The preparation of some heteroaromatic and aromatic aldehydes

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Dedicated to Gurnos Jones on the occasion of his 70th birthday
(received 20 Dec 99; accepted 20 Aug 00; published on the web 28 Aug 00)
DOI: http://dx.doi.org/10.3998/ark.5550190.0001.307

Abstract
Heteroaromatic α- and β-carboxaldehydes were prepared by the formylation with DMF of α-lithio benzofuran, benzothiophene, *N*-methylbenzimidazole and 10-methylphenothiazine obtained by direct lithiation and β-lithio compounds from lithium-bromine exchange. Dialkoxybenzaldehydes were prepared by the formylation of dialkoxybenzenes with hexamethylenetetramine (HMTA) or by the alkylation of dihydroxybenzaldehydes with alkyl bromides or iodides.

Keywords: Heteroaromatic aldehyde synthesis, dialkoxybenzaldehyde synthesis, lithio benzofuran, lithio benzothiophene, formylation, lithium-bromine exchange

Introduction

Heteroaromatic and aromatic aldehydes carrying additional substituents are important as versatile intermediates in the pharmaceutical industry and for organic synthesis in general. Ongoing studies on the synthesis of nitrones[1] required the preparation of heteroaromatic aldehydes and dialkoxybenzaldehydes. As the published methods for preparing many of these compounds are frequently low yielding and/or not suitable for large-scale preparation,[2] we now report the preparation of heteroaromatic aldehydes by the lithiation-formylation approach and of

dialkoxybenzaldehydes by the formylation of dialkoxy-benzenes or by the alkylation of dihydroxybenzaldehydes.

Results and Discussion

General Procedures. *N*-Methylformanilide in the presence of $POCl_3$ has been used for the preparation of heteroaromatic and aromatic aldehydes,[3] but requires that the position of the aromatic ring, at which the formyl group is desired to be introduced, is sufficiently reactive to allow selective formylation.

Direct lithiation and subsequent formylation with DMF is a facile procedure used to prepare heteroaromatic aldehydes with the formyl group adjacent to a heteroatom, regioselectively and in good yields. For example, the lithiation of furans/benzofurans[4a] and benzothiophenes[4b] always occurs at a free a-position.

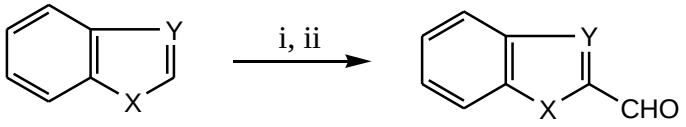
Benzofuran-2-carboxaldehyde (2a), benzothiophene-2-carboxaldehyde (2b) and *N*-methylbenzimidazole-2-carboxaldehyde (2c). Bisagni *et al.*, reported that benzofuran-2-carboxaldehyde **2a** was prepared in 38% yield by the Vilsmeier formylation of benzofuran **1a** with DMF and $POCl_3$.[5] Our work showed that direct lithiation of **1a** with *n*-BuLi, and subsequent formylation with DMF, gave **2a** in 67% yield.

Benzothiophene-2-carboxaldehyde **2b** was previously synthesized in 62% yield by the lithiation of benzothiophene **1b**, followed by the treatment with *N*-methylformanilide.[6] Use of DMF instead of *N*-methylformanilide produced **2b** in 81% yield.

Le Bris *et al.*[7] reported the preparation of *N*-methylbenzimidazole-2-carboxaldehyde **2c** in 50% yield by the SeO_2 oxidation of 1,2-dimethylbenzimidazole, however 1,2-dimethylbenzimidazole is very expensive. By using the lithiation-formylation approach, **2c** was obtained in 44% yield from *N*-methylbenzimidazole.

10-Methylphenothiazine-4-carboxaldehyde (4). 10-Ethylphenothiazine-4-carboxaldehyde was previously prepared in 69% yield by lithiation of 10-ethylphenothiazine with *sec*-BuLi and subsequent formylation with DMF.[8] However, similar treatment of 10-methylphenothiazine **3** with *sec*-BuLi and DMF did not afford 10-methylphenothiazine-4-carboxaldehyde **4**. Using *n*-BuLi instead of *sec*-BuLi as a lithiation reagent gave **4** (40%) together with two further compounds: **3** (12%) and by-product **A** (22%), which were all isolated by column chromatography (Scheme 1). The GC-MS spectra show that **4** and **A** are isomeric 10-methylphenothiazine carboxaldehydes with the same molecular weight and expected mass spectra splitting patterns. By-product **A** was difficult to isolate, because its chromatography characterization is close to that of the starting material **3**. The NMR spectrum of a small specimen of **A** was different from both 10-methylphenothiazine-4-carboxaldehyde and 10-methylphenothiazine-3-carboxaldehyde. Since there are seven aromatic hydrogen peaks overlapped in ^1H NMR spectrum of **A**, it is difficult to determine the position of the formyl

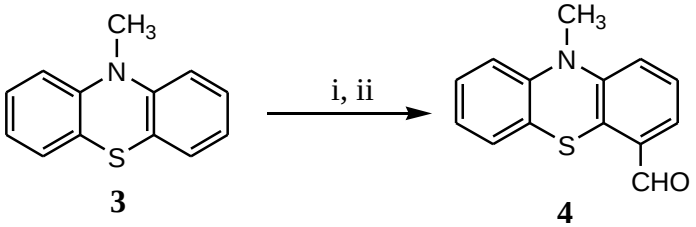
group from the splitting patterns of its ^{1}H NMR spectrum. Therefore, we believe that **A** is either 1- or 2-formylated product.



1a-c **2a-c**

	X	Y	Yield
2a	O	CH	67%
2b	S	CH	81%
2c	NMe	N	44%

i) *n*-BuLi, THF, -78^{o}C, 1 h; ii) DMF, -78^{o}C, 4 h



3 **4**

i) *n*-BuLi, THF, TMEDA, rt, 2 h; ii) DMF, rt, 1 h

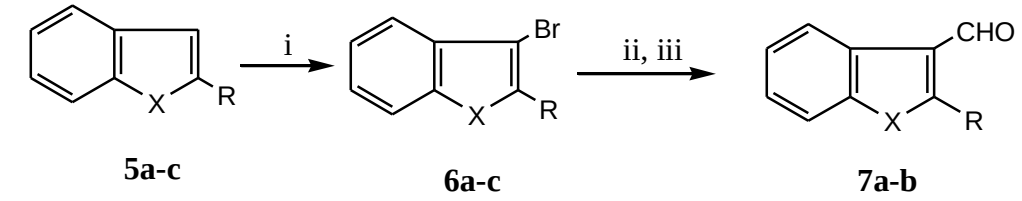
Scheme 1

2-Ethylbenzofuran-3-carboxaldehyde (7a) and 2-methylbenzothiophene-3-carboxaldehyde (7b). Bisagni *et al.* reported that 2-ethylbenzofuran-3-carboxaldehyde **7a** was prepared in 66% yield by the Vilsmeier formylation of 2-ethyl-benzofuran **5a** with DMF and $POCl_3$,[5] but these conditions in our hands gave a complex mixture. However, bromination of **5a**, according to the literature,[9] gave 3-bromo intermediate **6a** in 67% yield. Treatment of **6a** successively with *n*-BuLi and DMF gave the desired 2-ethylbenzofuran-3-carboxaldehyde **7a** in 78% yield. The bromination of 2-methylbenzothiophene **5b**, according to the reported method,[10] gave 3-bromo intermediate **6b**, which was converted into 2-methylbenzothiophene-3-carboxaldehyde **7b** in 42% yield *via* lithium-bromine exchange and formylation with DMF (Scheme 2).

Benzothiophene-3-carboxaldehyde **7c** was previously prepared in low yield (7%) by direct formylation of benzothiophene with *N*-methylformanilide and $POCl_3$.[2a] Campaigne *et al.* prepared **7c** in 36% yield from expensive 3-methylbenzothiophene in three steps.[2b] These reactions are not adaptable for large-scale preparation, as they require peroxide as a reactant and form by-products. According to the literature,[11] bromination of benzothiophene **5c** readily gave

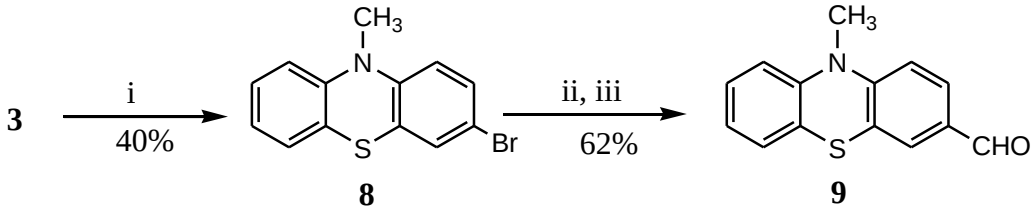
3-bromobenzothiophene **6c** in 60% yield. However, ^{1}H, ^{13}C NMR spectra show that the formylation of **6c** with *sec*-BuLi and DMF afforded an inseparable mixture due to their close R_f values of benzothiophene-3-carboxaldehyde **7c** and benzothiophene-2-carboxaldehyde **2b**. The formation of **2b** is presumably due to the exchange of benzothiophene-3-carbanion with the active proton at the 2-position, leading to benzothiophene-2-carbanion.

10-Methylphenothiazine-3-carboxaldehyde (9). 10-Methylphenothiazine-3-carboxaldehyde **9** was previously prepared in 60% yield by bromination of **3** with Br_2, followed by the subsequent lithium-bromine exchange and formylation with DMF.[12] We found that bromination of **3** with one equivalent of Br_2 gave a mixture of **3**, 3-bromo-10-methylphenothiazine **8** and 3,7-dibromo-10-methylphenothiazine with the ratio as 2:3:1 based on the crude ^{1}H NMR spectrum. The isolated yield of **8** is 40%. Treatment of **8** with *sec*-BuLi, and trapping the intermediate with DMF afforded 10-methylphenothiazine-3-carboxaldehyde **9** in 62% yield (Scheme 2).



5a-c **6a-c** **7a-b**

	X	R	**6**	**7**
a	O	Et	67%	78%
b	S	Me	70%	42%
c	S	H	60%	-



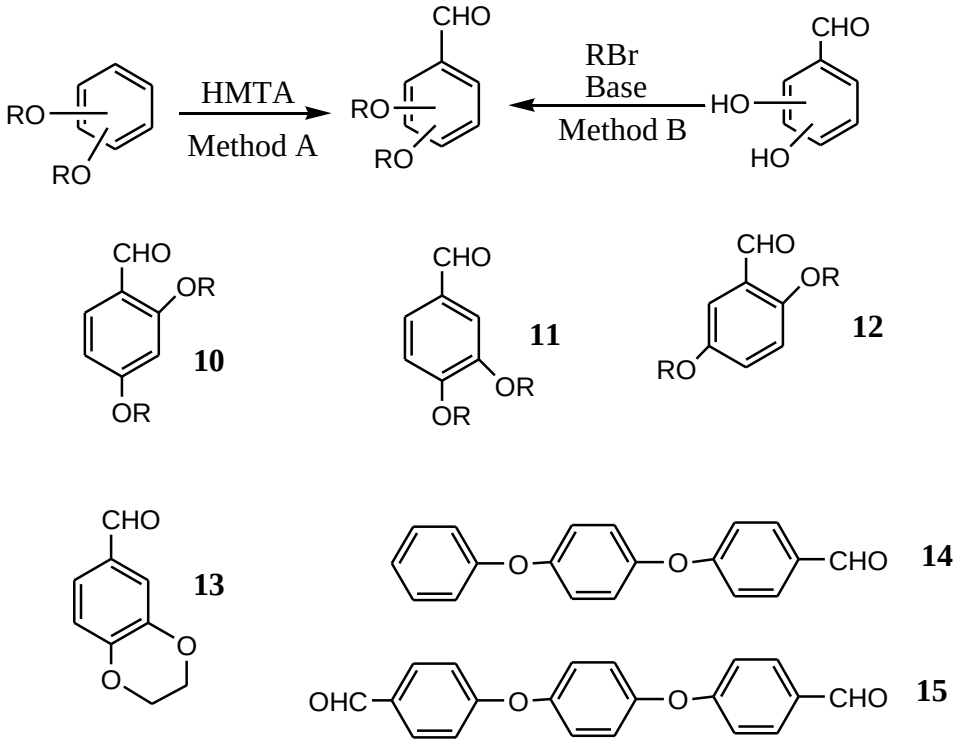
8 **9**

i) Br_2; ii) *n*-BuLi, THF, -78°C, 1 h; iii) DMF, -78°C, 4 h

Scheme 2

Two general methods have been reported for the preparation of dialkoxybenzaldehydes. The first method (method **A**) involves direct formylation of a dialkoxybenzene with hexamethylenetetramine (HMTA): Duff found that heating phenols with HMTA in glycerol in the presence of glyceroboric acid, followed by an aqueous work up gave salicylaldehyde in rather low yields.[13] Suzuki employed modified conditions with a stronger acid, such as

methanesulfonic, trifluoroacetic or polyphosphoric acid as a solvent,[14] which successfully introduced the formyl group onto several electron-deficient aromatic rings.[15] The second method (method **B**) involves alkylation of a dihydroxybenzaldehyde with an alkyl halide under basic conditions, e.g., potassium carbonate[16a-c] or sodium ethoxide [16d] (Scheme 3).



[a] Commercially available. [b] Failed by using either method A or method B. [c] Original target failed but gave cyclized compound 13. [d] Original target failed but gave 14 and 15.
Isolated yield (used method) for **10**, **11** and **12**

compd	R	**10**	**11**	**12**
a	Et	48 (**A**)	[a]	34 (**A**)
b	Ph	57 (**A**)	[b]	(**A**) [d]
c	$PhCH_2$	67 (**B**)	[a]	35 (**B**)
d	$ClCH_2CH_2$	51 (**B**)	(**B**) [c]	[b]
e	$CH^o CCH_2$	90 (**B**)	74 (**B**)	71 (**B**)

Scheme 3

Preparation of 2,4-dialkoxybenzaldehydes (10). 2,4-Diethoxybenzaldehyde **10a** was prepared by the reaction of 2,4-dihydroxybenzaldehyde with ethyl iodide in the presence of sodium

ethoxide.[16d] We prepared **10a** in 48% yield by the formylation of 1,3-diethoxybenzene with HMTA. Similar HMTA formylation of 1,3-diphenoxybenzene afforded novel 2,4-diphenoxybenzaldehyde **10b** in 57% yield.

According to the reported procedure,[16c] 2,4-bis(benzyloxy)benzaldehyde **10c** was produced in 67% yield by the alkylation of 2,4-dihydroxybenzaldehyde with benzyl bromide. A similar alkylation using 1-chloro-2-bromoethane furnished the new compound 2,4-bis(2-chloroethoxy)benzaldehyde **10d** in 51% yield.

Faulques *et al.*[17] reported the preparation of 2-hydroxy-4-(2-propynyloxy)benzaldehyde by using equimolar 2,4-dihydroxy-benzaldehyde and 3-bromo-1-propyne and isolated 2,4-bis(2-propynyloxy)benzaldehyde **10e** as a by-product in low yield (7%). We obtained **10e** in 90% yield with a 2.3:1 molar ratio of 3-bromo-1-propyne to 2,4-dihydroxybenzaldehyde.

Preparation of 3,4-dialkoxybenzaldehydes (11). Novel 3,4-bis(2-propynyloxy)benzaldehyde **11e** was readily prepared in 74% yield by the alkylation of 3,4-dihydroxybenzaldehyde with 3-bromo-1-propyne.

Attempts to prepare 3,4-diphenoxybenzaldehyde **11b** using either method **A** or method **B** failed. No 3,4-bis(2-chloroethoxy)benzaldehyde **11d** was produced by the alkylation of 3,4-dihydroxybenzaldehyde with $ClCH_2CH_2Br$. The cyclized compound 2,3-dihydro-1,4-benzodioxine-6-carboxaldehyde **13** was always obtained in up to 55% yield under various condition of reaction temperature and solvent.

Preparation of 2,5-dialkoxybenzaldehydes (12). 2,5-Diethoxybenzaldehyde **12a** was previously synthesized in 85% yield by the formylation of 1,4-diethoxybenzene with $SnCl_4$ and Cl_2CHOCH_3.[18] We found that the HMTA formylation of 1,4-diethoxybenzene gave **12a** in 34% yield. Similar alkylations of 2,5-dihydroxybenzaldehyde with benzyl bromide and 3-bromo-1-propyne furnished the new compounds **12c** and **12e** in 35% and 71% yields, respectively (Scheme 3).

Attempts to synthesize **12d** using either method **A** or method **B** failed. Formylation of 1,4-diphenoxybenzene with HMTA to **12b** introduced the formyl group onto a terminal benzene ring instead of the central benzene ring to give 4-(4-phenoxyphenoxy)benzaldehyde **14** (yield < 10%) and 4-[4-(4-formylphenoxy)phenoxy] benzaldehyde **15** (yield < 10%). This is presumably due to the fact that i) the central benzene ring is more hindered than the terminal ones; ii) reaction is easier in the *para*-position than the *ortho*-position; iii) the effect of a *meta*-phenoxy group is possibly deactivating.

In summary, multi-gram scale heteroaromatic 2-carboxaldehydes and 3-carboxaldehydes were prepared by a-lithiation or b-lithium-bromine exchange, followed by the formylation with DMF. Dialkoxybenzaldehydes were prepared either by the formylation of dialkoxybenzene with HMTA or by the alkylation of dihydroxybenzaldehydes with alkyl bromides.

Experimental Section

General Procedures. Melting points were determined using a Bristoline hot-stage microscope and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Gemini 300 NMR spectrometer (300 MHz and 75 MHz respectively) in $CDCl_3$ (with TMS for ^{1}H and $CDCl_3$ for ^{13}C as the internal reference). Elemental analyses were performed on a Carlo Erba-1106 instrument.

General procedure for preparation of 2a-c

To a solution of **1a-c** (8.5 mmol) in dry THF (40 mL), was added dropwise *n*-BuLi (6.0 mL, 1.42 M in hexane) at -78 ºC under N_2. The mixture was stirred at -78 ºC for 1 h and then DMF (1.24 g, 17.0 mmol) was added. After 4 h, the mixture was poured into aqueous HCl (4.5% w/v, 80 mL) and stirred at 0 ºC for 0.5 h. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic phase was dried over Na_2SO_4. After removal of the solvent *in vacuo*, the residue was purified by column chromatography with hexane/EtOAc as eluent to give **2a-c**.

Benzofuran-2-carboxaldehyde (2a). Colorless oil (bp[5] 135 ºC/18 mmHg); Yield, 67%; ^{1}H NMR : δ 7.31 (t, *J* = 7.2 Hz, 1H),7.46-7.57 (m, 3H), 7.72 (d, *J* = 7.8 Hz, 1H), 9.84 (s, 1H); ^{13}C NMR : δ 112.4, 117.7, 123.5, 124.0, 126.4, 129.0, 152.4, 156.0, 179.5. MS (EI): 146 (M, 100), 89 (80), 63 (50).

Benzothiophene-2-carboxaldehyde (2b). Colorless needles; Yield, 81%; mp 34-35 ºC (mp[6] 34-34.5 ºC); ^{1}H NMR : δ 7.37-7.60 (m, 2H), 7.82-7.90 (m, 2H), 7.95 (s, 1H), 10.05 (s, 1H); ^{13}C NMR : δ 123.1, 125.1, 126.1, 128.0, 134.4, 138.4, 142.4, 143.1, 184.5.

1-Methyl-1*H*-benzimidazole-2-carboxaldehyde (2c). Colorless needles; Yield, 44%; mp 110-111 ºC (mp[7] 110 ºC); ^{1}H NMR : δ 4.08 (s, 3H), 7.36-7.45 (m, 3H), 7.87-7.90 (m, 1H), 10.06 (s, 1H); ^{13}C NMR : δ 31.0, 110.4, 122.0, 123.8, 126.5, 136.7, 142.4, 145.9, 184.7.

General procedure for preparation of 10-methylphenothiazine-4-carboxaldehyde (4)

To a solution of 10-methyl-10*H*-phenothiazine **3** (2.0 g, 9.4 mmol) in dry ether (100 mL) was added TMEDA (3.0 mL, 20 mmol), followed by dropwised *n*-BuLi (6.0 mL, 1.42 M in hexane) at -78 ºC under N_2. The mixture was stirred at -78 ºC for 2 h and DMF (1.24 g, 17.0 mmol) was then added. After 1 h, the mixture was poured into aqueous HCl (4.5% w/v, 80 mL) and stirred at 0 ºC for 0.5 h. The ether phase was separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic phase was dried over Na_2SO_4. After removal of the solvent *in vacuo*, the residue was separated by column chromatography with hexane/EtOAc (3:1) as eluent and then recrystallized from EtOAc to give **4** (0.9 g, 40%). Yellow needles; mp 110-111 ºC; ^{1}H NMR : δ3.29 (s, 3H), 6.74 (d, *J* = 8.1 Hz, 1H), 6.85-6.93 (m, 2H), 7.09-7.22 (m, 3H), 7.37 (d, *J* = 6.9

Hz, 1H), 10.23 (s, 1H); ^{13}C NMR : δ 35.6, 114.1, 118.4, 122.1, 122.6, 124.4, 126.7, 127.1, 127.9, 128.8, 132.5, 145.6, 146.3, 190.2. Anal. Calcd for $C_{14}H_{11}NSO$: C, 69.68; H, 4.59; N, 5.80. Found: C, 70.01; H, 4.64; N, 5.86.

General procedure for preparation of 7a, 7b and 9

Sodium hydroxide (4.9 g, 123 mmol) was dissolved in glacial acetic acid (300 mL) under N_2. The compound **5a, 5b** or **3** (40 mmol) was added, followed by chloroform (50 mL). Bromine (6.7 g, 40 mmol) in glacial acetic acid (40 mL) was added dropwise during 2 h at 5-10 ºC. The suspension was stirred at room temperature for 2 h and then evaporated to dryness. The residue was dissolved in 10% $NaHCO_3$ and CH_2Cl_2. The aqueous phase was separated and extracted with CH_2Cl_2. The combined organic phase was dried over Na_2SO_4. After removal of the solvent *in vacuo*, the residue was separated by column chromatography with hexane/EtOAc (3:1) as eluent to give **6a, 6b** or **8**.

To a solution of the intermediate **6a, 6b** or **8** (6.0 mmol) in dry THF (40 mL), was added dropwise *s*-BuLi (5.4 mL, 1.1 M in hexane) at -78 ºC under N_2. The mixture was stirred at -78 ºC for 1 h and DMF (0.44 g, 6.0 mmol) was then added. After 1 h, the mixture was poured into aqueous HCl (4.5% w/v, 80 mL) and stirred at 0 ºC for 0.5 h. The THF phase was separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic phase was dried over Na_2SO_4. After removal of the solvent *in vacuo*, the residue was separated by column chromatography with hexane/EtOAc (3:1) as eluent to give **7a**, **7b** or **9**.

3-Bromo-2-ethylbenzofuran (6a). Colorless oil; Yield, 67%; ^{1}H NMR : δ 1.30 (t, *J* = 7.5 Hz, 3H), 2.80 (q, *J* = 7.5 Hz, 2H), 7.20-7.30 (m, 2H), 7.35-7.50 (m, 2H); ^{13}C NMR : δ 11.9, 20.2, 93.4, 111.0, 119.1, 123.0, 124.3, 128.4, 153.4, 156.6. MS (EI): 226 (40), 224 (40), 209 (100), 207 (100).

3-Bromo-2-methylbenzothiophene (6b). Colorless oil; Yield, 70%; ^{1}H NMR: δ 2.49 (s, 3H), 7.26-7.40 (m, 2H), 7.66-7.70 (m, 2H); ^{13}C NMR : δ 15.4, 106.5, 122.0, 122.5, 124.7, 124.8, 135.1, 137.1, 138.4.

2-Ethylbenzofuran-3-carboxaldehyde (7a). Colorless oil; Yield, 78%; ^{1}H NMR : δ 1.41 (t, *J* = 7.5 Hz, 3H), 3.10 (q, *J* = 7.5 Hz, 2H), 7.29-7.32 (m, 2H), 7.42-7.45 (m, 1H), 8.10-8.13 (m, 1H), 10.20 (s, 1H); ^{13}C NMR : δ 12.6, 20.5, 110.8, 116.7, 121.6, 124.3, 124.5, 125.0, 153.7, 171.4, 184.7. MS (EI): 174 (M, 100), 159 (45), 145 (40), 131 (50), 115 (30).

2-Methyl-benzothiophene-3-carboxaldehyde (7b). Colorless oil; Yield, 42%; ^{1}H NMR : δ 2.82 (s, 3H), 7.32 (t, *J* = 7.5 Hz, 1H), 7.41 (t, *J* = 7.5 Hz, 1H), 7.70 (d, *J* = 8.4 Hz, 1H), 8.54 (d, *J* = 8.1 Hz, 1H), 10.27 (s, 1H); ^{13}C NMR : δ 14.1, 121.4, 123.5, 125.0, 125.7, 129.8, 136.6, 137.1, 157.6, 184.2. Anal. Calcd for $C_{10}H_8OS$: C, 68.15; H, 4.58. Found: C, 68.06; H, 4.47.

10-Methylphenothiazine-3-carboxaldehyde (9). Colorless needles; Yield, 62% (based on **8**); mp 86-87 º C (mp[12] 86-87 ºC); ^{1}H NMR : δ 3.34 (s, 3H), 6.74- 6.79 (m, 2H), 6.94- 6.97 (m, 1H),

7.06- 7.14 (m, 2H), 7.52- 7.59 (m, 2H), 9.74 (s, 1H); ^{13}C NMR : δ 35.6, 113.5, 114.7, 122.3, 123.4, 123.7, 127.1, 127.6, 130.3, 130.9, 143.8, 150.8, 189.9.

General procedure for the preparation of dialkoxybenzaldehydes

Method **A**. A mixture of an appropriate dialkoxybenzene (40 mmol) and HMTA (12.8 g, 92 mmol) in the solvents (given below) was heated to reflux for 3 h. After cooling, the mixture was poured into water and extracted with EtOAc. The combined extracts were washed with water, dried over Na_2SO_4. After removal of the solvent *in vacuo*, the residue was separated by column chromatography with hexane/EtOAc (6:1) as eluent to give the dialkoxybenzaldehyde. Formylation of 1,4-diphenoxybenzene with HMTA gave **14** and **15** instead of the desired compound **12b**.

2,4-Diethoxybenzaldehyde (10a). (CH_3COOH/H_2O = 100/20 mL); Colorless needles; Yield, 48%; mp 69-70 ºC (mp[16d] 68-71 ºC); ^{1}H NMR : δ 1.40-1.48 (m, 6H), 4.04-4.12 (m, 4H), 6.40 (s, 1H), 6.49 (d, *J* = 8.7 Hz, 1H), 7.78 (d, *J* = 8.7 Hz, 1H), 10.31 (s, 1H); ^{13}C NMR : δ 14.4, 14.5, 63.8, 63.9, 98.7, 106.1, 118.7, 130.0, 163.0, 165.4, 188.2.

2,4-Diphenoxybenzaldehyde (10b). (CF_3COOH/CH_3COOH = 130/130 mL); Colorless needles; Yield, 57%; mp 52-53 ºC; ^{1}H NMR : δ 6.46 (s, 1H), 6.65 (d, *J* = 6.7 Hz, 1H), 7.00-7.18 (m, 6H), 7.31-7.39 (m, 4H), 7.88 (d, *J* = 8.7 Hz, 1H), 10.39 (s, 1H); ^{13}C NMR : δ 106.8, 111.9, 119.4, 120.2, 121.8, 124.5, 124.9, 130.0, 130.04, 130.2, 54.7, 155.8, 161.7, 164.1, 187.8. Anal. Calcd for $C_{19}H_{14}O_3$: C, 78.60; H, 4.87. Found: C, 78.97; H, 4.87.

2,5-Diethoxybenzaldehyde (12a). (CF_3COOH/CH_3COOH = 30/90 mL); Yield, 34%; mp 61-62 ºC (mp[18] 60-61 ºC); ^{1}H NMR : δ 1.36-1.46 (m, 6H), 4.00 (q, *J* = 6.9 Hz, 2H), 4.09 (q, *J* = 6.9 Hz, 2H), 6.91 (d, *J* = 9.0 Hz, 1H), 7.05-7.11 (m, 1H), 7.29 (d, *J* = 3.0 Hz, 1H), 10.46 (s, 1H); ^{13}C NMR : δ 14.6, 63.9, 64.7, 110.8, 114.3, 123.9, 125.0, 152.7, 156.0, 189.6.

4-(4-Phenoxyphenoxy)benzaldehyde (14). (CF_3COOH/CH_3COOH = 60/50 mL); Colorless needles; Yield, < 10%; mp 47-48 ºC (mp[19] 46-48 ºC); ^{1}H NMR : δ 7.02-7.14 (m, 9H), 7.33-7.38 (m, 2H), 7.85 (d, *J* =8.7 Hz, 2H), 9.91 (s, 1H). ^{13}C NMR : δ 117.1, 118.7, 120.3, 121.8, 123.4, 129.8, 131.1, 131.9, 150.3, 154.2, 157.1, 163.5, 190.7.

4-[4-(4-Formylphenoxy)phenoxy]benzaldehyde (15). Colorless needles; Yield, < 10%; mp 157-158 ºC (mp[19] 157-158 ºC); ^{1}H NMR : δ 7.08 (d, *J* = 8.2 Hz, 4H), 7.14 (s, 4H), 7.86 (d, *J* = 8.2 Hz, 4H), 9.94 (s, 2H). ^{13}C NMR : δ 117.5, 122.0, 131.4, 132.0, 151.8, 163.0, 190.6.

Method **B**. An appropriate dihydroxybenzaldehyde (20 mmol) was mixed with an alkyl bromide (46 mmol) in the presence of K_2CO_3 (anhydrous, 14 g). The reaction temperature, time and solvent are given below. After cooling, the mixture was poured into water and extracted with EtOAc. The combined extracts were washed with water, dried over Na_2SO_4. After removal of the solvent *in vacuo*, the residue was separated by column chromatography with hexane/EtOAc (3:1) as eluent to give the dialkoxybenzaldehyde. Alkylation of 3,4-dihydroxybenzaldehyde with $ClCH_2CH_2Br$ gave **13** instead of the desired compound **11d**.

2,4-Bis(benzyloxy)benzaldehyde (10c). (Reflux, 6 h; BuOH 30 mL); Colorless needles; Yield, 67%; mp 87-88 ºC (mp[16c] 87-88 ºC); ^{1}H NMR : δ 5.05 (s, 2H), 5.08 (s, 2H), 6.57 (s, 1H), 6.59 (d, *J* = 8.3 Hz, 1H), 7.34-7.38 (m, 10H), 7.81 (d, *J* = 8.3 Hz, 1H), 10.37 (s, 1H); ^{13}C NMR : δ 70.2, 99.9, 106.9, 119.3, 127.2, 127.4, 128.15, 128.2, 128.6, 130.3, 135.8, 162.6, 165.1, 188.0.

2,4-Bis(2-chloroethoxy)benzaldehyde (10d). (reflux, 20 h; CH_3COCH_3 60 mL); Colorless needles; Yield, 51%; mp 80-81 ºC; ^{1}H NMR : δ 3.82- 3.90 (m, 4H), 4.28-4.34 (m, 4H), 6.47 (s, 1H), 6.57 (d, *J* = 8.7 Hz, 1H), 7.82 (d, *J* = 8.5 Hz, 1H), 10.35 (s, 1H); ^{13}C NMR : δ 41.5, 68.2, 68.4, 99.7, 106.6, 119.7, 130.4, 162.1, 164.4, 187.9. Anal. Calcd for $C_{11}H_{12}O_3$: C, 50.21; H, 4.61. Found: C, 50.22; H, 4.58.

2,4-Bis(2-propynyloxy)benzaldehyde (10e). (80 ºC, 2.5 h; DMF 80 mL); Colorless needles; Yield, 90%; mp 113-114 ºC (mp[18] 110 ºC); ^{1}H NMR d (DMSO): 3.16 (s, 1H), 3.17 (s, 1H), 4.84 (s, 2H), 4.90 (s, 2H), 6.69 (d, *J* = 8.6 Hz, 1H), 6.78 (s, 1H), 7.73 (d, *J* = 8.6 Hz, 1H), 10.23 (s, 1H); ^{13}C NMRδ(DMSO): 55.8, 56.2, 77.5, 77.6, 77.8, 100.1, 107.5, 119.1, 129.5, 161.0, 163.3, 187.0.

3,4-Bis(2-propynyloxy)benzaldehyde (11e). (80 ºC, 2.5 h; DMF 80 mL); Colorless needles; Yield, 74%; mp 105-106 ºC; ^{1}H NMRδ(DMSO): 3.59 (s, 2H), 4.93 (s, 2H), 4.97 (s, 2H), 7.28 (d, *J* = 7.4 Hz, 1H), 7.55 (s, 1H), 7.63 (d, *J* = 7.8 Hz, 1H), 9.87 (s, 1H); ^{13}C NMR d (DMSO): 56.2, 56.4, 78.7, 78.9, 79.1, 112.0, 113.4, 126.7, 130.3, 147.3, 152.3, 191.7. Anal. Calcd for $C_{13}H_{10}O_3$: C, 72.88; H, 4.71. Found: C, 73.12; H, 4.71.

2,5-Bis(benzyloxy)benzaldehyde (12c). (reflux, 6 h; BuOH 30 mL); Colorless needles; Yield, 35%; mp 89-91 ºC; ^{1}H NMR: δ 5.01 (s, 2H), 5.10 (s, 2H), 6.97 (d, *J* = 9.1 Hz, 1H), 7.13-7.17 (m, 1H), 7.30-7.43 (m, 11H), 10.50 (s, 1H); ^{13}C NMR : δ 70.5, 71.1, 111.5, 114.9, 124.1, 125.4, 127.3, 127.5, 128.0, 128.2, 128.5, 128.6, 136.2, 136.5, 152.9, 155.8, 189.3.

2,5-Bis(2-propynyloxy)benzaldehyde (12e). (80 ºC, 2.5 h; DMF 80 mL); Colorless needles; Yield, 71%; mp 91- 92 ºC; ^{1}H NMR δ (DMSO): 3.43 (s, 1H), 3.50 (s, 1H), 4.80 (s, 2H), 4.92 (s, 2H), 7.28- 7.30 (m, 3H), 10.34 (s, 1H); ^{13}C NMR δ (DMSO): 56.0, 57.1, 78.1, 78.5, 78.6, 78.8, 111.8, 116.2, 123.6, 125.4, 151.7, 154.5, 188.5. Anal. Calcd for $C_{13}H_{10}O_3$: C, 72.88; H, 4.71. Found: C, 72.65; H, 4.74.

2,3-Dihydro-1,4-benzodioxine-6-carboxaldehyde (13). (reflux, 2- 6 h; DMF or CH_3COCH_3 60 mL); Colorless needles; Yield, 55%; mp 51-52 ºC (mp[20] 50-51 ºC); ^{1}H NMR : δ 4.28 (d, *J* = 4.2 Hz, 2H), 4.31(d, *J* = 4.1 Hz, 2H), 6.95 (d, *J* = 8.8 Hz, 1H), 7.37-7.39 (m, 2H), 9.80 (s, 1H); ^{13}C NMR : δ 63.9, 64.5, 117.6, 118.1, 124.0, 130.4, 143.8, 149.1, 190.5.

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