SYNTHESIS OF O-SUBSTITUTED BENZOPHENONES BY GRIGNARD REACTION OF 3-SUBSTITUTED ISOCOUMARINS

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ABSTRACT

A series of o-substituted benzophenones was prepared by efficient method involving the 3-substituted isocoumarins and phenylmagnesium bromide. The reaction was completed in presence of anhydrous ether under dry ice-solvent bath in few hours with modest to good yields.

Key words: Isocoumarins, diketones, aryl, phenyl magnesium bromide, ether, dry ice.

INTRODUCTION

Synthetic and naturally occurring isocoumarins possess important biological properties. They are useful intermediates in the synthesis of a variety of carbocyclic and heterocyclic compounds1-4. In continuous of our interest in carbon-carbon bond formation reaction1-12, the present paper presents an efficient method to synthesize o-substituted benzophenones (2) from 3-substituted isocoumarins (1) and phenyl magnesium bromide in presence of anhydrous ether under dry ice-solvent bath. Benzophenone and its derivatives are important intermediates in dyes, pharmaceutical and other chemical industries3,9,11. Benzophenone analogues synthesized by several scientists have been reported as effective anti-inflammatory agents13-15. Recently synthesis and structure-activity relationship of benzophenones as novel class of p38 MAP kinase inhibitors with high anti-inflammatory activity have been reported19. O-substituted benzophenones could provide more complex polyaromatics, for example, pentamethoxy-diphenylmethanone16, and similarly substituted benzophenones could lead to useful synthons for fullerenes. Generally, they are prepared via Friedel-Crafts acylation of aromatic compounds17-20, however this paper describes the Grignard reaction for their synthesis, (Scheme 1).

EXPERIMENTAL

Materials and Methods

Chemicals were purchased from Aldrich Chemical Co. and used as such without further purification. TLC was performed on silica plates with visualization by UV-light. Melting points were taken in open capillary tubes and corrected with reference to benzoic acid. IR spectra in KBr pellets were recorded on a Perkin Elmer (Model: 1600 FT-IR). 1H NMR and 13C NMR (100 MHz) spectra were recorded on a Bruker 400 MHz spectrometer in CDCl3 or DMSO (with TMS as internal references). LC–MS analyses were performed with LCMS-Agilent- 1100 series (DAD and MS). Mass spectra were recorded on Nucon Infrared spectrophotometer. Elemental analyses of all compounds were performed on Elementar Vario Micro CHNS analyzer.

Synthesis of o-substituted benzophenones from isocoumarins (1a-f)

Synthesis of the hitherto title compounds is as outlined in Scheme 1. Grignard reaction of 3-substituted isocoumarins (1) in anhydrous ether afforded substituted benzophenones (2) in modest to good yield. The results have been tabulated as Table 1. All products were characterized by IR, 1H NMR and mass spectrophotometers.

Typical Procedure:

To a stirred solution of 3-p-Methoxyphenylisocoumarin, 1a (20mmol) in anhydrous ether (50ml) maintained at -78°C in dry ice-solvent bath, phenyl magnesium bromide in ether (40 mmol) was added. Magnetic stirring was continued for 4 hrs and completion of the reaction was monitored by TLC using hexane and ethyl acetate 95:5 as eluant. The reaction mixture was worked up at room temperature by treating with aq. NH4Cl and then extracted with ethyl acetate. The crude product was purified by silica gel column (using hexane and ethyl acetate) as eluant. The product, 2a was obtained with 77% yield. The product obtained was characterized by IR, LCMS, HRMS, 1H-NMR and 13C-NMR techniques. The reaction of Phenyl magnesium bromide with various isocoumarins, 1a-f was tabulated (Table 1).

Table 1: Synthesis of o-substituted benzophenones from 3-substituted isocoumarins and phenyl magnesium bromide.

<table>
<thead>
<tr>
<th>Isocoumarins*, (1) / Products (2)</th>
<th>R</th>
<th>Yield%</th>
</tr>
</thead>
<tbody>
<tr>
<td>p-CH3-C6H4-a</td>
<td></td>
<td>77</td>
</tr>
<tr>
<td>p-CH2-C6H4-b</td>
<td></td>
<td>81</td>
</tr>
<tr>
<td>p-NO2-C6H4-c</td>
<td></td>
<td>73</td>
</tr>
<tr>
<td>p-Cl-C6H4-d</td>
<td></td>
<td>72</td>
</tr>
<tr>
<td>CH2CH2CH2CH3-e</td>
<td></td>
<td>80</td>
</tr>
<tr>
<td>1-Cyclohexyl, f</td>
<td></td>
<td>82</td>
</tr>
</tbody>
</table>

1^o Isocoumarin, 1a-f (20mmol) in anhydrous ether (50ml) in dry ice-solvent bath for 4 hours, isolated yield, 2.

The spectral data of compounds, 2a-2f is given below.

2-(2-Benzoylphenyl)-1-(4-methoxy phenyl) ethanone (2a) Gummy solid, IR cm⁻¹ 3053.6, 2953.6, 2984.6, 2867.8, 1724.8, 1676.4; 1H NMR (400 MHz, CDCl3) δ 7.93(s, 3H, OCH3), 6.86-6.89 (m, 2H), 7.33-7.55 (m, 7H), 7.81-7.83 (m, 3H), 7.91-8.06 (m, 2H); 13C NMR (100 MHz, CDCl3) 198.57 (CO), 130.58, 130.64, 131.59, 132.63, 132.74, 134.48, 137.86, 138.25, 139.39 (13C, Aryl), 168.18 (C=O) 198.57 (COCH3), 126.52, 128.33, 128.76, 129.73, 130.58, 130.64, 131.59, 132.63, 132.74, 134.48, 137.86, 138.25, 139.39 (13C, Aryl), 168.18 (C=O) 198.57 (COCH3), 126.52, 128.33, 128.76, 129.73, 130.58, 130.64, 131.59, 132.63, 132.74, 134.48, 137.86, 138.25, 139.39 (13C, Aryl), 168.18 (C=O) 198.57 (COCH3), 126.52, 128.33, 128.76, 129.73, 130.58, 130.64, 131.59, 132.63, 132.74, 134.48, 137.86, 138.25, 139.39 (13C, Aryl), 168.18 (C=O) 198.57 (COCH3), 126.52, 128.33, 128.76, 129.73, 130.58, 130.64, 131.59, 132.63, 132.74, 134.48, 137.86, 138.25, 139.39 (13C, Aryl), 168.18 (C=O).
The C-C bond formation was successfully carried out by Grignard reaction of isocoumarins giving rise to the diketoderivatives. These diketo derivatives may be used as synthetic intermediates in Aldol reaction (our laboratory group’s research area) to give biologically important polyaromatic hydrocarbons and in other reaction, may pave their way in synthesis of useful products.

ACKNOWLEDGEMENT

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REFERENCES


RESULTS AND DISCUSSION

The 3-substituted isocoumarins required for our reaction were prepared by reported procedure. Purified isocoumarins was then allowed to react with Phenyl magnesium bromide in presence of anhydrous ether at -78°C to afford the corresponding hemiacetal which afforded the desired diketo compound.

RESULTS AND DISCUSSION