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Original article

A synthesis of spirofuran-indenoquinoxalines *via* isocyanid-based one-pot four-component reaction

Nahid Sabouri [a], Gholam Hossein Mahdavinia [a,*], Behrouz Notash [b]

[a] Department of Chemistry Marvdasht Branch, Islamic Azad University, Marvdasht, Iran
[b] Department of Chemistry, Shahid Beheshti University, G. C., Evin, Tehran 1983963113, Iran

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ABSTRACT

A simple and versatile procedure for the combinatorial synthesis of (*Z*)-dialkyl-5-(alkylimino)-5*H*-spiro[furan-2,11′-indeno[1,2-*b*]quinoxaline]-3,4-dicarboxylates *via* the catalyst-free one-pot four-component reaction of ninhydrin, benzene-1,2-diamines, dialkyl acetylenedicarboxylates and isocyanides is described.

1. Introduction

Multicomponent reactions (MCRs), particularly one-pot processes, are of current interest to organic chemists because of being rapid, their convergence, productivity, facile execution [1] cost-effectiveness such as atom economy [2] and lower the costs of reagents and solvents [3], protection–deprotection steps, less tedious work-up and purification [4]. Multicomponent reactions provide unmatched opportunities for the expeditious increase of complexity and diversity in synthetic outcomes. Isocyanide-based multicomponent reactions (IMCRs) have emerged as an efficient and powerful tool in synthetic organic chemistry [5]. One class of these reactions is the generation of zwitterionic intermediates with the nucleophilic addition of isocyanides to activate acetylene [6].

Compounds containing furan rings are extensively found in many biologically active natural products. They are used in preparation of many pharmaceutical products such as ascorbic acid [7], ranitidine [8], phomactin A [9], azimilide [10], dantrolene [11], nitrofurazone [12], perillene [13], teubrevin G and teulepicin [14]. Moreover, in commerce and business, furans are important intermediates in the preparation of dyes, essential oils, agrochemical bioregulators, cosmetics and photosensitizers [15,16].

Much attention has been devoted to a large variety of nitrogen-containing heterocyclics and heterocyclic quinoxalines because of their pharmacological properties and clinical applications [17]. The quinoxaline derivatives are an important group of aza-polycyclics [18], while indenoquinoxaline derivatives are important classes of *N*-heterocycles since both are useful intermediates for spiroindeno synthesis. The main structure of many spiro compounds exhibit valuable (advantageous) pharmacological properties such anti-tumor agents [19,20], anti-cancer [21], natural alkaloids [22], and also biological properties like anti-bacterial, anti-microbial [23], with an inhibitor growth factor receptor [24] of particular interest. Spiroheterocycles are also of considerable interest because the presence of a spirocarbon provides a strengthening of the structure [22,25] and together with a variety of furanes are the main important core of many pharmacological agents [15].

Existing furan and quinoxaline moieties in one spiro molecule can be attractive to organic and biological chemists due to the incorporation of more than one heterocyclic scaffold in one structure causes interesting biological properties. We therefore sought to MW irradiation in good yields [26].

In continuation of this work, develop a simple and versatile procedure for the combinatorial synthesis of a spiro-substituted furan-indenoquinoxaline library for biological screening.

In 2004 Azizian *et al.*, reported the synthesis of spirofuran-indenoquinoxalines *via* a three-component condensation reaction in DMF using herein, we report a one-pot, four-component procedure for synthesis of (*Z*)-dialkyl-5-(alkylimino)-5*H*-spiro[furan-2,11′-indeno[1,2-*b*]quinoxaline]-3,4-dicarboxylates in excellent yields, *via* four component reaction ninhydrin, benzene-1,2-diamines,

* Corresponding author.
E-mail address: hmahdavinia@gmail.com (G.H. Mahdavinia).

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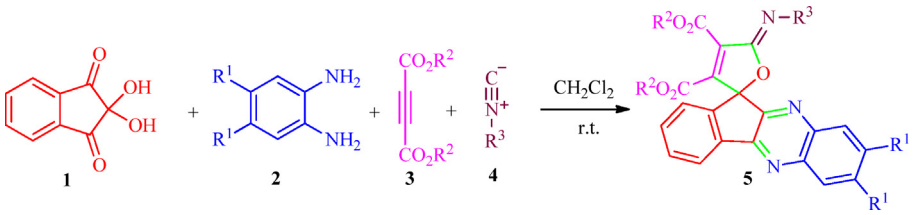


Scheme 1. Preparation of spirofuran-indenoquinoxalines derivatives.

and zwitterionic made up of dialkylacetylenedicarboxylates and alkylisocyanide in the CH_2Cl_2 at room temperature (Scheme 1).

2. Experimental

Melting points and IR spectra of all compounds were measured with an Electrothermal 9200 apparatus and a Perkin–Elmer 783 FTIR spectrometer, respectively. Also, the ^1H NMR and ^{13}C NMR spectrum were recorded on a Bruker Avance DPX-250 instrument using $CDCl_3$ and DMSO-d_6 as internal standard at 250 and 62.5 MHz, respectively. All of the compounds were purchased from Fluka, Merck, and Aldrich companies, and used without further purification.

2.1. General procedure for the preparation of compounds 5

Ninhydrin **1** (1 mmol), benzene-1,2-diamine **2** (1 mmol) were added at r.t. to CH_2Cl_2 (10 mL) while stirring. After *ca.* 10 min, the appropriate acetylenedicarboxylate **3** (1 mmol) in dichloromethane (5 mL) and the appropriate isocyanide **4** (1 mmol) in dichloromethane (5 mL) simultaneously were added dropwise over 20 min and the reaction mixture was stirred for 8 h. After completion of the reaction, the solvent was removed under vacuum and the product **5** was crystallized out from an EtOH–H_2O and washed with Et_2O (4 mL × 2) to give a white crystalline solid.

(*Z*)-Dimethyl-5-(*tert*-butylimino)-5*H*-spiro[furan-2,11′-indeno[1,2-*b*]quinoxaline]-3,4-dicarboxylate (**5a**): White crystal, mp: 277–279 °C; IR (KBr): ν_{max} 1750, 1725, 1685; ^1H NMR (250 MHz, $CDCl_3$): δ 1.56 (s, 9H, 3Me), 3.39 (s, 3H, OMe), 3.96 (s, 3H, OMe), 7.44–7.48 (m, 1H, Ar), 7.50–7.64 (m, 3H, Ar), 7.66–7.79 (m, 3H, Ar), 8.12–8.20 (m, 1H, Ar); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 30.70, 31.40, 54.09, 54.30, 61.12, 112.24, 113.31, 124.55, 126.87, 130.59, 130.98, 131.13, 132.22, 132.74, 133.24, 139.62, 141.92, 142.39, 144.44, 154.17, 157.32, 162.05.

(*Z*)-Dimethyl-5-(cyclohexylimino)-5*H*-spiro[furan-2,11′-indeno[1,2-*b*]quinoxaline]-3,4-dicarboxylate (**5b**): White crystal; mp 233–235 °C; IR (KBr): ν_{max} 1751, 1728, 1681, 1439; ^1H NMR (250 MHz, DMSO-d_6): δ 1.18–1.89 (m, 10H, $5CH_2$ of cyclohexyl), 4.09 (q, 1H, *J = 18.5 Hz*, CH–N of cyclohexyl), 3.31 (s, 3H, OMe), 3.91 (s, 3H, OMe), 7.53–7.56 (m, 1H, Ar), 7.65–7.77 (m, 3H, Ar), 7.80–7.95 (m, 3H, Ar), 8.16–8.21 (m, 1H, Ar); ^{13}C NMR (62.5 MHz, DMSO-d_6): δ 23.67, 25.20, 32.21, 32.31, 33.12, 38.13, 52.96, 53.24, 64.16, 88.12, 119.71, 123.34, 125.67, 125.94, 129.40, 130.05, 131.4, 131.61, 133.00, 137.06, 141.16, 141.5, 143.12, 162.22, 166.19.

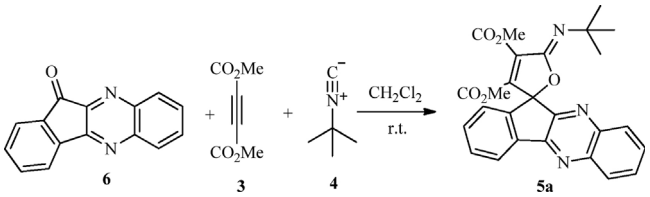
(*Z*)-Diethyl-5-(cyclohexylimino)-5*H*-spiro[furan-2,11′-indeno[1,2-*b*]quinoxaline]-3,4-dicarboxylate (**5c**): White crystal; mp 220–222 °C; IR (KBr): ν_{max} 2940, 1743, 1720, 1685, 1651; ^1H NMR (250 MHz, $CDCl_3$): δ 0.84 (m, 3H, Me), 1.45 (m, 3H, Me), 1.20–1.82 (m, 10H, $5CH_2$ of cyclohexyl), 3.61 (m, 1H, CH–N of cyclohexyl), 3.85 (dq, 2H, ^2J = 15.7 Hz, ^3J = 6.5 Hz, OCH_2), 4.51 (m, 2H, OCH_2), 7.28–8.23 (m, 8H, Arom.); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 13.78, 14.53, 25.07, 25.16, 2609, 33.58, 33.63, 57.14, 62.08, 62.95, 90.26, 123.15, 124.91, 129.65, 129.80, 130.45, 130.96, 131.86, 132.62, 138.36, 139.27, 142.12, 142.14, 143.36, 143.42, 154.46, 155.14, 157.68, 159.88, 162.16.

(*Z*)-Dimethyl-5-(*tert*-butylimino)-8′-methyl-5*H*-spiro[furan-2,11′-indeno[1,2-*b*]quinoxaline]-3,4-dicarboxylate (**5d**): White crystal; mp 222–225 °C; IR (KBr): ν_{max} 1752, 1731, 1666, 1649; ^1H NMR (250 MHz, $CDCl_3$): δ 1.25 (s, 9H, 3Me), 2.53 (s, 3H, Me), 3.44 (s, 3H, OMe), 4.03 (s, 3H, OMe), 7.49–8.20 (m, 7H, Ar.); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 29.95, 33.64, 53.15, 53.64, 55.68, 90.76, 123.24, 124.72, 129.66, 129.78, 130.47, 130.96, 131.86, 132.62, 138.30, 140.60, 141.02, 142.17, 143.29, 143.44, 153.06, 154.37, 157.58, 160.48, 162.86.

(*Z*)-Dimethyl-5-(cyclohexylimino)-8′-methyl-5*H*-spiro[furan-2,11′-indeno[1,2-*b*]quinoxaline]-3,4-dicarboxylate (**5e**): White crystal; mp 237–238 °C; IR (KBr): ν_{max} 1752, 1729, 1675, 1646; ^1H NMR (250 MHz, $CDCl_3$): δ 1.18–1.84 (m, 10H, $5CH_2$ of cyclohexyl), 2.51 (s, 3H, Me), 3.44 (s, 3H, OMe), 3.59 (m, 1H, CH–N of cyclohexyl), 4.03 (s, 3H, OMe), 7.38–8.25 (m, 7*H*, Ar); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 20.65, 20.84, 25.12, 26.06, 33.57, 53.11, 53.70, 57.24, 90.78, 122.96, 124.74, 128.95, 129.66, 131.84, 132.18, 138.65, 139.13, 140.35, 140.98, 141.56, 142.24, 142.33, 142.86, 153.51, 156.40, 160.45, 162.65.

(*Z*)-Dimethyl-5-(*tert*-butylimino)-7′,8′-dichloro-5*H*-spiro[-furan-2,11′-indeno[1,2-*b*]quinoxaline]-3,4-dicarboxylate (**5f**): White crystal; mp: 219–222 °C; IR (KBr): ν_{max} 1758, 1764, 1671, 1653; ^1H NMR (250 MHz, $CDCl_3$): δ 1.35 (s, 9*H*, Me), 3.35 (s, 3H, OMe), 3.84 (s, 3H, OMe), 7.17–8.22 (m, 6H, Ar); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 29.7, 52.78 53.3, 56.9, 78.49, 118.59, 123.06, 123.14, 124.50, 129.86, 130.57, 131.08, 131.68, 132.2, 132.81, 143.14, 153.74, 161.43, 163.64.

(*Z*)-Dimethyl-7′,8′-dichloro-5-(cyclohexylimino)-5*H*-spiro[-furan-2,11′-indeno[1,2-*b*]quinoxaline]-3,4-dicarboxylate (**5g**): White crystal; mp: 247–249 °C; IR (KBr): ν_{max} 1750, 1726, 1684, 1440; ^1H NMR (250 MHz, $CDCl_3$): δ 1.11–1.92 (m, 10H, $5CH_2$ of



Scheme 2. The synthesis of spirofuran-indenoquinoxalines *via* a three-component condensation reaction.

Table 1
Optimization of conditions for the formation of spirofuran-indenoquinoxaline **5a**.

Entry	Solvent	*T* (°C)	Time (h)	Yield (%)
1	EtOH	Reflux	10	None
2	CH_2Cl_2	Reflux	24	58
3	CH_2Cl_2	r.t.	8	98
4	EtOH	r.t.	24	None
5	THF	r.t.	24	30
6	H_2O	r.t.	24	None
7	MeOH	r.t.	24	None
8	Et_2O	r.t.	10	45