the aldehyde **2a** as the major product along with only a trace amount of formate ester **5**. Finally, the bromo compound **1a**′ was smoothly converted into the corresponding aldehyde using the NaH/DMF conditions.

The various conditions tried and the products obtained are presented in Table 1. In most cases, *N*-protected aldehydes were obtained in reasonable yields with the

Table 1. Preparation of *N*-protected indolaldehydes using 2-nitropropane

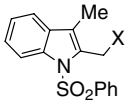
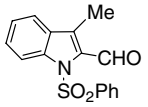
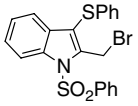
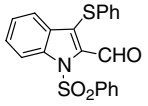
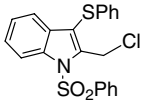
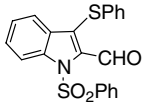
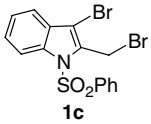
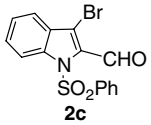
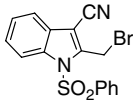
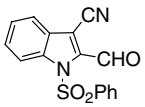
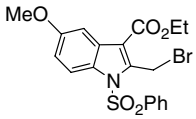
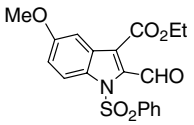
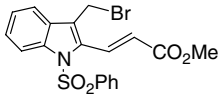
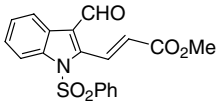
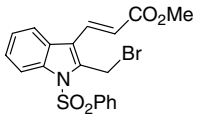
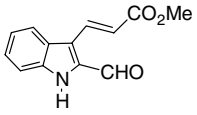
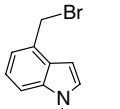
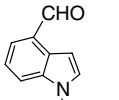
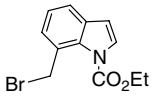
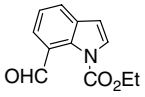
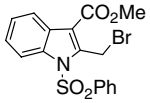
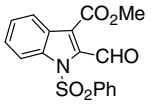
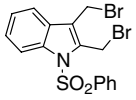
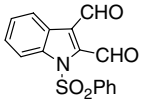
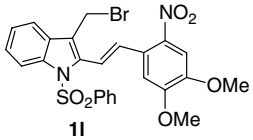
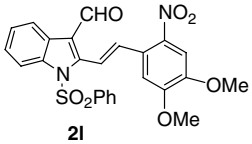
Entry	Bromo/chloroindoles[13]	Conditions	Aldehydes[14]	Yield (%)[a] mp
1	 **1a'** X = Br **1a"** X = Cl	NaH/DMF rt, 2 h	 **2a**[1g]	63 (210 °C) 58
2	 **1b'**	NaOEt/EtOH rt, 24 h NaH/DMF rt, 2 h	 **2b**	58 (110–112 °C) 65 (112 °C)
3	 **1b"**	NaH/DMF rt, 3 h	 **2b**	57 (112 °C)
4	 **1c**	NaOEt/EtOH rt, 15 h NaH/DMF rt, 4 h	 **2c**	42 (142 °C) 65 (142 °C)

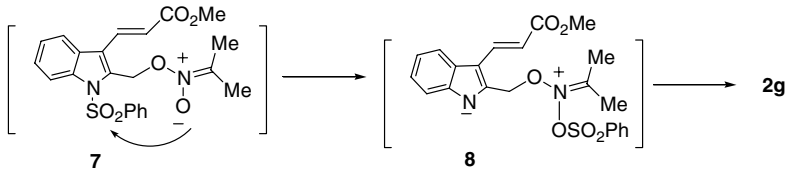
Table 1 (*continued*)

Entry	Bromo/chloroindoles[13]	Conditions	Aldehydes[14]	Yield (%)[a] mp
5	 **1d**	NaH/DMF rt, 15 h	 **2d**	0
6	 **1e**	NaH/DMF rt, 2.5 h	 **2e**	57 (132–134 °C)
7	 **1f**	NaH/DMF rt, 0.5 h	 **2f**	66 (192 °C)
8	 **1g**	NaH/DMF rt, 0.5 h	 **2g**	61 (145–147 °C)
9	 **1h**	NaOEt/EtOH rt, 15 h NaH/DMF rt, 3 h	 **2h**	55 (102 °C) 65
10	 **1i**	NaH/DMF rt, 0.5 h	 **2i**	61 (54–56 °C)
11	 **1j**	NaH/DMF rt, 2 h	 **2j**	63 (134–136 °C)
12	 **1k**	NaH/DMF rt, 3 h	 **2k**[2]	50 (162–164 °C)
13	 **1l**	NaH/DMF rt, 3 h	 **2l**	65 (220 °C)

[a] Isolated yield after column chromatography.

exception of bromo compound **1d** where the oxidation completely failed (entry 5). The dibromo compound **1k** led to the dialdehyde **2k** in 50% yield (entry 12). The *N*-protected indole-7-carboxaldehyde **2i**[1j] was also prepared in 61% yield (entry 10). It should be mentioned that indole-7-aldehyde is used as a crucial starting material for the synthesis of carbazole alkaloids.[11] The reaction of bromo compounds with 2-nitropropane using NaH/DMF produced the corresponding aldehydes in much better yields than the NaOEt/EtOH conditions. The oxidation is much faster using the NaH/DMF conditions. The *N*-protected chloromethylindoles **1a**″ and **1b**″ were also converted into the respective aldehydes in reasonable yields (entries 1 and 3). Even though the *C*-alkylation of 2-nitropropane anion is common to benzylic and heterocyclic chloro compounds,[12] we have not observed any alkylation products with bromomethyl indoles.

In the case of bromo compound **1g**, cleavage of the *N*-phenylsulfonyl group was observed (entry 8). The



Scheme 4.

cleavage of the *N*-protecting group in this case may be due to the intramolecular interaction of the nitronate anion with the *N*-phenylsulfonyl group to form the intermediate **8**, which on elimination may lead to the *N*-free aldehyde **2g** (Scheme 4).

In summary, the existing Hass procedure for the conversion of benzylic halides into aldehydes has been modified for the indole system. Using the modified procedure, the synthesis of several *N*-protected indolaldehydes has been achieved in good yields. Hopefully, the present procedure will be generally applicable to the smooth conversion of benzylic halides into the corresponding aldehydes. For the first time, a mild procedure has been developed for the conversion of *N*-protected bromomethylindoles into the indolylmethyl formate ester using DMF. Further studies on the synthetic utility of the indolaldehydes will be explored.

Acknowledgements

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13. The required bromo/chloroindoles **1a**–**l** were prepared via the allylic bromination/chlorination of the corresponding methylindoles using NBS/NCS in the presence of a catalytic amount of benzoyl peroxide in dry CCl_4 at reflux.
14. Typical experimental procedure for **2b**: A suspension of 50% NaH (78 mg, 1.64 mmol) in dry DMF (5 mL) was treated with 2-nitropropane (0.2 mL, 2.19 mmol) at 0 °C. The mixture was stirred for 15 min at this temperature under a nitrogen atmosphere and was treated dropwise with a solution of bromo compound **1b′** (0.5 g, 1.09 mmol) dissolved in dry DMF (3 mL). After the bromo compound was consumed (monitored by TLC) the reaction mixture was quenched with ice water (10 mL), extracted with $CHCl_3$ (2×10 mL) and dried (Na_2SO_4). Removal of the solvent, followed by column chromatographic purification (silica gel, EtOAc–hexane 1:9) afforded **2b** as a colorless solid (0.28 g, 65%); mp 112 °C; IR (KBr) ν_{max}: 1654, 1562, 1492, 1373, 1180, 1080 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 6.90 (d, $J = 7.8$ Hz, 1H), 6.99–7.02 (m, 1H), 7.10–7.28 (m, 5H), 7.34 (t, $J = 7.8$ Hz, 2H), 7.40 (t, $J = 3.4$ Hz, 1H), 7.47 (t, $J = 7.3$ Hz, 1H), 7.70 (d, $J = 7.3$ Hz, 2H), 8.20 (d, $J = 8.3$ Hz, 1H), 10.48 (s, 1H). MS (EI) *m/z* (%): 393 (M^+, 60%), 378 (75), 252 (89), 223 (88), 204 (100). Anal. Calcd for $C_{21}H_{15}NO_3S_2$: C, 64.10; H, 3.84; N, 3.56; S, 16.30. Found: C, 64.41; H, 4.09; N, 3.65; S, 16.19.
Data for **2c**: mp 142 °C; IR (KBr) ν_{max}: 1685, 1512, 1369, 1257, 1176, 1068 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.24–7.41 (m, 2H), 7.48–7.58 (m, 2H), 7.71–7.75 (m, 2H), 7.85 (d, $J = 7.3$ Hz, 1H), 8.17 (d, $J = 8.3$ Hz, 2H), 10.37 (s, 1H). MS (EI) *m/z* (%): 365 (M^{++}, 15%), 363 (M^+, 13) 333 (9), 256 (11), 224 (19), 105 (100). Anal. Calcd for $C_{15}H_{10}BrNO_3S$: C, 49.47; H, 2.77; N, 3.85; S, 8.80. Found: C, 49.37; H, 2.93; N, 3.76; S, 8.73.
Data for **2h**: mp 102 °C; IR (KBr) ν_{max}: 1693, 1577, 1450, 1377, 1184, 1145 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.36–7.43 (m, 4H), 7.48 (t, $J = 7.3$ Hz, 1H), 7.65 (d, $J = 7.3$ Hz, 1H), 7.68 (d, $J = 3.4$ Hz, 1H), 7.79 (t, $J = 4.4$ Hz, 2H), 8.20 (d, $J = 8.3$ Hz, 1H), 10.09 (s, 1H). MS

(EI) *m*/*z* (%): 285 (M^+, 54%), 229 (18), 186 (20), 144 (17), 77 (100). Anal. Calcd for $C_{15}H_{11}NO_3S$: C, 63.14; H, 3.89; N, 4.91. Found: C, 63.05; H, 3.69; N, 4.94.

Data for **2i**: mp 54–56 °C; IR (KBr) ν_{max}: 1739, 1672, 1315, 1041 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.41 (t, $J = 7.3$ Hz, 3H), 4.44 (q, $J = 7.3$ Hz, 2H), 6.66 (d, $J = 3.9$ Hz, 1H), 7.33 (t, $J = 7.6$ Hz, 1H), 7.64 (d, $J = 3.9$ Hz, 1H), 7.71–7.74 (m, 2H), 10.54 (s, 1H). MS (EI) *m*/*z* (%): 217 (M^+, 8%), 186 (11), 106 (41), 83 (40), 58 (100). Anal. Calcd for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.10; N, 6.45. Found: C, 66.48; H, 5.32; N, 6.43.

Data for **2l**: mp 220 °C; IR (KBr) ν_{max}: 1660, 1500, 1250, 1360, 1160 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$): δ 4.04 (s, 3H), 4.12 (s, 3H), 7.42–8.30 (m, 13H), 10.14 (s, 1H). Anal. Calcd for $C_{25}H_{20}N_2O_7S$: C, 60.97; H, 4.09; N, 5.69; S, 6.51. Found: C, 61.23; H, 4.15; N, 5.58; S, 6.64.