Short Note

Methyl 2-(1-methyl-3-oxoisoindolin-1-yl)acetate

Antonia Di Mola 1, Antonio Macchia 1, Laura Palombi 2  and Antonio Massa 1,  *  
1 Department of Chemistry and Biology, University of Salerno, Via Giovanni Paolo II, 84084 Fisciano (SA), Italy; toniadimola@libero.it (A.D.M.); amacchia@unisa.it (A.M.)
2 Department of Physical and Chemical Sciences, University of L’Aquila, via Vetoio, 67100 Coppito (AQ), Italy; lpalombi@unisa.it
* Correspondence: amassa@unisa.it; Tel.: +39-089969565

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Abstract: In this work, we report a facile access to a 3,3-disubstituted isoindolinone by means of Krapcho decarboxylation reaction of the respective substituted dimethyl malonate derivative. Good isolated yields were obtained under mild reaction conditions.

Keywords: isoindolinone; quaternary carbon; Krapcho reaction

1. Introduction

Isoindolinones are important heterocyclic compounds, found in a variety of natural products and in a great number of synthetic biologically active compounds (Figure 1) [1]. The isoindolinone core is composed of a γ-lactam fused with the benzene ring and can be either unsubstituted, or mono- or di-substituted in 3-position [1]. If, on one hand, the synthesis of 3-unsubstituted and 3-mono substituted isoindolinones is widely explored and many protocols are available [1,2] reports about the synthesis of 3,3-disubstituted derivatives are relatively few because the construction of a quaternary carbon is generally more challenging [3,4]. In our recent works, we have developed a convenient access to 3,3-disubstituted isoindolinones by cascade reactions of 2-acylbenzonitriles with several nucleophiles [5,6]. In particular, the investigation of the reactivity between 2-acylbenzonitrile and dimethyl malonate led to a very convenient synthesis of the new compound 1, dimethyl 2-(1-methyl-3-oxoisoindolin-1-yl)malonate [5], which can be of high interest for further transformations. Therefore, in the present work, we have investigated the reactivity of 1 in decarboxylation reaction to afford the useful molecule methyl 2-(1-methyl-3-oxoisoindolin-1-yl)acetate 2 under Krapcho reaction conditions [7,8].

![Chilenine](image1)

**Chilenine**

**HIV-reverse transcriptase inhibitor**

**Drug for the treatment of cardiac arrhythmias**

**Pazinaclone (anxiolytic)**

Figure 1. Examples of natural products and biologically active isoindolinones.

2. Result and Discussion

The convenience of performing decarboxylation of malonate dimethylesters under Krapcho reaction conditions is given by the fact that the methyl acetate derivative is directly obtained under
mild conditions [7,8]. On the other hand, the mostly used decarboxylation procedures are based on the treatment of malonate diesters or β-ketoesters with concentrated HCl at reflux; the respective malonic or β-ketoacids, obtained by hydrolysis under basic conditions, can also undergo decarboxylation under milder reaction conditions. However, in these cases, the final product is a carboxylic acid, while the harsh conditions employed can lead to low yields and decomposition products. The Krapcho protocol is based on the combined effect of a Lewis acid and water in high-boiling, polar aprotic solvents like DMSO (dimethyl sulfoxide), under neutral conditions. In preliminary experiments performed at 100 °C, we did not detect the formation of the product (Table 1, Entry 1). The increase of the reaction temperature at 130 °C led to the formation of the desired product 2. However, the optimized protocol depends also on the control of other two reaction parameters. In particular, at 0.10 molar concentration after 5 h of reaction time we observed about 60% conversion, determined by 1H NMR on the crude, and 40% isolated yield of 2 (Entry 2). Increasing the reaction time at 18 h, we observed an almost complete disappearance of 1 and a good isolated yield (Entry 3). The reaction was also performed in a more concentrated media (0.20 M), giving similar results in a shorter reaction time (Entry 4). The difference between observed conversion and isolated yield is due in part to loss of product during the extraction with water in the work-up procedure for the removal of DMSO and in part because of some amount of decomposition products.

Table 1. Optimization of decarboxylation reaction.

| Entry | T (°C) | t (h) | Conv. (%) | Yield (%) |
|-------|-------|-------|-----------|-----------|
| 1 c   | 100   | 18    | –         | –         |
| 2 c   | 130   | 5     | 60        | 40        |
| 3 c   | 130   | 18    | >95       | 65        |
| 4 d   | 130   | 9     | >95       | 70        |

a Determined by 1H NMR on the crude. b Isolated yields. c [1] = 0.10 M. d [1] = 0.20 M.

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 NMR spectra were recorded on Bruker (Rheinstetten, Germany) DRX 300 spectrometer (400 MHz, 1H, 100 MHz, 13C). Spectra were referenced to residual CHCl3 (7.26 ppm, 1H, 77.00 ppm, 13C). 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 in NMR spectrum (see Supplementary Materials for 1H NMR and 13C NMR spectra). 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.
3.2. General Procedure for Synthesis and Characterization of 2

In a Schlenk tube to a solution of dimethyl 2-(1-methyl-3-oxoisoindolin-1-yl)malonate 1 (30 mg, 0.11 mmol, 1 eq.) in DMSO (500 µL) and water (50 µL) was added anhydrous lithium chloride (18 mg, 4 eq.). The reaction mixture was stirred at 130 °C till starting material disappeared by thin layer chromatography (CHCl₃/AcOEt 1:4). The reaction mixture was diluted with ethyl acetate and washed with brine, 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 yellow wax-type solid. Yield: 70% (24 mg).

1H NMR (400 MHz, CDCl₃): δ 7.83 (d, J = 7.53 Hz, 1H), 7.57 (t, J = 7.39 Hz, 1H), 7.47 (t, J = 7.49 Hz, 1H), 7.37 (d, J = 7.56 Hz, 1H), 7.14 (bs, 1H), 3.72 (s, 3H), 2.96 (d, J = 16.3 Hz, 1H), 2.51 (d, J = 16.3 Hz, 1H), 1.59 (s, 3H).

13C NMR (100 MHz, CDCl₃): δ 171.6 (C=O), 168.9 (C=O), 151.1 (C_arom), 132.2 (C_arom), 130.6 (C_arom), 128.6 (C_arom), 124.2 (C_arom), 120.9 (C_arom), 58.8 (C), 52.0 (CH₃), 44.1 (CH₂), 24.9 (CH₃). HRMS (ESI) calcd for [C₁₂H₁₃NO₃ + H]⁺ 219.08954. Found: 219.08917.

4. Conclusions

In summary, we have described the synthesis of a 3,3-disubstituted isoindolinone, methyl 2-(1-methyl-3-oxoisoindolin-1-yl)acetate by means of the decarboxylation reaction of dimethyl 2-(1-methyl-3-oxoisoindolin-1-yl)malonate, under Krapcho reaction conditions. Good yields were obtained under the combined effect of LiCl and water in DMSO at 130 °C.

Supplementary Materials: 1H NMR and 13C 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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