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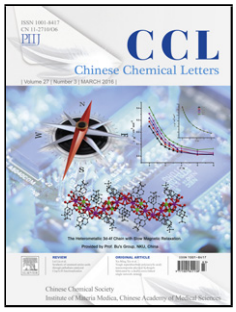

Title: A synthesis of spirofuran-indenoquinoxalines *via* isocyanid-based one-pot four-component reaction

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Graphical Abstract

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

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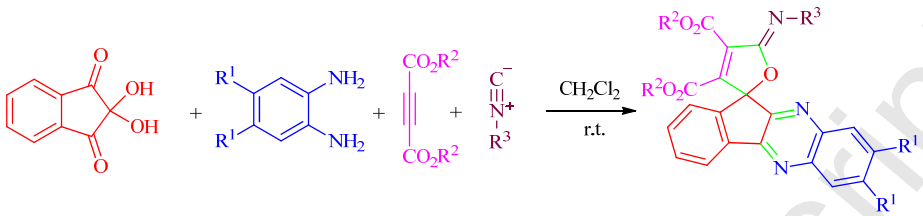

A synthesis of (*Z*)-dialkyl-5-(alkylimino)-5*H*-spiro[furan-2,11'-indeno[1,2-*b*]quinoxaline]-3,4- dicarboxylates *via* one-pot four-component reaction is described.

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Original article

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

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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 Azizan, *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'-

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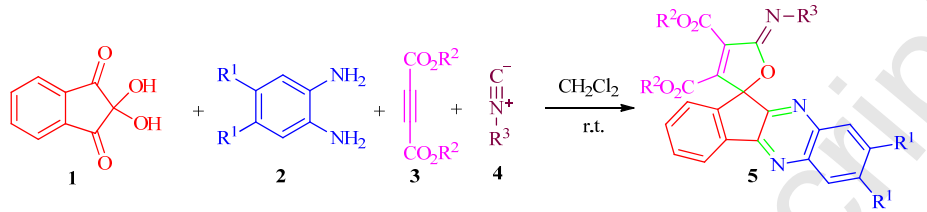
indeno[1,2-*b*]quinoxaline]-3,4-dicarboxylates in excellent yields, *via* four component reaction ninhydrin, benzene-1,2-diamines, and zwitterionic made up of dialkylacetylenedicarboxylates and alkylisocyanide in the CH_2Cl_2 at room temperature (Scheme 1).

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 ^{1}H 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.



Scheme 1. Preparation of spirofuran-indenoquinoxalines derivatives.

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; ^{1}H 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; ^{1}H 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; ^{1}H 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; ^{1}H 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; ^{1}H 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, 7H, 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.

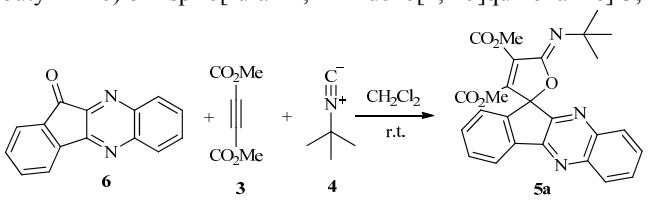
(*Z*)-Dimethyl-5-(*tert*-butylimino)-7',8'-dichloro-5*H*-spiro[furan-2,11'-indeno[1,2-*b*]quinoxaline]-3,4-dicarboxylate (**5f**): White crystal; mp: 219-222 °C; IR (KBr): ν_{max} 1758, 1764, 1671, 1653; ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.35 (s, 9H, Me), 3.35 (s, 3H, OMe), 3.84 (s, 3H, OMe), 7.17-8.22 (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; ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.11-1.92 (m, 10H, 5CH_2 of

cyclohexyl), 3.42 (s, 3H, OMe), 3.99 (s, 3H, OMe), 7.25-8.30 (m, 6H, Ar); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 25.6, 29.7, 33.16, 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.

3. Results and discussion

Recent success in conjunction with isocyanide-based, multicomponent reactions provided a means to constructing novel heterocycles systems [15]. The polycyclic heterocycles, like indenoquinoxalines, leads to forming the rings of spiroindeno-quinoxalines. In our initial test reaction, the three components, between 11*H*-indeno[1,2-*b*]quinoxalin-11-one **6a**, tert-butyl isocyanide **4** and dimethylacetylenedicaboxylate (DMAD) **3** without any catalyst in dry CH_2Cl_2 at r.t for 10 h, gave (*Z*)-dimethyl-5-(tert-butylimino)-5*H*-spiro[furan-2,11'-indeno[1,2-*b*]quinoxaline]-3,4-dicarboxylate **5a** in excellent yield (Scheme 2).



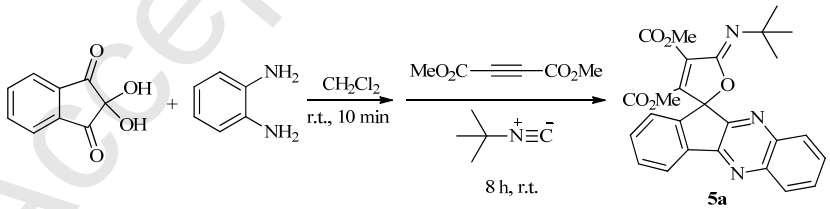
Scheme 2. The synthesis of spirofuran-indenoquinoxalines *via* a three-component condensation reaction.

To optimize the conditions, various aprotic and protic solvents were investigated at reflux and r.t. conditions. In protic solvents the desired product was not obtained. However, the desired product was formed in aprotic solvents and was produced under the. Best the conditions in dry CH_2Cl_2 at r.t. with excellent yield. The results are summarized in Table 1.

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

To minimize the steps required for the formation of the product and to simplify the procedure, a one-pot, four-component reaction was planned (Scheme 1) understanding the necessity to separate intermediate **6** as well as the control of reaction time. Our studies for this model reaction revealed that **5a** could be synthesized in a one-pot reaction if **6a** was prepared *in situ* from condensation of ninhydrin **1** with benzene-1,2-diamine **2a** at r.t. within 10 min., then treated with equimolar amounts of DMAD and tert-butyl isocyanide within 8 h at r.t (Scheme 3). Therefore, the implication of 11*H*-indeno[1,2-*b*]quinoxalin-11-one **6a** in the initial reaction is confirmed.



Scheme 3. A synthesis of spirofuran-indenoquinoxalines *via* isocyanid-based one-pot four-component reaction

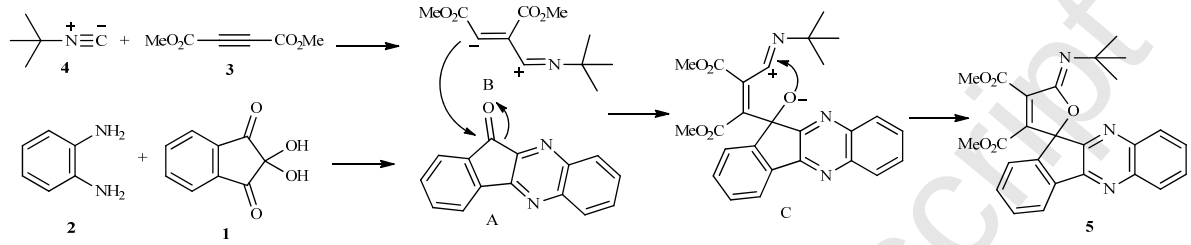
Having optimized the conditions, various isocyanide **4** and acetylenedicarboxylate **3** were condensed with ninhydrin **1** and benzene-1,2-diamines **2** to afford the corresponding products **5a-5g** (Scheme 1). The results presented in Table 2 show that the various benzene-1,2-diamine and the methyl and ethyl acetylenedicarboxylates and isocyanides were successfully applied in this process to afford the corresponding (*Z*)-dialkyl-5-(alkylimino)-5*H*-spiro[furan-2,11'-indeno[1,2-*b*]quinoxaline]-3,4-dicarboxylates in excellent yields.

Table 2
One-pot, four-component synthesis of spirofuran-indenoquinoxalines **5a–5g**.

Entry	R^1	R^2	R^3	Product	Yield (%)
1	H	Me	*t*-Bu	**5a**	97
2	H	Me	Cyclohexyl	**5b**	98
3	H	Et	Cyclohexyl	**5c**	94
4	Me	Me	*t*-Bu	**5d**	98
5	Me	Me	Cyclohexyl	**5e**	96

6	Cl	Me	*t*-Bu	**5f**	86
7	Cl	Me	Cyclohexyl	**5g**	84

The plausible mechanism for the synthesis of (*Z*)-dialkyl-5-(alkylimino)-5*H*-spiro[furan-2,11'-indeno[1,2-*b*]quinoxaline]-3,4-dicarboxylate compounds **5** is shown in Scheme 4. We envisioned that this reaction could be realized in a one-pot, two-step manner. Initially, ninhydrin **1** and the benzene-1,2-diamine **2** react to form the corresponding indenoquinoxalinone **A**, the zwitterionic intermediate **B**, formed by the 1:1 interaction between the isocyanide and acetylenedicarboxylate, which attacks preferentially the carbonyl group of indeno-quinoxalines **6**, leading to dipolar intermediate **C**, and subsequently leading to ring five-membered and the spirocyclic product **5a**.



Scheme 4. Proposed mechanism for the synthesis of (*Z*)-dimethyl-5-(tert-butylimino)-5*H*-Spiro[furan-2,11'-indeno[1,2-*b*]quinoxaline]-3,4-dicarboxylate.

In order to elucidate the structure of these compounds, we determined the structure of compound **5a** by X-ray crystallography [27]. The ORTEP diagram of **5a** is presented in Fig. 1.

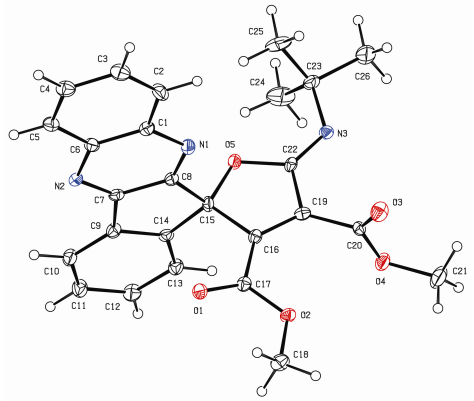


Fig. 1. ORTEP diagram of **5a**. Thermal ellipsoids are at 30% probability level.

4. Conclusion

In conclusion, we have succeeded in developing a novel approach and a clean, convenient, simple and inexpensive method for the synthesis of spiroindenoquinoxalines *via* a one-pot reaction. This procedure offers significant advantages because of the minimization of labor, time, and cost. Noteworthy, our work presents a very easy and simple reaction, at r.t conditions, without any catalyst and in a short time frame. Additionally, the products obtained can be easily isolated *via* crystallization.

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[27] (a) X-Ray data for **5a**: $C_{26}H_{23}N_3O_5$, M = 457.47, orthorhombic system, space group $P2_12_12_1$, a = 11.053(2), b = 12.311(3), c = 16.914(3) Å, V= 2301.6(8) $Å^3$, Z= 4, D_{calc} = 1.320 $g.cm^{-3}$, μ(Mo-Kα)= 0.093 mm^{-1}, T = 120(2) K, crystal size of 0.50 x 0.38 x 0.10 mm^3. The X-ray diffraction measurement was made on a STOE IPDS-2T diffractometer with graphite monochromated Mo-Kα radiation. The structure was solved using SHELXS. The structure refinement and data reduction was carried out with SHELXL using the X-STEP32 suite of programs. The non-hydrogen atoms were refined anisotropically by full matrix least-squares on F^2 values to final R_1= 0.0901, wR_2 = 0.1158 and S = 1.069 with 312 parameters using 6009 independent reflections. Hydrogen atoms were added in idealized positions. The crystallographic information file has been deposited with the Cambridge Data Centre, CCDC 1032226; (b) X-STEP32 Version1.07b, X-ray structure evaluation package, 2000, Stoe&Cie, Darmstadt, Germany.