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Synthesis of 3-Benzylphthalide Derivatives by Using a TDAE Strategy

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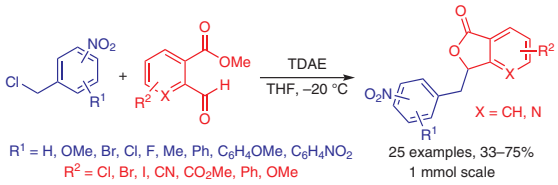

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Abstract A one-pot synthesis of new 3-benzylphthalide derivatives was developed by using a strategy based on tetrakis(dimethylamino)ethylene (TDAE). The reactions in the presence of TDAE of substituted benzyl chlorides with methyl 2-formylbenzoate or of substituted methyl-2-formylbenzoates with 4-nitrobenzyl chloride furnished the corresponding isobenzofuran-1(3*H*)-one products in moderate to good yields.

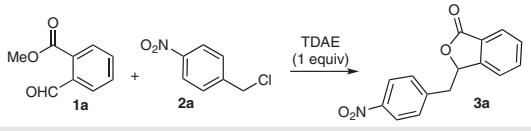
Key words benzylphthalides, methyl formylbenzoate, nitrobenzyl chlorides, isobenzofuranones

Phthalides (isobenzofuranones) are important compounds in organic and medicinal chemistry. Phthalides are common structural motifs that are often present in natural products,[1] pharmaceuticals, and bioactive molecules.[2] They also act as key building blocks in organic synthesis. Many methods for synthesizing functionalized phthalides have been developed, and the usual protocols involve multistep intra- or intermolecular cyclizations.[3] In particular, the reaction of *ortho*-formylbenzoates with benzyl chlorides in the presence of Cp_2TiCl and Zn to afford phthalides has been reported.[4]

Tetrakis(dimethylamino)ethylene (TDAE) is an organic reducing agent that reacts with halogenated derivatives to generate carbanions under mild conditions.[5] Since 2003, the TDAE methodology has been widely explored. Several reactions between nitrobenzylic substrates and various electrophiles, such as aromatic aldehydes, ketones, α-keto esters, α-keto lactams, diethyl oxomalonate, and sulfonimine derivatives, have been developed. This strategy requires a substrate with an appropriate redox potential to react with TDAE. Generally, we have used nitrobenzylic derivatives or various heterocycles (with or without a nitro group) and, in 2018, we reported the first example involving benzonitrile derivatives.[6]

In continuation of our program directed toward the development of original synthetic methods using the TDAE methodology in medicinal chemistry,[7] we report an original and efficient synthesis of new phthalides based on the TDAE strategy. This method offers the advantage of avoiding the use of metals, unlike that of Mukherjee and Roy.[4]

First, the reaction between 4-nitrobenzyl chloride (**2a**) and methyl 2-formylbenzoate (**1a**) in the presence of TDAE was selected as a model for a preliminary study (Scheme 1).



Scheme 1 Reaction of 4-nitrobenzyl chloride (**2a**) with methyl 2-formylbenzoate (**1a**) in the presence of TDAE

We investigated the influence of such parameters the solvents (DMF, THF, or MeCN), the amount of methyl 2-formylbenzoate (**1a**; 1.5 or 2 equiv), the reaction time, and the temperature (Table 1). The first tests (Table 1, entries 1–3) carried out with standard solvents for this method led us to choose THF as the optimal solvent (entry 3). We then changed other parameters: the amount of methyl 2-formylbenzoate (**1a**), the reaction time, and the temperature. With regard to the amount of methyl 2-formylbenzoate (**1a**), an excess was necessary to increase the reaction yield, as observed in our previously studies.[6] The influence of a temperature of –20 °C (entry 5; yield: 71%) versus 0 °C (entry 7; 56%) confirmed the importance of a low temperature to initiate the reaction through the formation of a charge-transfer complex between 4-nitrobenzyl chloride (**2a**) and TDAE. At 0 °C, some of the starting material was recovered unchanged (entry 7). The best yield (71%) of 3-(4-nitroben-

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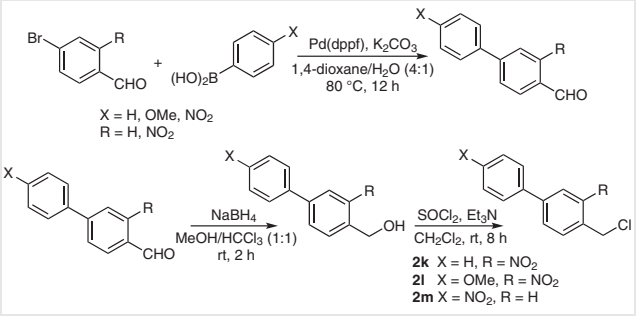
zyl)isobenzofuran-1(3*H*)-one (**3a**) was obtained by using two equivalents of methyl-2-formylbenzoate (**1a**) and one equivalent of 4-nitrobenzyl chloride (**2a**) in the presence of one equivalent of TDAE at –20 °C in THF for one hour, followed by three hours at room temperature (entry 5). Finally, we examined the corresponding reaction of 4-nitrobenzyl bromide under the conditions of Table 1, entry 5, but only 63% of product **3a** was recovered. This decrease in yield was associated with the appearance of the dimeric byproduct 1,2-bis(4-nitrophenyl)ethane. The change of the reaction time at rt (after 1 h at low temperature) does not increase the yield (entry 8 and 9).

Table 1 Optimization of the Reaction of 4-Nitrobenzyl Chloride (**2a**) with Methyl 2-Formylbenzoate (**1a**) in the Presence of TDAE[a]

Entry	Solvent	1a (equiv)	Temp (°C)	Time at rt (h)	Yield[b] (%)
1	DMF	1.5	–30	3	59
2	MeCN	1.5	–30	3	57
3	THF	1.5	–30	3	64
4	THF	2	–30	3	69
5	THF	2	–20	3	71
6	THF	2	–10	3	68
7	THF	2	0	3	56
8	THF	2	–20	0.5	56
9	THF	2	–20	8	66

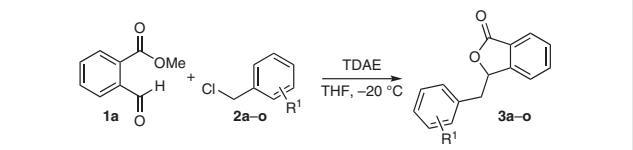
[a] All the reactions were performed by using TDAE (1 equiv).
[b] Yield of the chromatographically isolated pure product relative to **2a**.

Seeking to establish the scope of this reaction and its added value, we performed more experiments. No reaction occurred with nonsubstituted benzyl chloride or with benzyl chlorides substituted with an electron-donating group in the absence of a nitro group. In the benzylic series, under the optimized conditions, a nitro group appears to be a prerequisite for this reaction. For benzyl chlorides substituted with other electron-withdrawing groups, no reaction was observed under the optimized conditions in the case of 4-(chloromethyl)benzonitrile, but a previous study performed with the CN group have shown that it requires a different protocol and optimization study.[6f] Other electron-withdrawing groups requiring optimization (COR, COOR) will be the subject of future studies. We therefore extended this reaction to other nitrobenzyl chlorides **2a–o**, which were either commercially available or were prepared (**2k–m**) as shown in Scheme 2. Benzylic chlorides **2k–m** were prepared in three steps from the corresponding bromobenzaldehydes by a Suzuki–Miyaura cross-coupling reaction followed by reduction of the aldehyde and chlorination of the resulting alcohol.



Scheme 2 Synthesis of benzylic chlorides **2k–m**

The reaction of methyl 2-formylbenzoate (**1a**; 2 equiv) with substituted benzyl chlorides **2a–o** in anhydrous THF in the presence of TDAE at –20 °C for one hour followed by three hours at room temperature led to the corresponding derivatives **3a–o** in moderate to good yields (33–72%), as shown in Scheme 3 and Table 2.[8] For low yields, no identifiable byproducts (dimer, reduction product, etc.) were obtained, only degradation products (tar).



Scheme 3 Generalization of the reaction of methyl 2-formylbenzoate (**1a**) with nitrobenzylic chlorides **2a–o** by using the TDAE strategy

Table 2 Reaction of Methyl 2-Formylbenzoate (**1a**) with Nitrobenzylic Chlorides **2a–o** by Using the TDAE Strategy[a]

Entry	R^1	Product	Yield[b] (%)
1	4-NO_2	**3a**	71
2	2-NO_2	**3b**	69
3	2-NO_2-4,5-$(OMe)_2$	**3c**	67
4	2-NO_2-4,5-OCH_2O-	**3d**	69
5	2-NO_2-5-Br	**3e**	68
6	2-NO_2-5-Cl	**3f**	41
7	2-NO_2-5-Me	**3g**	68
8	2-NO_2-5-OMe	**3h**	65
9[c]	3-OMe-4-NO_2	**3i**	46
10[c]	3-Me-4-NO_2	**3j**	60
11	2-NO_2-4-Ph	**3k**	72
12	2-NO_2-4-(4-$MeOC_6H_4$)	**3l**	65
13[c]	4-(4-$O_2NC_6H_4$)	**3m**	47
14	3-F-4-NO_2	**3n**	33
15	2-NO_2-4-Br	**3o**	51

[a] Reaction conditions: methyl 2-formylbenzoate (**1**; 2 equiv), nitrobenzylic chloride **2** (1 equiv), TDAE (1 equiv), anhyd THF.
[b] Yield of the chromatographically isolated pure product relative to the nitrobenzylic chloride **2**.
[c] Anhyd DMF as solvent.

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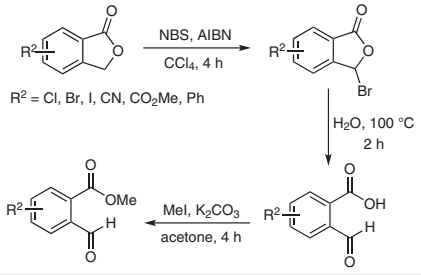
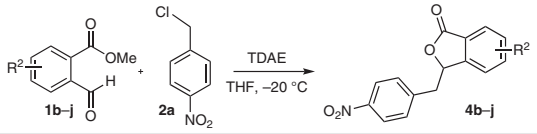
It is difficult to correlate certain types of substituent with the yield because the effect of the substituents occurs during the two phases of the process (Phase 1: activation of the substrate and formation of the carbanion; Phase 2: reactivity of the carbanion during the nucleophile addition on the aldehyde). However, the low yields of **3f** (41%) and **3n** (33%) appear to be due to the electron-withdrawing effect of fluorine or chlorine which stabilizes the carbanion, making it unreactive toward nucleophilic addition.

To extend this reaction to various formylbenzoates, several substituted methyl 2-formylbenzoates were prepared in good yield by the three-step procedure shown in Scheme 4. Radical bromination of substituted isobenzofuran-1-(3*H*)-ones with 1.2 equivalents of NBS gave substituted 3-bromoisobenzofuran-1-(3*H*)-ones that were converted into substituted 2-formylbenzoic acids by the action of water. The substituted 2-formylbenzoic acids reacted with methyl iodide in acetone for two hours to give the corresponding substituted methyl 2-formylbenzoates.[9]



Scheme 4 Synthesis of various 2-formylbenzoates

These new substituted methyl-2-formylbenzoates **1b–j** reacted with 4-nitrobenzyl chloride (**2a**) under the usual conditions, i.e., 4-nitrobenzyl chloride (1 equiv) with substituted methyl-2-formylbenzoates **1b–j** (2 equiv) in the presence of TDAE at –20 °C for one hour in anhydrous THF followed by three hours at room temperature to give the corresponding phthalide derivatives **4b–j** in moderate to good yields of 35–75% (Scheme 5 and Table 3).[10] For low yields, no identifiable byproducts (dimer, reduction product, etc.) were obtained, only degradation products (tar).



Scheme 5 Generalization of the reaction of 4-nitrobenzyl chloride (**2a**) with substituted methyl 2-formylbenzoates **1b–k** by using the TDAE strategy

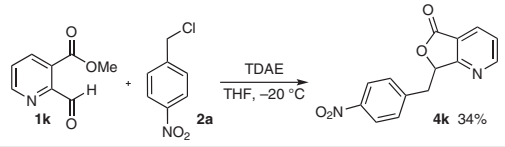
As shown in the series, no clear correlation was observed between the effect of the electronegativity of the substituent in the methyl 2-formylbenzoate and the reaction yield. With substrate **1j** containing two methoxy groups (Table 3, entry 9), the yield fell to 35%, probably due to the electron-donating effect of the alkoxy groups which deactivates the formyl group.

Table 3 Reaction of 4-Nitrobenzyl Chloride **2a** with Substituted Methyl 2-Formylbenzoates **1b–k** by Using the TDAE Strategy

Entry[a]	R^2	Product	Yield[b] (%)
1	5-Cl	**4b**	46
2	5-Br	**4c**	59
3	4-Br	**4d**	64
4	5-I	**4e**	75
5	4-CN	**4f**	46
6	4-CO_2Me	**4g**	49
7	4-Ph	**4h**	50
8	5-Ph	**4i**	71
9	4,5-$(OMe)_2$	**4j**	35

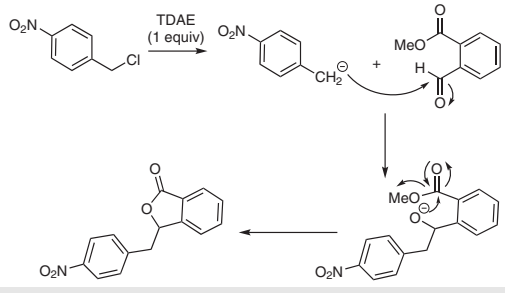
[a] All reactions were performed by using the substituted methyl 2-formylbenzoate **1b–j** (2 equiv), 4-nitrobenzyl chloride **2a** (1 equiv), and TDAE (1 equiv) in anhyd THF.
[b] Yield of chromatographically isolated pure product relative to 4-nitrobenzyl chloride (**2a**).

To extend this reaction to heterocyclic substrates, we studied the reaction of methyl 2-formylnicotinate (**1k**) with 4-nitrobenzyl chloride (**2a**) in the presence of TDAE. This reaction gave the corresponding phthalide **4k** in 34% yield (Scheme 6).



Scheme 6 Reaction of 4-nitrobenzyl chloride (**2a**) with methyl 2-formylnicotinate (**1k**) by using the TDAE strategy

The formation of these phthalide derivatives can be explained by a nucleophilic addition of a nitrobenzyl carbanion, formed by the action of TDAE on 4-nitrobenzyl chloride, to the carbonyl group of the methyl 2-formylbenzoate, followed by lactonization through intramolecular transesterification (Scheme 7).



Scheme 7 Mechanism of the reaction of 4-nitrobenzyl chloride (**2a**) with methyl 2-formylbenzoate (**1a**) in the presence of TDAE

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In conclusion, two new series of highly substituted phthalide derivatives were obtained through the TDAE strategy in a one-pot process. This method offers the advantage of avoiding the use of metals, compared with the method of Mukherjee and Roy;[4] moreover, 3-benzylphthalides are not accessible by other innovative methods based on dehydrogenative coupling reactions.[3c] In the presence of TDAE, the reactions of substituted benzyl chlorides with methyl 2-formylbenzoate or of substituted methyl-2-formylbenzoates with 4-nitrobenzyl chloride gave the corresponding isobenzofuran-1(3*H*)-one products in moderate to good yields.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/a-1290-8349.

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(8) **3-Benzyl-2-benzofuran-1(3*H*)-ones 3a–o; General Procedure**
The appropriate substituted benzylic chloride **2a–o** (1 mmol, 1 equiv) in anhyd THF (15 mL) was added to methyl 2-formylbenzoate (**1a**; 328 mg, 2 mmol, 2 equiv) under nitrogen in a two-necked flask. TDAE (200 mg, 1 equiv) was added dropwise, and the solution was cooled to –20 °C, maintained at this temperature for 1 h, and then kept at rt for 3 h. The solution was then extracted with EtOAc (3 × 20 mL) and the extracts were washed with brine (3 × 20 mL), dried ($MgSO_4$), and concentrated. The crude product was purified by chromatography [silica gel, CH_2Cl_2–PE (1:1)] and recrystallized from EtOH.
3-(4-Nitrobenzyl)-2-benzofuran-1(3*H*)-ones (**3a**)
White solid; yield: 190.99 mg (71%); mp 169 °C. ^{1}H NMR (250 MHz, DMSO-d_6): δ = 3.24 (dd, *J* = 14.3, 7.8 Hz, 1 H, CH_2), 3.63 (dd, *J* = 14.3, 4.1 Hz, 1 H, CH_2), 5.99 (dd, *J* = 7.7, 4.1 Hz, 1 H, CH), 7.54 (d, *J* = 8.7 Hz, 2 H, ArH), 7.59 (t, *J* = 7.4 Hz, 3 H, ArH), 7.74 (d, *J* = 7.6 Hz, 1 H, ArH), 8.16 (d, *J* = 8.6 Hz, 2 H, ArH). ^{13}C NMR (62.5 MHz, DMSO-d_6): δ = 38.9, 80.4, 122.9, 123.2 (2 C), 124.9, 125.4, 129.4, 130.8 (2 C), 134.3, 144.4, 146.4, 149.0, 169.4. HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{15}H_{12}NO_4$: 270.0761; found: 270.0763.

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(10) **3-(4-Nitrobenzyl)-2-benzofuran-1(3*H*)-ones 4b–j; General Procedure**
A two-necked flask equipped with a N_2 inlet was charged with a solution of 4-nitrobenzyl chloride (**2a**; 171 mg, 1 mmol, 1 equiv) and the appropriate methyl 2-formylbenzoate **1b–j** (2 mmol, 1.5 equiv) in anhyd DMF (15 mL) at –20 °C under nitrogen, and then TDAE (200 mg, 1 equiv) was added dropwise. The solution was maintained at –20 °C for 1 h and then kept at rt for 2 h at –20 °C. The product workup was as described above for products **3a–o**.
6-Chloro-3-(4-nitrobenzyl)-2-benzofuran-1(3*H*)-one (**4b**)
White solid; yield: 139.69 mg (46%); mp 157 °C. ^{1}H NMR (250 MHz, DMSO-d_6): δ = 3.26 (dd, *J* = 14.3, 7.8 Hz, 1 H, CH_2), 3.63 (dd, *J* = 14.3, 4.2 Hz, 1 H, CH_2), 6.00 (dd, *J* = 7.7, 4.2 Hz, 1 H, CH), 7.53 (d, *J* = 8.7 Hz, 2 H, ArH), 7.78 (d, *J* = 8.1 Hz, 1 H, ArH), 7.84 (d, *J* = 1.6 Hz, 1 H, ArH), 7.87 (dd, *J* = 8.1, 1.9 Hz, 1 H, ArH), 8.16 (d, *J* = 8.7 Hz, 2 H, ArH). ^{13}C NMR (62.5 MHz, DMSO-d_6): δ = 39.8, 80.5, 123.2 (2 C), 124.5, 124.9, 127.5, 130.9 (2 C), 134.2, 134.3, 144.2, 146.4, 147.7, 168.1. HRMS (ESI): *m/z* [M + NH_4]$^+$ calcd for $C_{15}H_{14}ClN_2O_4$: 321.0637; found: 321.0636.

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