



ELSEVIER

Contents lists available at ScienceDirect

Comptes Rendus Chimie

www.sciencedirect.com



Full paper/Mémoire

Three-component synthesis of novel spirooxindole–furan derivatives using pyridinium salts

Robabeh Baharfar^{*}, Sakineh Asghari, Farya Zaheri, Narges Shariati

Department of Chemistry, University of Mazandaran, P. O. Box 47415, Babolsar, Iran

ARTICLE INFO

Article history:

Received 12 April 2016

Accepted 5 July 2016

Available online xxxx

Keywords:

Spirooxindole

Interrupted Feist–Bénary reaction

Isatin

1,3-dicarbonyl compounds

Pyridinium salts

ABSTRACT

A simple and efficient synthesis of novel spirooxindole–furan derivatives has been investigated by a modified version of the “interrupted” Feist–Bénary (IFB) reaction of isatin derivatives, 1,3-dicarbonyl compounds and *N*-phenacyl pyridinium salts in the presence of triethylamine. The reaction has been carried out under mild conditions in ethanol, and the products were obtained in good to moderate yields with a simple work-up procedure.

© 2016 Académie des sciences. Published by Elsevier Masson SAS. All rights reserved.

1. Introduction

The oxindole framework has generated considerable interest as a core constituent of many natural products and biologically active molecules. In particular, spirooxindoles are important heterocyclic compounds due to their various biological and pharmacological properties. They are widely used as antimicrobial [1], antitumor [2], and therapeutic agents [3]. On the other hand, furan derivatives have exhibited attractive biological activities, such as antitumor [4], antimicrobial [5,6], antispasmodic [7] and cytotoxic properties [8]. Also, synthesis and pharmacological application of various spirooxindole–furan derivatives have been reported [9–11].

The interrupted Feist–Bénary reaction (IFB) is a base-catalyzed condensation of α -haloketones with 1,3-dicarbonyl compounds, which form highly substituted dihydrofuran derivatives [12,13]. Recently a modified Feist–Bénary reaction for the synthesis of bis-spirooxindole-fused dihydrofurans has been reported

[14]. Also a new variant of this reaction has been reported, including α -tosyloxyacetophenones as electrophiles instead of α -haloketones. It has been shown that phenacyl bromides are poor reactants in the Feist–Bénary reaction, but replacing Br with the tosyloxy group has led to good results [15].

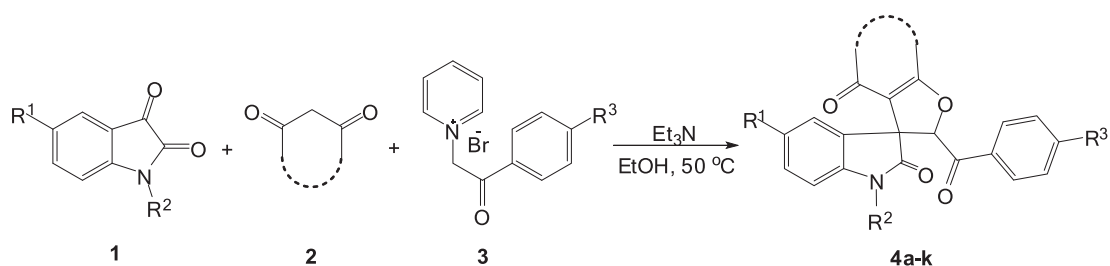
In order to expand the scope of the IFB reaction, and in continuation of our previous works for the synthesis of novel heterocyclic compounds [16–19], we report herein an efficient procedure for the synthesis of new spirooxindole–furan derivatives via the Feist–Bénary reaction of *N*-phenacyl pyridinium salts as a reactive electrophile with 1,3-dicarbonyl compounds and isatin derivatives (Scheme 1).

2. Results and discussion

In order to optimize the conditions, we studied the reaction of *N*-phenacyl pyridinium bromide, dimedone and isatin as the model reaction under various conditions (Table 1). First, the reaction was examined in the presence of different bases. As shown, using triethylamine gave better yields than the other bases (Table 1, entry 5). Then, the effect of various solvents and different temperatures

^{*} Corresponding author.

E-mail address: baharfar@umz.ac.ir (R. Baharfar).



Scheme 1. Preparation of novel spirooxindole–furan derivatives.

Table 1
Optimization of the reaction conditions.^a

Entry	Base (eq)	Solvent	Temp. (°C)	Time (h)	Yields (%)
1	–	EtOH	50	24	–
2	K ₂ CO ₃ (1)	EtOH	50	15	45
3	DBU (1)	EtOH	50	15	60
4	DABCO (1)	EtOH	50	18	65
5	NEt ₃ (1)	EtOH	50	10	85
6	NEt ₃ (0.25)	EtOH	50	24	30
7	NEt ₃ (0.5)	EtOH	50	24	55
8	NEt ₃ (2)	EtOH	50	10	85
9	NEt ₃ (1)	THF	50	15	50
10	NEt ₃ (1)	H ₂ O	50	12	45
11	NEt ₃ (1)	DCM	50	14	72
12	NEt ₃ (1)	–	50	24	60
13	NEt ₃ (1)	EtOH	25	24	40
14	NEt ₃ (1)	EtOH	Reflux	10	80

^a Reaction conditions: *N*-phenacyl pyridinium bromide (1 mmol), dimedone (1 mmol), isatin (1 mmol), different conditions, stirring.

were examined. Using EtOH, the reaction afforded the corresponding product with a good yield (85%) after 10 h at 50 °C (Table 1, entry 5). We also evaluated the amount of triethylamine required for the reaction. It was found that the use of 1 eq of NEt₃ is sufficient to promote the reaction. In the presence of more than this amount of the base, neither the yield nor the reaction time was improved.

After optimization of the model reaction, a variety of spirooxindole–furan derivatives were synthesized with the three-component reaction of isatin derivatives with 1,3-dicarbonyl compounds and pyridinium salts according to Scheme 1. The target compounds were obtained in good yields with high purity (Table 2). The structure of products was confirmed by IR, ¹H and ¹³C NMR spectroscopy and mass spectrometry.

The mass spectrum of **4a** displayed the molecular ion (M⁺) peak at *m/z* 387, which was consistent with the product's structure. The ¹H NMR spectrum of **4a** in CDCl₃ exhibited two singlets at 1.15 and 1.22 ppm due to the two methyl groups of dimedone, two doublets at 2.14 and 2.31 ppm (²*J*_{HH} = 16.4 Hz), two doublets 2.65 and 2.68 ppm (²*J*_{HH} = 18.0 Hz) for diastereotopic protons of two CH₂ groups, and one singlet at 6.48 ppm for CH group of furan ring. The aromatic protons appeared as one doublet at 6.45 ppm (³*J*_{HH} = 7.6 Hz) and four multiplets at around 6.59–7.44 ppm. The proton of NH in oxindole moiety was observed as one broad singlet at 8.10 ppm. The proton-decoupled ¹³C NMR spectrum of **4a** showed 22 distinct resonances, in agreement with the proposed structure. The spiro carbon displayed a signal at 58.9 ppm.

A plausible mechanism for the formation of products **4a–k** is given in Scheme 2. Initially, Knoevenagel condensation between isatin derivatives and CH-acid of 1,3-dicarbonyl compounds in the presence of triethylamine affords adduct **5**. Also the pyridinium salt is deprotonated by triethylamine to give pyridinium ylide **6**. In the second step, a Michael addition of the pyridinium ylide **6** to adduct **5** produces dipolar intermediate **7**. Finally, the attack of enolate moiety in **7** to the electrophilic carbon bearing the leaving pyridyl group leads to spirooxindole fused furan derivative.

3. Experimental

3.1. Materials and techniques

All chemicals and reagents were purchased from Fluka and Merck and used without further purification. Melting points were measured with an Electrothermal 9100 apparatus. NMR spectra were recorded with a Bruker DRX-400 AVANCE instrument (400.1 MHz for ¹H, 100.6 MHz for ¹³C) with CDCl₃ as solvent. Chemical shifts (δ) are given in parts per million (ppm) relative to TMS, and coupling constants (*J*) are reported in hertz (Hz). IR spectra were recorded on an FT-IR Bruker vector 22 spectrometer. Mass spectra were recorded on a Finnigan-Matt 8430 mass spectrometer operating at an ionization potential of 70 eV.

3.2. General procedure for the synthesis of compounds **4a–k**

N-Phenacyl pyridinium bromide derivatives were obtained by the reaction of phenacyl bromide derivatives and pyridine in acetonitrile medium. Triethylamine (1 mmol) was added to a mixture of isatin (1 mmol) and 1,3-dicarbonyl compounds (1 mmol) and *N*-phenacyl pyridinium bromide in ethanol (5 ml) preheated at 50 °C. The reaction mixture was then stirred at 50 °C for appropriate time. After completion of the reaction, monitored by TLC on SiO₂ using EtOAc/hexane (1:1) as the eluent, the solvent was removed under reduced pressure and the product was obtained by recrystallization from diethyl ether.

3.3. Physical and spectral data for compounds **4a–k**

3.3.1. 2-Benzoyl-6,6-dimethyl-6,7-dihydro-2H-spiro[benzofuran-3,3'-indoline]-2',4(5H)-dione (**4a**)

White powder, mp: 275–277 °C; yield (0.33 g, 85%); IR (KBr) (*ν*_{max}, cm⁻¹): 3430 (NH), 2939 (C_{sp3}–H), 1725, 1696

Download English Version:

<https://daneshyari.com/en/article/6468725>

Download Persian Version:

<https://daneshyari.com/article/6468725>

[Daneshyari.com](https://daneshyari.com)