

Short Note

Dimethyl 2-(1-Methyl-3-oxo-1,3-dihydroisobenzofuran-1-yl)malonate

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Abstract: In this work we report a facile access to a 3,3-disubstituted isobenzofuranone by tandem addition/cyclization reaction to methyl 2-acetylbenzoate in the presence of dimethyl malonate, under basic conditions.

Keywords: phthalide; isobenzofuranone; quaternary carbon; cascade reactions

1. Introduction

Phthalides, also known with the name of isobenzofuranones, are important heterocyclic compounds, found in a variety of natural products and synthetic biologically active compounds (Figure 1) [1]. This heterocyclic core is formed by a γ -lactone fused with a benzene ring. It can be either unsubstituted, mono- or di-substituted in 3-position [1]. If on one hand, the synthesis of 3-unsubstituted and 3-mono substituted phthalides is widely explored and many protocols are available [1], reports about the synthesis of 3,3-disubstituted derivatives are relatively few because the construction of a quaternary carbon is generally more challenging [2,3]. Accordingly, we have developed convenient tandem reactions for the access to 3-mono substituted phthalides by addition/cyclization reactions of several nucleophiles to methyl 2-formylbenzoate under mild conditions in the presence of K_2CO_3 [4]. A conceptually similar approach has been exploited for a convenient synthesis of 3-mono substituted isoindolinones analogues, another important class of heterocyclic compounds, by tandem reactions of 2-formyl benzonitriles [5]. The investigation of the reactivity of the analogue ketones 2-acylbenzonitriles allowed the synthesis of 3,3-disubstituted isoindolinones [6,7]. Therefore, in the present work we have investigated the reactivity of methyl 2-acetylbenzoate in the presence of dimethyl malonate in order to synthesize a representative 3,3-disubstituted phthalide.

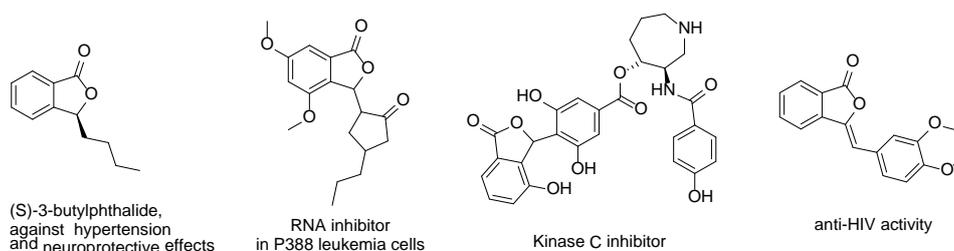
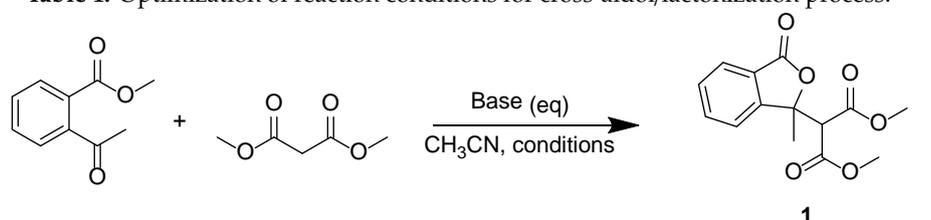


Figure 1. Examples of biologically active phthalides.

2. Result and Discussion

The first set of experiments was directed to investigate the feasibility of the reaction between the readily available methyl 2-acetylbenzoate and dimethyl malonate in the presence of K_2CO_3 , both under solvent free-conditions and in acetonitrile (Table 1, entries 1–4). Since we have supposed that the reaction can proceed via a cross aldol reaction followed by a lactonization, the lower reactivity of the ketone group with respect to the aldehyde of methyl 2-formylbenzoate [4], should explain the lack of reactivity at room temperature. Accordingly, moderate isolated yields were obtained at 50 °C and after prolonged reaction time in acetonitrile as a solvent at a rather high molar concentration, in the presence of 3 eq. of K_2CO_3 . However, in order to obtain very good yields, the use of a stronger base like KOH was necessary. This reaction proved to be effective and reproducible especially when dry conditions were employed in order to avoid background basic hydrolysis of malonate diesters. The efficacy of the use of KOH can be easily correlated to the necessity to increase the molar concentration of the resulting carboanion of dimethyl malonate. The product was easily isolated and purified by chromatography and characterized by High Resolution Mass Spectrometry (HRMS) and after comparison of spectroscopic data with analogue compounds [4].

Table 1. Optimization of reaction conditions for cross-aldol/lactonization process.



Entry	Base (eq)	Solvent (M)	T (°C)	t (h)	Yield (%) ^a
1	K_2CO_3 (1)	Solvent-free	t.a.	15	n.d.
2	K_2CO_3 (2)	CH_3CN (1.40)	t.a.	15	n.d.
3	K_2CO_3 (3)	CH_3CN (1.87)	50	24	46
4	K_2CO_3 (3)	CH_3CN (1.87)	50	48	58
5	KOH (1)	CH_3CN (1.87)	t.a.	24	68
6	KOH (1)	CH_3CN (1.87)	t.a.	48	89

^a Isolated yields.

3. Materials and Methods

3.1. General Information

Reactions were performed using commercially available compounds without further purification and analytical grade solvents. All the reactions were monitored by thin layer chromatography (TLC) on precoated silica gel plates (0.25 mm) and visualized by fluorescence quenching at 254 nm. Flash chromatography was carried out using silica gel 60 (70–230 mesh, Merck, Darmstadt, Germany). The nuclear magnetic resonance (NMR) spectra were recorded on Bruker (Rheinstetten, Germany) DRX 300 spectrometer (300 MHz, 1H , 75 MHz, ^{13}C). Spectra were referenced to residual $CHCl_3$ (7.26 ppm, 1H , 77.00 ppm, ^{13}C). The following abbreviations are used to indicate the multiplicity in NMR spectra: s-singlet, d-doublet, m-multiplet, bs-broad signal. Coupling constants (J) are quoted in Hertz. NMR spectrum. High resolution mass spectra (HRMS) were acquired using a Bruker solariX XR Fourier transform ion cyclotron resonance mass spectrometer (Bruker Daltonik GmbH, Bremen, Germany) equipped with a 7T refrigerated actively shielded superconducting magnet. The samples were ionized in a positive ion mode using an electrospray (ESI) ionization source.

All spectra and additional information are available online as Supplementary Materials.

3.2. General Procedure for Synthesis and Characterization of 1

Method 1:

Methyl 2-acetylbenzoate (50 mg, 0.28 mmol, 1 eq.) was added to a suspension of anhydrous potassium carbonate K_2CO_3 (115 mg, 0.84 mmol, 3 eq.) and dimethylmalonate (96 μ L, 3 eq.) in dry acetonitrile (150 μ L). The reaction mixture was stirred at 50 °C till starting material disappeared by thin layer chromatography (Hexane/AcOEt 7:3). The crude was diluted with chloroform and washed with 1 N HCl, then the organic phase was dried on anhydrous sodium sulphate and concentrated under reduced pressure to give an oil. Purification by flash chromatography on silica gel (Hexane/AcOEt 8:2) gave the pure product as a pale oil.

Method 2:

In a round bottom flask under nitrogen atmosphere, to a suspension of anhydrous potassium hydroxide KOH (16 mg, 0.28 mmol, 1 eq.) in dry acetonitrile (150 μ L) was added dimethylmalonate (96 μ L, 3 eq.) and methyl 2-acetylbenzoate (50 mg, 0.28 mmol, 1 eq.) The reaction mixture was stirred at room temperature until the starting material disappeared by thin layer chromatography (Hexane/AcOEt 7:3). The crude was diluted with chloroform and washed with 1 N HCl, then the organic phase was dried on anhydrous sodium sulphate and concentrated under reduced pressure to give an oil. Purification by flash chromatography on silica gel (Hexane/AcOEt 8:2) gave the pure product as a pale oil.

Pale oil

Yield: 89% (69.0 mg). 1H NMR ($CDCl_3$, 300 MHz): 7.85 (d, 1H, $J = 6.0$ Hz), 7.65 (d, 2H, $J = 6.0$ Hz), 7.57–7.51 (m, 1H), 4.02 (s, 1H), 3.71 (s, 3H), 3.61 (s, 3H), 1.86 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 168.9 (C=O), 166.2 (C=O), 165.8 (C=O), 150.7 (C_{arom}), 134.1 (C_{arom}), 129.5 (C_{arom}), 126.1 (C_{arom}), 125.3 (C_{arom}), 122.6 (C_{arom}), 84.4 (C), 58.7 (CH), 52.7 (CH_3), 52.6 (CH_3), 24.5 (CH_3). HRMS (ESI) calculated for $[C_{14}H_{14}O_6 + H]^+$ 279.08631. Found: 279.08586.

4. Conclusions

In summary, we have reported a new methodology for the synthesis of a 3,3-disubstituted phthalide, by tandem cross aldol reaction/lactonization reaction between methyl 2-acetylbenzoate and dimethyl malonate. Very high yields were obtained when KOH was used in acetonitrile in rather high concentration media.

Supplementary Materials: HRMS, 1H NMR, ^{13}C NMR spectra and MOL structures are available online.

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Conflicts of Interest: The author declares no conflict of interest.

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