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Efficient assembly of quinoxaline derivatives from benzene-1,2-diamines, dialkyl acetylenedicarboxylates and ninhydrin

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Abstract: The hitherto unreported, highly functionalized alkyl 2-(2-hydroxy-1,3-dioxo-2,3-dihydro-1*H*-inden-2-yl)-2-(3-oxo-3,4-dihydroquinoxalin-2-yl)acetate derivatives **4** have been synthesized in excellent yields via a one-pot three-component reaction of benzene-1,2-diamines, dialkyl acetylenedicarboxylates, and ninhydrin under mild conditions.

Keywords: benzene-1,2-diamines; dialkyl acetylenedicarboxylates; ninhydrin; quinoxaline.

Introduction

Quinoxaline and its derivatives are attractive chemical candidates in medicinal chemistry due to their capacity to generate biological responses in their interaction with several biological targets [1–5]. They constitute the basis of many insecticides, fungicides, herbicides, as well as are important for human health. Numerous methods are available for the synthesis of quinoxalines including the Bi-catalyzed oxidative coupling of epoxides and ene-1,2-diamines [6], cyclization of α-arylimino oximes [7], heteroannulation of nitroketene *N,S*-arylaminoacetals with $POCl_3$ [8], and condensation of *o*-phenylenediamines and 1,2-dicarbonyl compounds in the presence of various catalysts [9–17]. A literature search has revealed that synthesis of quinoxalines substituted with an indene moiety has not been described. Recently, we have developed an efficient method for the synthesis of functionalized quinoxaline [18–20]. In this article we report an efficient synthesis of functionalized alkyl 2-(2-hydroxy-1,3-dioxo-2,3-dihydro-1*H*-inden-2-yl)-2-(3-oxo-3,4-dihydroquinoxalin-2-yl)acetates **4** (Scheme 1).

Results and discussion

The reaction of benzene-1,2-diamines **1** with acetylenic esters **2** and ninhydrin **3** in MeCN yielded the corresponding functionalized alkyl 2-(2-hydroxy-1,3-dioxo-2,3-dihydro-1*H*-inden-2-yl)-2-(3-oxo-3,4-dihydroquinoxalin-2-yl) acetate derivatives **4** in 83–94% yield (Scheme 1). The structures of compounds **4** are in full agreement with their spectral data. For example, the ^{1}H-NMR spectrum of **4a** exhibits four singlets for methoxy (δ 3.65), methine (δ 4.71), hydroxyl (δ 6.38), and NH (δ 12.59) protons, along with multiplets (7.06–8.08 ppm) for the aromatic protons. The proton-decoupled ^{13}C-NMR spectrum of **4a** exhibits 20 signals in agreement with the proposed structure. An additional support for the proposed structures was obtained by analysis of the infrared and mass spectra and the results of the elemental analysis.

The suggested mechanism is given in Scheme 2. On the basis of well-established chemistry of amines and DMAD [19–21], it can be suggested that the reaction between benzene-1,2-diamine and dialkyl acetylenedicarboxylate generates dihydroquinoxaline **5**. The intermediate product **5** possesses an enamine character and thus undergoes readily a reaction with ninhydrin **3** to produce the final product **4**.

Conclusion

A mild, eco-friendly, one-pot synthesis of a series polysubstituted alkyl 2-(2-hydroxy-1,3-dioxo-2,3-dihydro-1*H*-inden-2-yl)-2-(3-oxo-3,4-dihydroquinoxalin-2-yl)acetates via the reaction of benzene-1,2-diamines, dialkyl acetylenedicarboxylate, and ninhydrin was developed. The advantages of the present method are high efficiency, generality, and a clean reaction profile.

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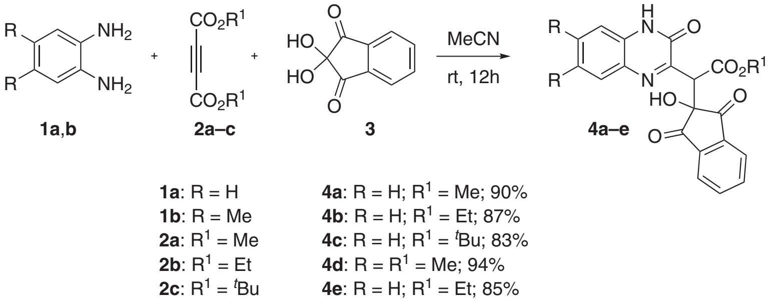
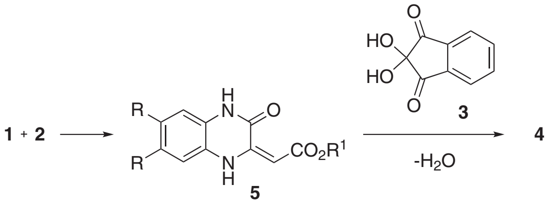


Scheme 1



Scheme 2

Experimental

All commercially available chemicals and reagents were used without further purification. Melting points were determined on an Electrothermal 9100 apparatus and are not corrected. IR spectra were recorded in KBr pellets on a Shimadzu 460 spectrometer. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Bruker AVANCE 400 spectrometer using DMSO-d_6 as solvent. Electron-impact mass spectra were obtained at 70 eV on a Finnigan-MAT-8430 mass spectrometer. Elemental analyses for C, H and N were obtained on a Heraeus CHNO-Rapid analyzer.

General procedure for the preparation of 4a–e

In a round bottom flask equipped with a magnetic stirrer, benzene-1,2-diamine (1 mmol) or 4-methylbenzene-1,2-diamine (1 mmol) and dialkyl acetylenedicarboxylate (1 mmol) in acetonitrile (5 mL) were charged and the mixture was stirred vigorously at room temperature for 10 min. Then, ninhydrin (1 mmol) was added and the mixture was stirred at room temperature for an additional 12 h. After completion of the reaction, as indicated by TLC (EtOAc-hexane 1:3), the resulting precipitate was filtered and washed with ethanol to afford pure product **4**.

Methyl 2-(2-hydroxy-1,3-dioxo-2,3-dihydro-1*H*-inden-2-yl)-2-(3-oxo-3,4-dihydroquinoxalin-2-yl)acetate (4a) Yellow solid; yield 0.34 g (90%); mp 220°C; IR: ν_{max} 3224–3327 (OH), 1748 (C=O), 1705 (C=O), 1658 cm^{-1} (C=O); ^{1}H NMR: δ 3.65 (s, 3H, MeO), 4.71 (s, CH), 6.38 (s, OH), 7.06 (d, ^3J = 6.8, CH), 7.12–7.43 (m, 3 CH), 8.00 (m, 4 CH), 12.59 (s, NH); ^{13}C NMR: δ 53.8 (CH), 54.4 (MeO), 75.6 (C), 117.3, 124.9, 125.0, 125.1, 128.0, 131.5, 132.4, 133.5, 137.6, 138.1, 141.8, 143.0, 155.3, 156.6 (C=O), 169.1 (C=O), 198.4 (C=O), 199.8 (C=O); EI-MS: *m/z* 378 (4, M$^+$), 218 (96), 176 (100), 148 (63), 104 (52). Anal. Calcd for $C_{20}H_{14}N_2O_6$ (378.34): C, 63.49; H, 3.73; N, 7.40. Found: C, 63.55; H, 3.75; N, 7.42.

Ethyl 2-(2-hydroxy-1,3-dioxo-2,3-dihydro-1*H*-inden-2-yl)-2-(3-oxo-3,4-dihydroquinoxalin-2-yl)acetate (4b) Yellow solid; yield 0.34 g (87%); mp 195–197°C; IR: ν_{max} 3284 (NH), 3220 (OH), 1742 (C=O), 1702 (C=O), 1651 cm^{-1} (C=O); ^{1}H NMR: δ 1.14 (t, ^3J = 7.2, CH_3), 4.12 (q, ^3J = 7.2 Hz, CH_2O), 4.69 (s, CH), 6.42 (s, OH), 7.08 (m, 2CH), 7.21 (d, ^3J = 8.0 Hz, CH), 7.42 (t, ^3J = 7.2, CH), 8.00 (m, 4H), 12.59 (s, NH); ^{13}C NMR: δ 14.2 (CH_3), 53.4 (CH), 61.3 (CH_2O), 74.4 (C), 116.8, 123.8, 123.9, 127.2, 128.9, 130.4, 132.6, 136.4, 136.8, 140.7, 140.9, 141.9, 154.1, 154.3 (C=O), 168.2 (C=O), 197.4 (C=O), 198.6 (C=O); EI-MS: *m/z* 346 (7), 232 (90), 186 (100), 104 (52), 76 (24). Anal. Calcd for $C_{21}H_{16}N_2O_6$ (392.37): C, 64.28; H, 4.11; N, 7.14. Found: C, 64.34; H, 4.08; N, 7.10.

***tert*-Butyl 2-(2-hydroxy-1,3-dioxo-2,3-dihydro-1*H*-inden-2-yl)-2-(3-oxo-3,4-dihydroquinoxalin-2-yl)acetate (4c)** Yellow solid; yield: 0.34 g (81%); mp 210–212°C; IR: ν_{max} 3284 (NH), 3219 (OH), 1739 (C=O), 1698 (C=O), 1649 cm^{-1} (C=O); ^{1}H NMR: 1.52 (s, ^{t}Bu), 4.69 (s, CH), 6.36 (s, OH), 7.05 (d, ^3J = 7.1, CH), 7.14–7.41 (m, 3CH), 8.00 (m, 4CH), 12.43 (s, NH); ^{13}C NMR: δ 27.2 (Me_3C), 53.2 (CH), 74.4 (C), 82.1 (Me_3*C*), 116.9, 123.7, 124.1, 126.7, 128.7, 130.4, 133.6, 136.8, 138.0, 140.7, 141.7, 143.0, 155.4, 154.7 (C=O), 168.7 (C=O), 197.4 (C=O), 198.6 (C=O); EI-MS: *m/z* 420 (4, M$^+$), 260 (96), 186 (100), 132 (18), 104 (45), 91 (9), 76 (28). Anal. Calcd for $C_{23}H_{20}N_2O_6$ (420.43): C, 65.71; H, 4.79; N, 6.66. Found: C, 65.78; H, 4.83; N, 6.61.

Methyl 2-(6,7-dimethyl-3-oxo-3,4-dihydroquinoxalin-2-yl)-2-(2-hydroxy-1,3-dioxo-2,3-dihydro-1*H*-inden-2-yl)acetate (4d) Yellow solid; yield 0.38 g (94%); mp 238–240°C; IR: ν_{max} 3251 (NH), 3187 (OH), 1735 (C=O), 1690 (C=O), 1645 cm^{-1} (C=O); ^{1}H NMR: δ 2.08 (s, CH_3), 2.18 (s, CH_3), 3.62 (s, MeO), 4.66 (s, CH), 6.21 (s, OH), 6.96 (s, CH), 7.11 (s, CH), 8.03 (m, 4CH), 12.43 (s, NH); ^{13}C NMR: δ 19.4 (Me), 20.2 (Me), 52.6 (MeO), 53.2 (CH), 74.4 (C), 116.0, 123.8, 124.0, 127.1, 128.9, 130.4, 132.6, 136.4, 136.8, 140.7, 141.0, 141.9, 153.9, 154.2 (C=O), 168.8 (C=O), 197.3 (C=O), 198.6 (C=O); EI-MS: *m/z* 246 (100), 215 (51), 187 (58), 104 (46), 76 (31). Anal. Calcd for $C_{22}H_{18}N_2O_6$ (406.40): C, 65.02; H, 4.46; N, 6.89. Found: C, 65.09; H, 4.41; N, 6.92.

Ethyl 2-(6,7-dimethyl-3-oxo-3,4-dihydroquinoxalin-2-yl)-2-(2-hydroxy-1,3-dioxo-2,3-dihydro-1*H*-inden-2-yl)acetate (4e) Yellow solid; yield 0.35 g (83%); mp 218–220°C; IR: ν_{max} 3292 (NH), 3240 (OH), 1732 (C=O), 1689 (C=O), 1643 (C=O) cm^{-1}; ^{1}H NMR: δ 1.30 (t, ^3J = 7.0, Me), 2.02 (s, Me), 2.19 (s, Me), 4.10 (q, ^3J = 7.0, CH_2O), 4.67 (s, CH), 6.20 (s, OH), 6.98 (s, CH), 7.09 (s, CH), 7.91 (d, ^3J = 7.0, CH), 8.03 (m, 3H), 12.45 (s, NH); ^{13}C NMR: δ 14.3 (Me), 19.4 (Me), 20.2 (Me), 53.5 (CH), 61.2 (CH_2O), 74.4 (C), 116.7, 123.8, 123.9, 127.2, 128.9, 130.4, 132.6, 136.4, 136.8, 140.7, 140.9, 141.9, 154.1, 154.3 (C=O), 168.2 (C=O), 197.2 (C=O), 198.6 (C=O); EI-MS: *m/z* 374 (4), 260 (95), 214 (100), 86 (58), 158 (42), 132 (23), 104 (51). Anal. Calcd for $C_{23}H_{20}N_2O_6$ (420.43): C, 65.71; H, 4.79; N, 6.66. Found: C, 65.77; H, 4.77; N 6.71.

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