Single-Step Conversion of Electron-Deficient Aldehydes into the Corresponding Esters in Aqueous Alcohols in the Presence of Iodine and Sodium Nitrite

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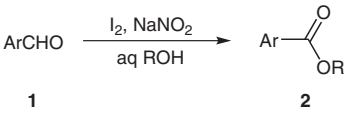
Abstract: The direct conversion of aldehydes into their corresponding esters in the presence of iodine and sodium nitrite in aqueous alcohols is reported. In all these reactions, alcohol serves as reactant and also as reaction medium. Almost quantitative yields were obtained with aldehydes containing electron-withdrawing substituents and heterocyclic aldehydes.

Key words: esterification, electron-deficient aldehydes, iodine, sodium nitrite, nucleophilic addition

Esters serve as equivalents for carbonyl and carboxyl compounds. In addition, these compounds have many commercial and biological applications.[1] Esters can be synthesized in a number of traditional ways.[2] Unfortunately, in many of these esterification reactions, the oxidative pathway has restrictive requirements: dehydrating agent, expensive metal catalysts,[2b] long reaction times,[2c] oxidants in greater than stoichiometric amounts,[2c,d] anhydrous solvents,[2c] corrosive acids,[2d] and an inert atmosphere.[2h] Also many reported procedures are unsatisfactory for aldehydes containing electron-withdrawing substituents.[2h]

A number of literature reports have shown iodine to be an excellent catalyst for various transformations of carbonyl compounds including aldehydes.[3] For example, iodine in the presence of an excess of base[4] and with (diacetoxyiodo)benzene[5] was used to convert aldehydes into the corresponding esters in alcohol.

Our successful regioselective iodination of phenols with iodine and sodium nitrite [I_2, $NaNO_2$ (1:1), green reagent] in aqueous methanol prompted us to study the application of this reaction to aldehydes.[6] Interestingly, the reaction of aromatic aldehydes (1 equiv) with iodine and sodium nitrite in aqueous alcohol led to the formation of esters as the final products, rather than the expected iodinated aromatic compounds. A blank reaction of an aldehyde and aqueous alcohol with iodine at 70 °C and at room temperature yielded the corresponding acetal.[7] In the above reaction, sodium nitrite alone fails to bring about either esterification or acetalization, thus confirming the importance of the combination of iodine and sodium nitrite as a reagent in esterification (Scheme 1).



Scheme 1

Generally, iodine is a good water purifier and is also necessary to control thyroid disorders.[8] Sodium nitrite, a naturally occurring chemical, used as a meat preservative and an antidote for cyanide poisoning, has many other medicinal applications.[6,9] We report here the development of a novel, low-cost, and green chemical method for the selective conversion of aldehydes into esters in the presence of iodine and sodium nitrite.

We herein report an effective protocol that facilitates the direct esterification of aldehydes, especially aromatic aldehydes with electron-withdrawing substituents; methanol, ethanol, or a variety of alcohols including diols can be used in the presence of iodine and sodium nitrite. This method is robust, straightforward, and scalable. There is no need for anhydrous solvents or an inert atmosphere to be used. A simple chromatographic separation using a silica gel column (NH-type) is effective for the purification of the esters. This purification procedure prevents the product from undergoing partial deesterification and deacetalization[10] during workup and isolation.

We chose 4-nitrobenzaldehyde (**1a**) as a model substrate to establish the reaction conditions in aqueous methanol (Table 1). The best result was obtained when one equivalent of iodine and one equivalent of sodium nitrite were used at 70 °C for 18 hours; this furnished **2a** as the sole product in 99% yield (entry 4). The purity of the crude product **2a** thus obtained (entry 4) was confirmed by ^{1}H NMR analysis. Inspection of entries 1–4 in Table 1 reveals that esterification is dependent on the reaction temperature and time sequence. In marked contrast, the reaction proceeds well at room temperature, but gives a low yield of **2a** even after a long reaction time (entry 1), and the use of less iodine and sodium nitrite results in lower yields of **2a** (entries 5–8). In both cases it was found (by TLC and ^{1}H NMR analysis of the crude mixtures) that the starting compound **1a** remained in the reaction mixture. Although our newly developed esterification reaction was slow, as described above, the long reaction time was drastically reduced when microwave irradiation was used (70 °C, 4 min) (Table 1, entry 4). This effect may result

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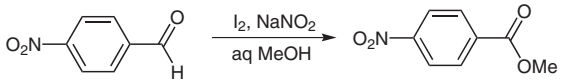
from a polar reaction mechanism,[11] which will be shown later.

Table 1 Optimization of Reaction Conditions



1a **2a**

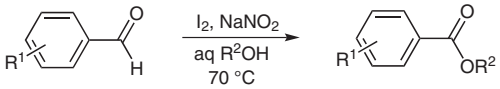
Entry	I_2 (equiv)	$NaNO_2$ (equiv)	Time (h)	Temp (°C)	Yield[a] (%)
1	1	1	24	r.t.	46
2	1	1	6	70	34
3	1	1	12	70	79
4	1	1	18	70	99 (97)[b]
5	0.5	0.5	18	70	41
6	1	0.5	18	70	28
7	0.5	1	18	70	47
8	0.05	0.05	18	70	trace

[a] Isolated yield.
[b] The yield in parentheses is for a reaction conducted under microwave irradiation for 4 min at 70 °C.

With these encouraging results in hand, the scope of the iodine and sodium nitrite catalyzed esterification reaction was examined with a series of aromatic or heterocyclic aldehydes and aliphatic aldehydes substituted with phenyl groups in a variety of alcohols as solvents and reactants. The results were dependent on the nature of the aldehyde substituents, and excellent yields were obtained with electron-deficient substrates (Table 2).

Aromatic aldehydes with electron-withdrawing substituents were effectively converted into the corresponding esters (Table 2, entries 1–4 and 6–10). The isolated yield of **2l** is only 7%, but ^{1}H NMR analysis of the crude reaction mixture indicated 67% conversion of **1f** into ester **2l** (Table 2, entry 11); this loss is due to the adsorption of compound **2l** onto the NH-type silica gel during purification. 4-Nitro- and 4-cyanobenzaldehydes were neatly converted into their pure methyl esters in nearly quantitative yields when methanol was used as solvent and reactant (Table 1, entry 4; Table 2, entry 8). In contrast, the ethyl esters derived from 4-nitro- and 4-cyanobenzaldehyde formed in slightly lower yields when ethanol was used as solvent and reactant (Table 2, entries 1 and 9). These results encouraged us to examine the esterification of aldehydes in a variety of alcohols (Table 2, entries 2–5). The results in Table 2 (entries 1–5, 8, and 9) clearly show that the efficiency of the reaction decreases in the following order: methanol > ethanol > propanol, and primary alcohol > secondary alcohol > tertiary alcohol. The branching in the structure of the alcohol seems to reduce the yield of the ester as in the case of isopropyl and isobutyl alcohol. Surprisingly, in the presence of *tert*-butyl alcohol no reaction was observed, and starting compound **1a** was recovered quantitatively (Table 2, entry 5). These results may be attributed to steric hindrance of the alcohol.[4,12,13] In addition, the higher yield in methanol compared to other alcohols is likely due to methanol (smaller size) being a better nucleophile.[13]

Table 2 Esterification of Aromatic Aldehydes with Electron-Withdrawing Substituents



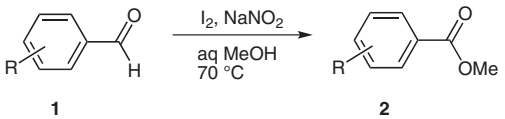
1 **2**

Entry	**1**	R^1	R^2	Time (h)	**2**	Yield[a] (%)
1	**1a**	4-NO_2	Et	18	**2b**	96 (93)[b]
2	**1a**	4-NO_2	*n*-Pr	18	**2c**	91
3	**1a**	4-NO_2	*i*-Pr	24	**2d**	79
4	**1a**	4-NO_2	*i*-Bu	36	**2e**	86
5	**1a**	4-NO_2	*t*-Bu	36	**2f**	n.r.[c]
6	**1b**	3-NO_2	Me	18	**2g**	92
7	**1c**	2-NO_2	Me	18	**2h**	89
8	**1d**	4-CN	Me	18	**2i**	98 (94)[b]
9	**1d**	4-CN	Et	18	**2j**	94
10	**1e**	4-Cl	Me	24	**2k**	89
11	**1f**	4-CO_2H	Me	24	**2l**	7[d]

[a] Isolated yield.
[b] The yields in parentheses are for reactions conducted under microwave irradiation for 4 min at 70 °C.
[c] The starting material was quantitatively recovered; n.r. = no reaction.
[d] ^{1}H NMR analysis of the crude reaction mixture indicated 67% conversion of **1f** into ester **2l**.

The reaction of 4-methoxybenzaldehyde gave the corresponding methyl ester in low yield (28%) after 36 hours of reaction time (Table 3, entry 1). However, 4-methoxybenzaldehyde, 3-methoxybenzaldehyde, and 2-methoxybenzaldehyde were only mildly reactive in esterification, even by microwave irradiation, for 12 min (entries 1–3). Surprisingly, 4-methyl- and 3-methylbenzaldehyde were unreactive, even after 24 hours at 70 °C (entries 4 and 5); this is different from the reaction of 2-methylbenzaldehyde (entry 6). It appears that the applicability of iodine and sodium nitrite in the reactions of aromatic aldehydes with electron-donating substituents is limited under the conditions developed by us. In addition, we did not observe any iodinated products;[6] only the remaining unchanged aldehyde along with the ester that forms in the reaction were detected (Table 3).

Table 3 Esterification of Aromatic Aldehydes with Electron-Donating Substituents



1 2

Entry	1	R	Time	2	Yield[a] (%)
1	**1g**	4-OMe	36 h 12 min	**2m**	28 (48)[b]
2	**1h**	3-OMe	12 min	**2n**	(46)[b]
3	**1i**	2-OMe	12 min	**2o**	(31)[b]
4	**1j**	4-Me	24 h	**2p**	n.r.[c]
5	**1k**	3-Me	24 h	**2q**	n.r.[c]
6	**1l**	2-Me	24 h	**2r**	39[d]

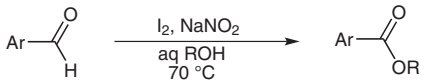
[a] Isolated yield.
[b] The yields in parentheses are for reactions conducted under microwave irradiation at 70 °C (average of two runs).
[c] Determined by GC; starting material was quantitatively recovered; n.r. = no reaction.
[d] A mixture of acetal and ester formed.

Unsubstituted aromatic aldehydes **1m** and **1n** afforded the corresponding esters in moderate yields (Table 4, entries 1 and 2). Aliphatic aldehydes **1o** and **1p** substituted with phenyl groups were converted into the corresponding esters at 70 °C (entries 3 and 4). In these cases, the yields were slightly improved after longer reaction times (entries 1–4). However, TLC and NMR analyses of the crude products indicated that a major portion of the corresponding aldehydes remained in the reaction mixture along with the newly formed esters even after long reaction times. The efficacy of this methodology can also be extended to heterocyclic aldehydes. Heterocyclic aldehydes **1q** and **1r** could be smoothly converted into their methyl esters in high yields (96–98%) (entries 5 and 6).

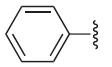
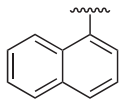
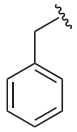
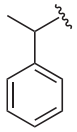
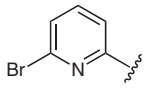
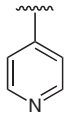
To further explore the scope of the iodine and sodium nitrite catalyzed esterification reaction, the esterification of **1a** (1 equiv) in a variety of organic solvents was examined, with various alcohols (1.25 equiv) as a reactant (Table 5). The results in Table 5 indicate the sensitivity of our new reagent system for esterification. The esterification of **1a** proceeded quite well in polar solvents (entries 1 and 2).

In general, our new reagent (I_2/$NaNO_2$) is very effective in the conversion of aldehydes substituted with electron-withdrawing groups into the corresponding esters. The use of microwave irradiation reduced the long reaction time in our esterification procedure. The unique characteristic of this method, using iodine and sodium nitrite in aqueous alcohol, is that it selectively iodinates aromatic rings of polyfunctionalized phenols,[6] but in the case of multifunctionalized aldehydes, iodine and sodium nitrite chemoselectively convert the aldehydes into esters (Tables 2– 5). Moreover, this procedure demonstrates that

Table 4 Esterification of Simple Aromatic, Aliphatic, and Heterocyclic Aldehydes

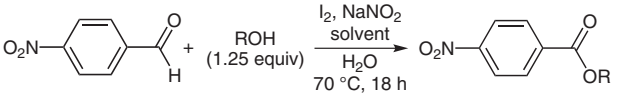


1 2

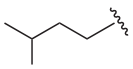
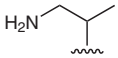
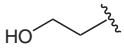
Entry	1	Ar	R	Time (h)	2	Yield[a] (%)
1	**1m**		Me	24 36 48	**2s**	46[b] 54[b] 58
2	**1n**		Me	24 36	**2t**	33[b,c] 40[b,c]
3	**1o**		Et	24 36	**2u**	29[b,c] 34[c]
4	**1p**		Me	24 36	**2v**	23[c] 27[c]
5	**1q**		Me	14	**2w**	98
6	**1r**		Me	14	**2x**	96

[a] Isolated yield.
[b] Average of three runs.
[c] The starting material was quantitatively recovered.

Table 5 Esterification of **1a** with Less Common Alcohols



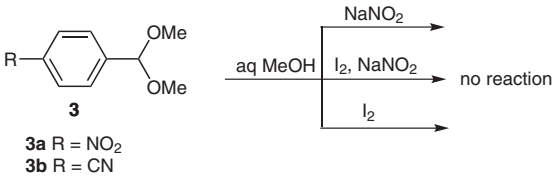
1a 2

Entry	Solvent	R	2	Yield[a] (%)
1	toluene	Me	**2a**	83
2	CH_2Cl_2	Me	**2a**	94
3	CH_2Cl_2		**2y**	75
4	CH_2Cl_2		**2z**	83
5	CH_2Cl_2		**2a′**	81

[a] Isolated yield.

esters do not result from oxidation of the aldehydes to carboxylic acids and subsequent Fischer-type esterification in alcoholic solvents. This conclusion is supported by the

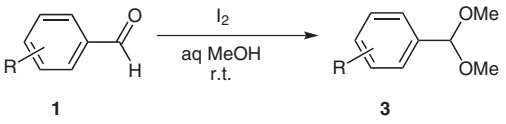
observation that esterification of 4-formylbenzoic acid occurred at the formyl group, rather than at the carboxyl group, and that benzoic acid was not esterified. Interestingly, attempts to obtain esters (**2a** or **2i**) from the corresponding acetals (**3a** or **3b**) in aqueous methanol by using sodium nitrite, iodine and sodium nitrite, or iodine were unsuccessful, even after 24 hours at room temperature or at 70 °C; all starting materials were quantitatively recovered from these reactions (Scheme 2). These observations support the conclusion that under our reaction conditions esters are not formed from acetals.



Scheme 2

In addition, the blank reaction conditions discussed earlier are good for the preparation of acetals (Table 6).[10,12,13] Sun et al. also reported deprotection of acetals to give the corresponding aldehydes in excellent yields within minutes under neutral conditions in the presence of a catalytic amount of iodine at room temperature.[14]

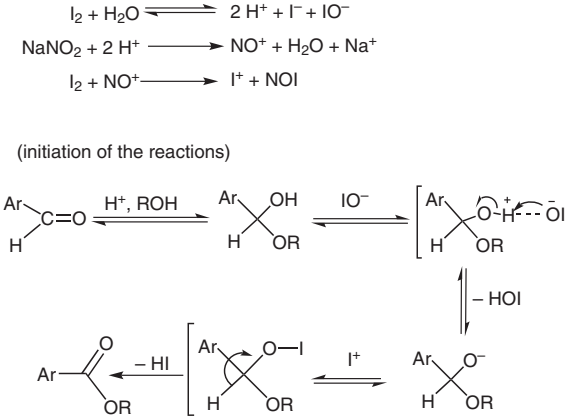
Table 6 Preparation of Acetals **3** from Benzaldehydes **1**



Entry	**1**	R	Time (h)	**3**	Yield[a] (%)
1	**1a**	4-NO_2	1.5	**3a**	97
2	**1d**	4-CN	2.0	**3b**	95
3	**1e**	4-Cl	2.5	**3c**	95
4	**1f**	4-CO_2H	1.5	**3d**	98

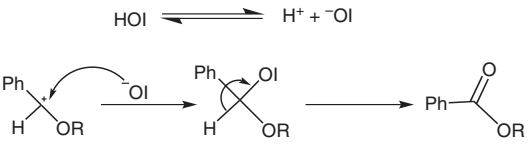
[a] Isolated yield.

The experimental results support the following reaction mechanism for esterification: aldehyde ↔ hemiacetal ↔ ester rather than through the commonly accepted aldehyde ↔ acid ↔ ester or aldehyde ↔ acetal ↔ ester mechanism.[2d,15] When iodine dissolves in aqueous alcohol, the solution becomes acidic (Scheme 3). Under mildly acidic conditions, sodium nitrite ($NaNO_2$) forms the nitrosyl ion (NO^+), which acts as a Lewis acid and converts iodine (I_2) into the iodine cation (I^+) (Scheme 3).[6,16] Iodine appears to play a catalytic role in the conversion of aldehydes into hemiacetals, as shown in Scheme 3; this is further facilitated by the oxoiodate(I) ion (IO^-) generated in the medium. Initially, the carbonyl oxygen atom is protonated, rendering its carbon more electrophilic, and associates with the alcoholic hydroxy group, leaving the oxygen of the alcohol more nucleophilic. This situation favors nucleophilic addition of alcohols to the carbonyl carbon and, subsequently, formation of the hemiacetals. In the presence of sodium nitrite, esters form from the hemiacetals via a hemiacetal–iodate complex and an iodo–hemiacetal adduct.[5] These two species form by hydrogen bonding between the oxoiodate(I) ion (IO^-) and the hydroxy group of the hemiacetal and by bonding of the iodine cation (I^+) with the resulting hemiacetal anion; this is followed by facile α-hydrogen elimination, as hydrogen iodide, to form the ester (Scheme 3). Obviously, the observed reactivity of the aromatic aldehydes, which is limited to nucleophilic addition of alcohols to form esters, is due to variations in the degree of electrophilicity of the carbonyl carbon, as determined by the resonance effects of the substituents.



Scheme 3 Proposed mechanism

If the iodo–hemiacetal adduct is generated by attack of oxoiodate(I) anions (IO^-) on the alkoxymethyl cation, an ester will form even in the absence of sodium nitrite. However, the formation of esters was not observed in the absence of sodium nitrite (Scheme 4).



Scheme 4

In summary, although the literature enumerates a number of reagents for esterification, the advantages of the procedure described in this paper is that aldehydes with electron-withdrawing substituents and heterocyclic aldehydes are chemoselectively converted into esters in nearly quantitative yields. Another advantage of our method is the use of environmentally acceptable and less expensive reagents and the simplicity of the experimental procedure and subsequent workup. The described methods can readily be scaled up to multigram reactions. Additional experiments that explore the scope and limitations of this method are currently underway in our laboratory.

All solvents and chemicals were purchased from TCI and used without further purification. H_2O was of Milli-Q grade with a specific resistance greater than 18 Ω·cm. A microwave synthesizer (Green Motif I, IDX Corporation, Tokyo) was employed for microwave-assisted synthesis. Reaction progress and compound purity were monitored by TLC (hexane–EtOAc, 10:2); UV light at shorter wavelengths was used for visualization. Flash chromatography was performed on NH-type silica gel (particle size 100–200 mesh), and for additional purification alumina (70–230 mesh ASTM) was used, as needed. For the oxidation of aldehydes to acetals (shown in Table 6), recycling preparative gel permeation chromatography (GPC) ($CHCl_3$) was used for purification. Melting points were determined on a Yanaco micro-melting-point apparatus, and are uncorrected. When necessary, a Shimadzu GC-9A gas chromatograph (GC) was used to analyze reactions. ^1H and ^{13}C NMR spectra were recorded using a JEOL ECP-500 (500 and 125 MHz, respectively) and a JEOL ECP-300 (300 and 75 MHz, respectively) spectrometer. The ^1H and ^{13}C chemical shifts were referenced to TMS (δ = 0.00) and the solvent residual peak. Mass spectra were recorded on a JEOL JMS-MS700 mass spectrometer using xenon (6 kV, 10 mA) as the FAB gas. IR spectra were obtained on a JASCO FT-IR 410 spectrophotometer.

Oxidation of Aldehydes 1 to Esters 2; General Procedure

Conventional heating: I_2 (1 mmol) was added to a stirred soln of the appropriate aldehyde (1 mmol) in the appropriate alcohol (4 mL) at r.t. After the I_2 had completely dissolved in the alcohol, $NaNO_2$ (1 mmol) in H_2O (1 mL) was added. The resulting reaction mixture was stirred at r.t. for 10 min, and then the mixture was heated to 70 °C. The reaction progress was monitored by TLC (NH-type). After completion of the reaction, the reaction mixture was slowly cooled to r.t., then washed with 1 M aq $Na_2S_2O_3$ (10 mL) to remove the I_2, and, subsequently, extracted with $CHCl_3$ (3 × 10 mL). The combined organic phase was dried ($MgSO_4$), filtered, and concentrated under reduced pressure in a rotary evaporator and the resulting residue was purified by column chromatography (NH-type silica gel).

Microwave heating: The microwave synthesizer was equipped with a magnetic stirrer and a thermocouple to monitor the temperature, which was set by varying the microwave power. For the esterification reactions, 200 W energy was used to maintain the reaction temperature at 70 °C. The volume and the composition of the reaction mixture was the same as under conventional conditions.

*Esterification of **1a** in organic solvents*: A 25-mL reaction flask equipped with a magnetic stirring bar was charged with **1a** (1 mmol), $NaNO_2$ (1 mmol) in H_2O (1 mL), I_2 (1 mmol), the appropriate alcohol (1.25 mmol), and organic solvent (3 mL) (Table 5). The mixture was vigorously stirred for 0.5 h at r.t. and then at 70 °C for 18 h and was then allowed to reach r.t.; then the reaction mixture was washed with 1 M aq $Na_2S_2O_3$ (10 mL) and subsequently extracted with $CHCl_3$ (3 × 10 mL). The combined organic phase was dried ($MgSO_4$) for 2 h, filtered, and concentrated under reduced pressure in a rotary evaporator. The crude compound was purified by column chromatography (NH-type silica gel).

Column chromatography: Compounds **2a** (Table 1, entry 4) and **2i** (Table 2, entry 8) were obtained in pure form from the corresponding aldehydes without any further purification. Purity was confirmed by ^1H NMR analysis. All other compounds were obtained in pure form by simply passing the product through a glass column (2 ft length and 0.5 ft diameter) filled with 100–200 mesh NH-type silica gel (2 g) and with hexane–EtOAc (9:1, 20 mL) as the eluent. Compounds **2s** and **2u** were purified additionally on an alumina column.

Methyl 4-Nitrobenzoate (2a)[2g]
White crystalline solid; mp 91.0–92.0 °C (Lit.[17] 94.0–95.0 °C).

^1H NMR (500 MHz, $CDCl_3$): δ = 3.90 (s, 3 H), 8.11 (d, *J* = 8.5 Hz, 2 H), 8.19 (d, *J* = 8.5 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 52.7, 123.4, 130.6, 135.4, 150.4, 165.0.

MS–FAB: *m/z* (%) = 73 (100), 147 (60), 207 (10) [M + 3 H^+ + Na^+].

Ethyl 4-Nitrobenzoate (2b)[18]
White crystalline solid; mp 57.0–58.0 °C (Lit.[18] 54.9–55.1 °C).

^1H NMR (500 MHz, $CDCl_3$): δ = 1.41 (t, *J* = 7.5 Hz, 3 H), 4.42 (q, *J* = 6.5 Hz, 2 H), 8.20 (d, *J* = 9.0 Hz, 2 H), 8.28 (d, *J* = 9.0 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.2, 61.9, 123.4, 130.6, 135.8, 150.4, 164.6.

MS–FAB: *m/z* (%) = 150 (40), 196 (100) [M + H^+].

Propyl 4-Nitrobenzoate (2c)[19]
Colorless oil.

^1H NMR (500 MHz, $CDCl_3$): δ = 0.96 (t, *J* = 8.0 Hz, 3 H), 1.75 (q, *J* = 6.0 Hz, 2 H), 4.25 (t, *J* = 7.0 Hz, 2 H), 8.12 (d, *J* = 8.0 Hz, 2 H), 8.19 (d, *J* = 8.0 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 10.2, 21.8, 67.3, 123.3, 130.4, 135.7, 150.3, 164.5.

Isopropyl 4-Nitrobenzoate (2d)[2i]
White crystalline solid; mp 104.0–106.0 °C (Lit.[2i] 106.0–108.0 °C).

^1H NMR (500 MHz, $CDCl_3$): δ = 1.33 (d, *J* = 6.0 Hz, 6 H), 5.23 (m, 1 H), 8.13 (d, *J* = 8.5 Hz, 2 H), 8.21 (d, *J* = 8.5 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.8, 69.6, 123.4, 130.5, 136.2, 151.9, 164.1.

Isobutyl 4-Nitrobenzoate (2e)[20]
White crystalline solid; mp 68.0–69.0 °C (Lit.[20] 68.0–68.5 °C).

^1H NMR (500 MHz, $CDCl_3$): δ = 1.05 (d, *J* = 6.5 Hz, 6 H), 2.11–2.13 (m, 1 H), 4.17 (d, *J* = 6.5 Hz, 2 H), 8.23 (d, *J* = 9.0 Hz, 2 H), 8.30 (d, *J* = 9.0 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 19.0, 27.7, 71.8, 123.4, 130.5, 135.8, 150.4, 164.6.

Methyl 3-Nitrobenzoate (2g)[17]
Pale yellow solid; mp 79.0–80.0 °C (Lit.[17] 78.0–79.0 °C).

^1H NMR (500 MHz, $CDCl_3$): δ = 3.91 (s, 3 H), 7.57 (t, *J* = 8.0 Hz, 1 H), 8.28 (d, *J* = 8.0 Hz, 1 H), 8.32 (d, *J* = 8.0 Hz, 1 H), 8.77 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 52.7, 124.5, 127.3, 129.5, 131.8, 135.1, 148.2, 164.8.

Methyl 2-Nitrobenzoate (2h)[21]
Colorless oil turning pale yellow.

^1H NMR (500 MHz, $CDCl_3$): δ = 3.92 (s, 3 H), 7.64–7.68 (m, 2 H), 7.74 (d, *J* = 7.5 Hz, 1 H), 7.91 (d, *J* = 8.0 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 53.2, 123.8, 127.5, 129.8, 131.7, 132.8, 165.8.

Methyl 4-Cyanobenzoate (2i)[2g]
White crystalline solid; mp 69.0 °C (Lit.[22] 66.0–67.0 °C).

^1H NMR (500 MHz, $CDCl_3$): δ = 3.96 (s, 3 H), 7.74 (d, *J* = 8.5 Hz, 2 H), 8.13 (d, *J* = 8.5 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 52.6, 116.4, 117.9, 130.0, 132.2, 133.9, 165.4.

Ethyl 4-Cyanobenzoate (2j)[18]
White crystalline solid; mp 49.0–50.0 °C (Lit.[23] 51.0–53.0 °C).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.32 (t, *J* = 7.5 Hz, 3 H), 4.31 (q, *J* = 7.0 Hz, 2 H), 7.65 (d, *J* = 8.5 Hz, 2 H), 8.05 (d, *J* = 8.0 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.1, 61.6, 116.1, 117.8, 129.9, 132.0, 134.2, 164.8.

Methyl 4-Chlorobenzoate (2k)[2g]
Pale yellow crystals; mp 40.0–42.0 °C (Lit.[17] 44.0 °C).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.91 (s, 3 H), 7.40 (d, *J* = 8.5 Hz, 2 H), 7.96 (d, *J* = 8.5 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 52.2, 128.1, 128.7, 130.9, 139.3, 166.2.

MS–FAB: *m*/*z* (%) = 155 (100) [$M^+ - CH_3$].

4-(Methoxycarbonyl)benzoic Acid (2l)[24]
White solid; mp 221–223 °C (Lit.[24] 219.0–222.0 °C).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.20 (s, 3 H), 7.61–7.70 (m, 4 H).

Methyl 4-Methoxybenzoate (2m)[25]
White solid; mp 48–50 °C (Lit.[25] 47–48 °C).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.85 (s, 3 H), 3.88 (s, 3 H), 6.92 (d, *J* = 9.5 Hz, 2 H), 8.00 (d, *J* = 9.5 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 51.8, 55.3, 113.5, 122.5, 131.5, 163.3, 166.8.

Methyl 3-Methoxybenzoate (2n)[26]
Colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.85 (s, 3 H), 3.90 (s, 3 H), 7.10 (d, *J* = 8.0 Hz, 1 H), 7.34 (t, *J* = 8.0 Hz, 1 H), 7.55–7.63 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 52.0, 55.2, 113.9, 119.3, 121.8, 129.2, 131.3, 159.4, 166.8.

Methyl 2-Methoxybenzoate (2o)[27]
Colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.29 (s, 3 H), 3.78 (s, 3 H), 6.81–6.83 (m, 2 H), 7.18 (m, 1 H), 7.44 (d, *J* = 7.5 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 52.4, 56.8, 111.7, 119.2, 119.5, 130.9, 133.4, 158.4, 166.3.

Methyl Benzoate (2s)[2g]
Colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.89 (s, 3 H), 7.40 (m, 2 H), 7.51 (d, *J* = 7.5 Hz, 1 H), 8.03 (d, *J* = 8.0 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 51.9, 128.2, 129.4, 130.0, 132.7, 166.9.

MS–FAB: *m*/*z* (%) = 55 (100), 69 (95), 95 (60), 137 (75) [$M^+ + H^+$].

Methyl 1-Naphthoate (2t)[2g]
Colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.93 (s, 3 H), 7.40–7.54 (m, 3 H), 7.80 (d, *J* = 8.5 Hz, 1 H), 7.94 (d, *J* = 8.5 Hz, 1 H), 8.10 (*J* = 7.5 Hz, 1 H), 8.82 (d, *J* = 7.5 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 52.1, 124.4, 125.8, 126.1, 127.0, 127.7, 128.5, 130.2, 131.3, 133.3, 133.8, 168.0.

Ethyl 2-Phenylacetate (2u)[28]
Colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.21 (t, *J* = 7.0 Hz, 3 H), 3.59 (s, 2 H), 4.10 (q, *J* = 7.0 Hz, 2 H), 7.24–7.30 (m, 5 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.0, 41.3, 60.6, 126.9, 128.4, 129.1, 134.0, 171.4.

Methyl 2-Phenylpropanoate (2v)[29]
Colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.49 (d, *J* = 7.5 Hz, 3 H), 3.66 (s, 3 H), 3.72–3.73 (m, 1 H), 7.25–7.32 (m, 5 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 18.5, 45.4, 52.0, 127.1, 127.4, 128.6, 140.5, 168.4.

MS–FAB: *m*/*z* (%) = 73 (100), 147 (40), 165 (70) [$M + H^+$].

Methyl 6-Bromo-2-pyridinecarboxylate (2w)[30]
White crystalline solid; mp 94–96 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.00 (s, 3 H), 7.70–7.73 (m, 2 H), 8.10 (d, *J* = 7.5 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 53.0, 123.9, 131.7, 139.1, 141.9, 148.5, 164.2.

Methyl Isonicotinate (2x)[31]
Colorless oil

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.88 (s, 3 H), 7.77 (s, 2 H), 8.70 (s, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 52.5, 122.7, 137.1, 150.4, 165.4.

Isopentyl 4-Nitrobenzoate (2y)[32]
Yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.90 (d, *J* = 6.5 Hz, 6 H), 1.60–1.61 (m, 2 H), 1.71 (m, 1 H), 4.33 (t, *J* = 6.0 Hz, 2 H), 8.02 (d, *J* = 8.5 Hz, 2 H), 8.20 (d, *J* = 8.5 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.3, 24.9, 37.1, 64.5, 123.4, 130.5, 135.7, 150.4, 164.6.

2-Amino-1-methylethyl 4-Nitrobenzoate (2z)
White crystalline solid; mp 128.0–129.0 °C.

IR (neat): 721, 1078, 1335, 1518, 3108 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.35 (d, *J* = 6.0 Hz, 3 H), 3.21 (s, 2 H, NH_2), 3.52–3.57 (m, 1 H), 4.06–4.11 (m, 1 H), 4.49 (s, 1 H), 8.02 (d, *J* = 9.0 Hz, 2 H), 8.21 (d, *J* = 9.0 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.1, 62.1, 78.9, 124.6, 130.3, 134.5, 151.1, 164.2.

MS–FAB: *m*/*z* (%) = 167 (63), 207 (47), 225 (100) [$M + H^+$].

HRMS (ESI): *m*/*z* calcd for $C_{10}H_{12}N_2O_4$: 223.0755 [M – H]; found: 223.0748.

2-Hydroxyethyl 4-Nitrobenzoate (2a′)[33]
White crystalline solid; mp 51.6 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.27 (br s, 1 H, OH), 3.92 (s, 2 H), 4.44 (s, 2 H), 8.16 (d, *J* = 7.0 Hz, 2 H), 8.20 (d, *J* = 7.0 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 60.9, 67.2, 123.4, 130.7, 135.2, 150.5, 164.9.

Oxidation of Aldehydes 1 to Acetals 3; General Procedure
A reaction flask was charged with the appropriate aldehyde (1 mmol) and I_2 (1 mmol), followed by MeOH (3 mL) and H_2O (1 mL). The resultant reaction mixture was stirred at r.t. After completion of the reaction as indicated by TLC, the reaction mixture was washed with $Na_2S_2O_3$ and extracted with $CHCl_3$ (3 × 10 mL). The combined $CHCl_3$ extract was dried ($MgSO_4$) and the solvent was removed under reduced pressure; this provided the corresponding acetal. Acetals **3a** and **3d** were obtained in pure form and **3b** and **3c** were further purified by column chromatography (NH-type silica gel).

Under similar conditions, 4-chlorobenzaldehyde (**1e**) yielded a mixture of 1-chloro-4-(dimethoxymethyl)benzene (**3c**) (34%), 1-chlo-

ro-4-(diethoxymethyl)benzene (**3e**) (30%), and 1-chloro-4-[ethoxy(methoxy)methyl]benzene (**3f**) (28%) when a MeOH–EtOH mixture (1:1) was used as solvent and reactant in a reaction time of 2.5 h. These three compounds were separated by GPC from the crude mixture.

Compound 3f
Colorless oil.

IR (neat): 810, 1054, 1095, 2992 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.23 (t, *J* = 7.5 Hz, 3 H), 3.29 (s, 3 H), 3.53–3.61 (m, 2 H), 5.43 (s, 1 H), 7.32 (d, *J* = 8.0 Hz, 2 H), 7.39 (d, *J* = 8.0 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 15.1, 52.3, 61.1, 101.4, 128.1, 128.3, 134.1, 137.1.

MS–FAB: *m/z* (%) = 171 (100), 202 (55) [$M^+ + 2\ H^+$].

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References

(1) (a) Coleman, W. M. III; Dube, M. F. *J. Sci. Food. Agric.* **2005**, *85*, 2645. (b) Harris, J. M.; Kozlowski, A. *J. Controlled Release* **2001**, *72*, 217. (c) Hou, Y.; Meyers, C. Y. *ARKIVOC* **2000**, *(i)*, 95. (d) *Volatile Compounds in Foods and Beverages*; Maarse, H., Ed.; Marcel Dekker, CRC Press: New York, **1991**, 554. (e) Masamoto, J. *Prog. Polym. Sci.* **1993**, *18*, 1.

(2) (a) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley: New York, **1999**, 296. (b) Grigg, R.; Mitchell, T. R. B.; Sutthivaiyakit, S. *Tetrahedron* **1981**, *37*, 4313. (c) O'Connor, B.; Just, G. *Tetrahedron Lett.* **1987**, *28*, 3235. (d) Gopinath, R.; Patel, B. K. *Org. Lett.* **2000**, *2*, 577. (e) Travis, B. R.; Sivakumar, M.; Hollist, G. O.; Borhan, B. *Org. Lett.* **2003**, *5*, 1031. (f) Quian, G.; Rui, Z.; Ji, D.; Lu, G.; Qi, Y.; Suo, J. *Chem. Lett.* **2004**, *33*, 834. (g) Lerebours, R.; Wolf, C. *J. Am. Chem. Soc.* **2006**, *128*, 13052. (h) Raj, I. V. P.; Sudalai, A. *Tetrahedron Lett.* **2005**, *46*, 8303. (i) Won, J.-E.; Kim, H.-K.; Kim, J.-J.; Yim, H.-S.; Kim, M.-J.; Kang, S.-B.; Chung, H.-A.; Lee, S. G.; Yoon, Y.-J. *Tetrahedron* **2007**, *63*, 12720.

(3) (a) Mitek, K.; Zupan, M.; Stavber, S.; Iskra, J. *J. Org. Chem.* **2007**, *72*, 6534. (b) Bandgar, B. P.; Bettigeri, S. V. *J. Chem. Res.* **2004**, 389.

(4) Togo, H.; Iida, S. *Synlett* **2006**, 2159.

(5) Karade, N. N.; Budhewar, V. H.; Katkar, A. N.; Tiwari, G. B. *ARKIVOC* **2006**, *(xi)*, 162.

(6) Kiran, Y. B.; Konakahara, T.; Sakai, N. *Synthesis* **2008**, 2327.

(7) (a) Borah, R.; Kalita, D. J.; Sarma, J. C. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **2002**, *41*, 1032. (b) Deka, N.; Kalita, D. J.; Borah, R.; Sarma, J. C. *J. Org. Chem.* **1997**, *62*, 1563. (c) Karimi, B.; Golshani, B. *Synthesis* **2002**, 784. (d) Banik, B. K.; Chapa, M.; Marquez, J.; Cardona, M. *Tetrahedron Lett.* **2005**, *46*, 2341.

(8) (a) Pedersen, K. M.; Laurberg, P.; Nøhr, S.; Jørgensen, A.; Andersen, S. *Eur. J. Endocrinol.* **1999**, *140*, 400. (b) Georgitis, W. J.; McDermott, M. T.; Kidd, G. S. *Mil. Med.* **1993**, *158*, 794. (c) LeMar, H. J.; Georgitis, W. J.; McDermott, M. T. *J. Clin. Endocrinol. Metab.* **1995**, *80*, 220.

(9) (a) Delvi, R. R.; Sawant, S. G.; Terse, P. S. *Vet. Res. Commun.* **1990**, *14*, 411. (b) Björne, H.; Petersson, J.; Phillipson, M.; Weitzberg, E.; Holm, L.; Lundberg, J. O. *J. Clin. Invest.* **2004**, *113*, 106. (c) Finan, A.; Keenan, P.; O'Donovan, F.; Mayne, P.; Murphy, J. *Br. Med. J.* **1998**, *317*, 1138.

(10) Gregg, B. T.; Golden, K. C.; Quinn, J. F. *Tetrahedron* **2008**, *64*, 3287.

(11) *Microwaves in Organic Synthesis*; Loupy, A., Ed.; Wiley-VCH: Weinheim, **2002**, 61–114.

(12) Won, J. E.; Kim, H. K.; Kim, J. J.; Yim, H. S.; Kim, M. J.; Kang, S. B.; Chung, H. A.; Lee, S. G.; Yoon, Y. J. *Tetrahedron* **2007**, *63*, 12720.

(13) Zhao, H.; Song, Z.; Cowins, J. V.; Olubajo, O. *Int. J. Mol. Sci.* **2008**, *9*, 33.

(14) Sun, J.; Dong, Y.; Cao, L.; Wang, X.; Wang, S.; Hu, Y. *J. Org. Chem.* **2004**, *69*, 8932.

(15) (a) Craig, C. J.; Horning, E. C. *J. Org. Chem.* **1960**, *25*, 2098. (b) Nikaido, M.; Aslanian, R.; Scavo, F.; Helquist, P.; Aakermark, B.; Baeckvall, J. E. *J. Org. Chem.* **1984**, *49*, 4738. (c) Sinha, A. K.; Sharma, A.; Swaroop, A.; Kumar, V. *Tetrahedron* **2007**, *63*, 1000.

(16) (a) Cotton, F. A.; Wilkinson, G.; Murillo, C. A.; Bochmann, M. *Advanced Inorganic Chemistry*, 6th ed.; Wiley: New York, **1999**. (b) Bozell, J. J.; Hoberg, J. O. *Tetrahedron Lett.* **1998**, *39*, 2261. (c) Bosch, E.; Kochi, J. K. *J. Org. Chem.* **1994**, *59*, 5573. (d) Boothe, R.; Dial, C.; Conaway, R.; Pagnl, R. M.; Kabalka, G. W. *Tetrahedron Lett.* **1986**, *27*, 2207.

(17) Jain, S. L.; Sain, B. *Appl. Catal., A* **2006**, *301*, 259.

(18) Yang, C.; Williams, J. M. *Org. Lett.* **2004**, *6*, 2837.

(19) Zhiyuan, W.; Junhui, K.; Mingxin, Y. *J. Chem. Res.* **2007**, *6*, 323.

(20) Logue, M. W.; Han, B. H. *J. Org. Chem.* **1981**, *46*, 1638.

(21) Rasala, D.; Gawinecki, R. *Magn. Reson. Chem.* **1992**, *30*, 740.

(22) Sakamoto, T.; Ohsawa, K. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2323.

(23) Chambers, M. R. I.; Widdowson, D. A. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1365.

(24) Konosonoks, A.; Wright, P. J.; Tsao, M.; Pika, J.; Novak, K.; Mandel, S. M.; Krause Bauer, J. A.; Bohne, C.; Gudmundsdottir, A. D. *J. Org. Chem.* **2005**, *70*, 2763.

(25) Maraš, N.; Polanc, S.; Kočevar, M. *Tetrahedron* **2008**, *64*, 11618.

(26) Watson, D. A.; Fan, X.; Buchwald, S. L. *J. Org. Chem.* **2008**, *73*, 7096.

(27) Noonan, C.; Baragwanath, L.; Connon, S. J. *Tetrahedron Lett.* **2008**, *49*, 4003.

(28) Suh, Y. S.; Lee, J.-S.; Kim, S.-H.; Rieke, R. D. *J. Organomet. Chem.* **2003**, *684*, 20.

(29) Moroda, A.; Togo, H. *Tetrahedron* **2006**, *62*, 12408.

(30) Asberom, T.; Zhao, Z. Q.; Bara, T. A.; Clader, J. W.; Greenlee, W. J.; Hyde, L. A.; Josien, H. B.; Li, W.; McPhail, A. T.; Nomeir, A. A.; Parker, E. M.; Rajagopalan, M.; Song, L. X.; Wong, G. T.; Zhang, L. L.; Zhang, Q.; Pissarnitski, D. A. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 511.

(31) Craig, D.; Henry, G. D. *Tetrahedron Lett.* **2005**, *46*, 2559.

(32) Renate, M.; Wolfgang, S.; Reinhold, G. EP 137285, **1979**, *Chem. Abstr.* **1980**, *92*, 138653.

(33) Curini, M.; Epifano, F.; Marcotullio, C. M.; Rosati, O. *Synlett* **1999**, 777.