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## Note

# Cascade synthesis of racemic 3-arylphthalides

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Use of the modified reagent system of $NaBH_4$-Amberlyst-15 ($H^+$) for the reduction of *o*-aroylbenzoates **1a-f** followed by simple trituration in aqueous HCl, results in the formation of 3-arylphthalide **3a-f** in very short reaction time.

**Keywords:** 3-Arylphthalides, $NaBH_4$-Amberlyst-15 ($H^+$), *o*-aroylbenzoates

**IPC: Int.Cl.[8] C07C**

Many natural products have phthalide skeletons[1] most of which display a wide variety of significant biological activity[2]. They have also been employed as key intermediates for the synthesis of natural products[3]. They are useful synthons/intermediates in the synthesis of polycyclic compounds like isocoumarines[4], anthraquinones[5] and anthracyclines[6]. Owing to the importance of this class of compounds, several groups[7] have reported the synthesis of these compounds. Use of either *o*-substituted benzoic acids or phthalic acid derivatives have been major popular starting points. For instance, reaction of phthalaldehydic acid with aryl magnesium halides[8] and acid-catalyzed condensation of phthaladehydic acids with aromatic substrates[9] is reported to give the desired 3-substituted phthalides.

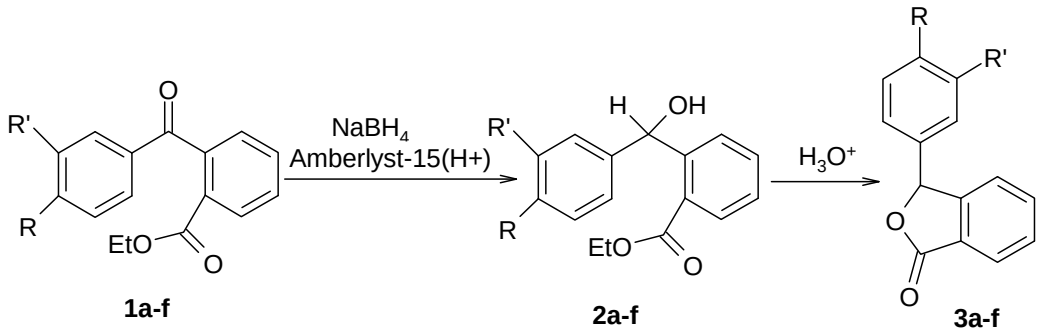
Though methods employing phthalic acid derivatives are known, surprisingly reduction of *o*-aroyl benzoic acids followed by cyclization has not been reported for this class of compounds. Incidentally, reduction of γ-keto acids followed by cyclization is a convenient route for the synthesis of substituted-γ-lactones[10]. The reason for the lack of report of this obvious route was perhaps the un-reactive carbonyl group, which is flanked between two aryl rings and presence of a substituent at the *o*-position; the factors, namely, mesomeric effect and steric crowding, respectively, perhaps make the reaction difficult. Amberlyst™ (Rohm and Hass) ion exchange resins involve certain copolymers with sulfonic acid functional group. These have been found to be useful in many functional group conversions. The use Amberlyst-15 ($H^+$) co-catalyst with $NaBH_4$ is reported to be useful in the reduction of moderately electrophilic carbonyl group[11]. Therefore, it was decided to employ $NaBH_4$-Amberlyst-15 ($H^+$) for effecting the reduction of the diaryl keto group.

## Results and Discussion

The ethyl ester of variously substituted *o*-benzoyl acids **1a-f** was dissolved in dry THF (10 mL) and then was stirred with Amberlyst-15 ($H^+$) and sodium borohydride (3 meq) for about 30 min. As expected, the desired reduction did take place. It was realized that the corresponding hydroxy compound **2a-f** has an ester group in close proximity and is amenable to exhibit intramolecular transesterification. The synthesis of optically active γ-substituted-γ-lactones by simple trituration of the intermediated γ-hydroxy-esters in mildly acidic medium[12] has been recently reported. It was reasonable to expect similar behaviour of the hydroxyesters **2a-f** under similar conditions. Accordingly, after the reduction step, monitored by thin layer chromatography, the solvent was removed under reduced pressure, and aqueous HCl (1:1) was added to the reaction mixture. The further reaction needed only 20 to 30 min for completion. The compound isolated after purification was found to be the expected 3-arylphthalides **3a-f** (**Scheme I**).

## Experimental Section

Melting points are uncorrected. IR spectra were recorded on Shimatzu FTIR-4200, and $^1$H NMR (δ, ppm) were scanned on Varian EM-360L (60 MHz) spectrometer in $CDCl_3$ using TMS as an internal standard. The starting materials, namely, the ethyl ester of variously substituted *o*-benzoyl acids **1a-f**, could be obtained by Fridel-Crafts acylation of various substituted/unsubstituted benzenes with phthalic anhydride followed by esterification.




**1a-f** **2a-f** **3a-f**

**Scheme I**

**General procedure for the synthesis of 3-arylphthalides, 3a-f**: The ethyl ester of substituted *o*-benzoyl benzoic acid (10 mmol) **1** was dissolved in dry THF (10 mL) and then was stirred with Amberlyst-15 ($H^+$) (10 g, 1 mmol) and sodium borohydride (3 meq) for about 30 min. After the reduction, THF was removed by distillation under reduced pressure, 15 mL of dil. HCl was added to the residue and the reaction was stirred further. Progress of the reaction was monitored by TLC. Completion of cyclization required about 20 to 30 min. Then the reaction mixture was extracted with chloroform, washed with water and was dried over anhydrous sodium sulphate. The product obtained was purified by crystallization from chloroform:petroleum ether, 1:1 (**Table I**).

**3-Phenylphthalide, 3a**: m.p. 114°C, (Lit.[13] m.p. 114°C). Yield: 64.76%; The IR (KBr) showed major band at 1760 $cm^{-1}$ for the lactone ring; $^1H$ NMR ($CDCl_3$): δ 7.89-7.90 (d, 1H), 7.56-7.59 (t, 1H, *J* = 7.5Hz), 7.47-7.50 (d, 1H) 7.26-7.33 (m, 3H), 7.20-7.22 (t, 1H), 7.11-7.19 (m, 2H), 6.34 (s, 1H for aliphatic proton).

**3-(4-Methylphenyl)phthalide, 3b**: m.p. 127°C. Yield: 62.50%; The IR (KBr) showed major band at 1765 $cm^{-1}$ for the lactone ring; $^1H$ NMR ($CDCl_3$): δ 7.94 (d, 1H), 7.65 (d, 1H), 7.56 (d, 1H) 7.36-7.37 (m, 3H), 7.33 (t, 1H), 7.26-7.28 (m, 2H), 6.39 (s, 1H for aliphatic proton), 2.40 (s, 3H, $-CH_3$).

**3-(4-Methoxyphenyl)phthalide, 3c**: m.p. 125°C, (Lit.[13] m.p. 128°C). Yield: 68.75%; The IR (KBr) showed major band at 1760 $cm^{-1}$ for the lactone ring; $^1H$ NMR ($CDCl_3$): δ 7.90 (d, 1H), 7.51 (d, 1H), 7.30 (t, 1H) 6.95-7.20 (m, 5H), 6.32 (s, 1H for aliphatic proton), 3.70 (s, 3H, $-OCH_3$).

**3-(4-Chlorophenyl)phthalide, 3d**: m.p. 124°C. Yield: 69.52%; The IR (KBr) showed major band at 1770 $cm^{-1}$ for the lactone ring; $^1H$ NMR ($CDCl_3$): δ 7.85 (d, 1H), 7.45 (d, 1H), 7.45 (t, 1H) 6.85-7.10 (m, 5H), 6.12 (s, 1H for aliphatic proton).

**Table I** — Physical characterization data and yields of 3-arylphthalides

| Compd | R | R′ | Yield % | m.p. °C |
|---|---|---|---|---|
| **3a** | H | H | 64.76 | 114 |
| **3b** | $CH_3$ | H | 62.50 | 127 |
| **3c** | $OCH_3$ | H | 68.75 | 125 |
| **3d** | Cl | H | 69.52 | 124 |
| **3e** | Br | H | 61.59 | 130 |
| **3f** | $CH_3$ | $CH_3$ | 68.07 | 126 |

**3-(4-Bromophenyl)phthalide, 3e**: m.p. 130°C. Yield: 61.59%; The IR (KBr) showed major band at 1770 $cm^{-1}$ for the lactone ring; $^1H$ NMR ($CDCl_3$): δ 7.85 (d, 1H), 7.45 (d, 1H), 7.45 (t, 1H) 6.85-7.10 (m, 5H), 6.15 (s, 1H for aliphatic proton).

**3-(3′,4′-Dimethylphenyl)phthalide, 3f**: m.p. 126°C. Yield: 68.07%; The IR (KBr) showed major band at 1760 $cm^{-1}$ for the lactone ring; $^1H$ NMR ($CDCl_3$): δ 7.95 (d, 1H), 7.65 (d, 1H), 7.55 (t, 1H) 6.85-7.10 (m, 4H), 6.15 (s, 1H for aliphatic proton), 2.40(s, 6H).

## Conclusion

The problem of unreactive carbonyl group was successfully solved by using a co-catalyst, Amberlyst-15 ($H^+$). The reduced hydroxy ester could be cyclized by simple trituration at RT in presence of acid. The process does not require the isolation of the intermediate reduced product. The two steps, namely, reduction and the cyclization, could be effected in a cascade manner. This methodology provides an easy and convenient means of preparing the 3-aryl-

phthalide in satisfactory yields and with easily available starting materials. The inconvenience of use of expensive organometallic reagents and hence the dry conditions, required in many of the previous reports, can be avoided. The new route should also provide for the synthesis of a number of polycyclic compounds in which 3-arylphthalides are used as intermediates[3-6]. The methodology also offers an easy route to obtain non-racemic 3-arylphalides by replacement of ethyl group in **2a-f** by a chiral alcohol part. Some exciting results have been obtained in this regard, which will soon be communicated.

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