

## The synthesis of unusual isocoumarin derivatives: the chemistry of homophthalic acid

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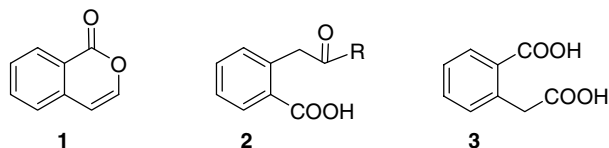
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**Abstract**—Homophthalic acid was reacted with thionyl chloride/DMF and ethyl chloroformate/NEt<sub>3</sub> in the presence and absence of NaN<sub>3</sub>. In all cases completely different isocoumarin derivatives were obtained. These unusual isocoumarin derivatives were characterized and their mechanism of formation is discussed.

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Isocoumarins **1** represents an important class of naturally occurring lactones that display a wide range of biological activities<sup>1</sup> such as protease inhibitory properties,<sup>2</sup> antifungal,<sup>3</sup> cytotoxic,<sup>4</sup> antimicrobial,<sup>5</sup> antiallergic and antimicrobial<sup>6</sup> and antimalarial<sup>7</sup> effects. These properties of isocoumarin derivatives and the increasing number of new isocoumarins in Nature have stimulated continued interest in their synthesis. Recently, several methods have been reported for the synthesis of isocoumarins such as palladium catalyzed reactions, electrophilic aromatic substitution, cyclization of 2-allyl- and alkenylbenzoic acid, etc.<sup>8,2</sup> The six-membered heterocyclic ring skeleton of isocoumarins can be readily obtained from aromatic keto acids **2** as well as from phthalic acid **3**.<sup>2</sup> Nakajima et al.<sup>9</sup> and others<sup>10</sup> reported the synthesis of 3-substituted coumarins by condensation of a range of acid chlorides with homophthalic acid at 200 °C.



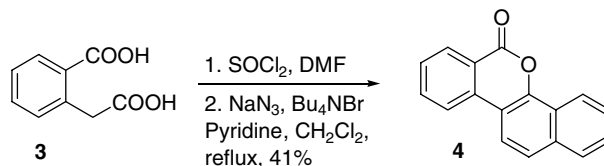
**Keywords:** Homophthalic acid; Isocoumarin; Dibenzocromenone; Sodium azide; Acyl azide.

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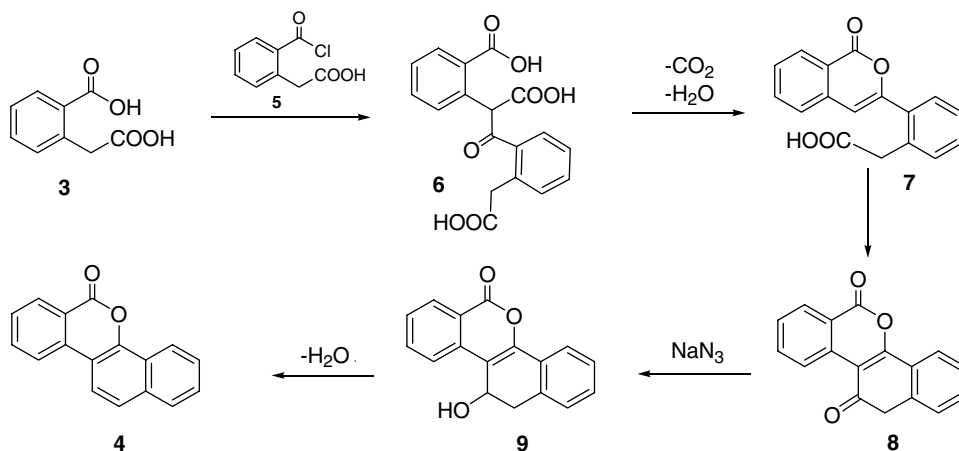
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Our investigation began with an attempted synthesis of the diazide derived from homophthalic acid (**3**). *N,N*-Dimethylchlorosulfite methaniminium chloride, formed from thionyl chloride and dimethylformamide, has been shown as an efficient reagent for the synthesis of acyl azides from carboxylic acids.<sup>11</sup> Thus in our study, homophthalic acid **3** was reacted with thionyl chloride, DMF and sodium azide in the presence of tetrabutylammonium bromide as catalyst using CH<sub>2</sub>Cl<sub>2</sub> as the solvent. Unfortunately, the desired diazide derived from homophthalic acid was not detected. Only, 6*H*-dibenzo[*c,h*]chromen-6-one<sup>12</sup> (**4**) was formed in 41% yield, which was characterized by comparison of its spectral data with those published in the literature (Scheme 1).

A tentative mechanism for the formation of **4** is outlined in Scheme 2. This reaction presumably occurs by the initial attack of acid chloride **5**, formed under the reaction conditions, at the methylene group of homophthalic acid to form condensation product **6** (Scheme 2). Intermediate **6** undergoes decarboxylation and cyclization to produce isocoumarin derivative **7**. Further cyclization of **7** and reduction of the carbonyl group in **8** with NaN<sub>3</sub><sup>13</sup>



Scheme 1.



Scheme 2.

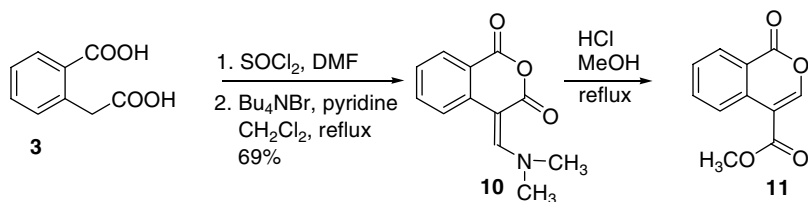
followed by H<sub>2</sub>O elimination results in the formation of **4**. This method represents an easy synthesis of dibenzochromen-6-one derivatives in a single step.

Since the azide anion was not incorporated into **4**, the same reaction was run in the absence of NaN<sub>3</sub>. Instead of the formation of dibenzochromen-6-one **4**, aminomethylene compound **10** was formed as the sole product in 69% yield (Scheme 3). Intermediate **10** was identified by comparison of the spectral data with those reported in the literature, obtained under Vilsmeier conditions.<sup>14</sup>

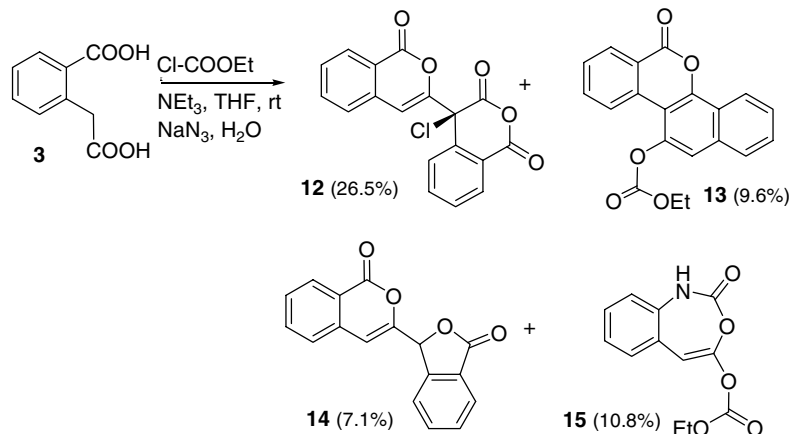
Intermediate **10** was further converted to isocoumarin derivative **11** in 76% yield by reaction with methanol sat-

urated with hydrogen chloride. As an alternative method for the formation of acyl azides, homophthalic acid **3** was treated with ethyl chloroformate in the presence of triethylamine followed by the addition of a solution of NaN<sub>3</sub> in water. A careful examination of the reaction mixture revealed the formation of four compounds **12–15** (isolated yields: 26.5%, 9.6%, 7.1%, 10.8%, respectively) (Scheme 4). Compound **12** precipitated from the reaction media. The other isomers were separated on a silica gel column eluting with dichloromethane.

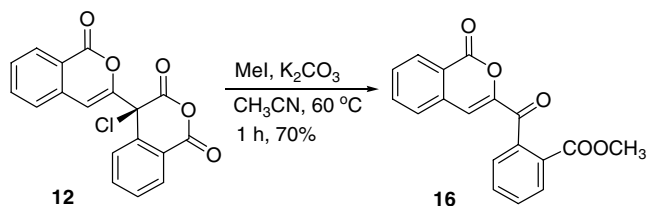
COSY, HMQC and HMBC experiments allowed the assignment of structures **12–15**. For the formation of **13** we suggest a similar mechanism to that depicted in Scheme 2. The intermediate **8** formed can undergo tau-



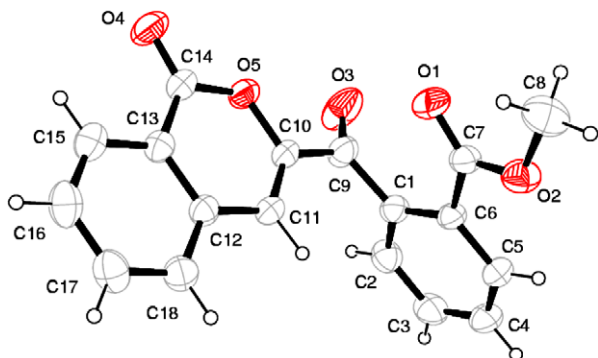
Scheme 3.



Scheme 4.



Scheme 5.

Figure 1. ORTEP drawing of **16** at the 50% probability level.

omerization to form the corresponding enol, from which it can easily be trapped with ethyl chloroformate in the presence of a base. An HMBC experiment on **12** confirmed its structure, in particular, from correlation of the carbon atom bearing the chlorine atom with the double bond proton located on the isocoumarin ring and the  $\alpha$ -proton of the other benzene ring. Furthermore, the presence of 18 carbon resonances and other spectral data supported the formation of an anhydride structure. We assume that compound **14** is a secondary product formed from **12** under the reaction conditions. The ring opening of **12** followed by decarboxylation and substitution of the chlorine atom by a carboxylate anion would form lactone **14**. A HMBC experiment on **14** revealed a strong correlation ( $^3J_{\text{CH}}$ ) between the carbon atom (CH) of the lactone ring with the double bond proton as well as with the  $\alpha$ -proton of the second benzene ring. Furthermore, the chemical shifts of the all carbon atoms and other spectral data were in agreement with the proposed structure. For the formation of **15** the following mechanism is suggested. The initially formed acyl chloride can react with azide to give the acyl azide which can then rearrange to the corresponding isocyanate followed by trapping of the isocyanate functionality with the acid  $-\text{OH}$  group under the reaction conditions. Enolization of the carbonyl group followed

by trapping with ethyl chloroformate results in the formation of compound **15**.

The chlorine-containing compound **12** was treated with  $\text{CH}_3\text{I}$  in the presence of  $\text{K}_2\text{CO}_3$  in acetonitrile leading to the isocoumarin derivative **16** as a single compound in 70% yield (Scheme 5). Again, COSY, HMQC and HMBC experiments confirmed the structure. HMBC indicated the presence of a strong correlation between the carbonyl group of the ketone and the double bond proton and the *ortho*-aromatic proton. Finally, an X-ray diffraction analysis of **16** was undertaken. The results of this study confirmed, unambiguously the proposed structure (Fig. 1). The compound crystallize in the triclinic space group  $P\bar{1}$  (No. 2) with  $Z=2$ ; the isochromene moiety is planar. The C(1)–C(6) disubstituted benzene ring is twisted at a dihedral angle of  $84.10(5)^\circ$  with respect to the isochromene ring system.

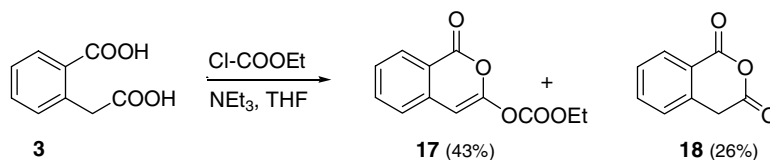
Next, homophthalic acid **3** was reacted with ethyl chloroformate and triethylamine in the absence of  $\text{NaN}_3$ . Surprisingly, none of the products obtained in Scheme 4 were formed. Instead, isocoumarin derivative **17**<sup>15</sup> was formed, in 43% yield, as the major product along with anhydride **18** in 26% yield (Scheme 6). The structure of **17** was deduced from NMR spectral data.

In conclusion, the attempted synthesis of a diazide derived from homophthalic acid failed, however, unusual coumarin derivatives formed instead. The products isolated were different depending on whether the reaction was carried out in the presence or absence of  $\text{NaN}_3$ , despite the fact that the  $\text{N}_3^-$  anion was not incorporated into the molecule.  $\text{NaN}_3$  plays an important role in determining the mode of these reactions; this role is currently under investigation.

Crystallographic data (excluding structure factors) for the structures in this Letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 626642. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

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Scheme 6.

meter purchased under Grant No. 2003/219 of the University Research Fund.

### Supplementary data

Spectral data on all compounds including the NMR spectra are provided. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.01.098.

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