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Uncatalyzed condensation between aryl-1,2-diamines and diethyl bromomalonate: a one-pot access to substituted ethyl 3-hydroxyquinoxaline-2-carboxylates

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Abstract—A one-pot method for the synthesis of substituted ethyl 3-hydroxyquinoxaline-2-carboxylates under solvent and catalyst free conditions has been developed.

1. Introduction

Substituted quinoxalines are an important class of benzo-heterocycles,[1] which constitute the building blocks of some organic semiconductors[2] and a wide range of pharmacologically active compounds having anticancer,[3] antimicrobial,[3,4] antibacterial[5] and antitumour[6] activities. Some quinoxaline derivatives serve as DNA photo-cleaver,[7] antagonists of the 5-HT_3 receptor,[8a] inhibitors of HCV NS5B RNA-dependent RNA polymerase[8b] and MAO-A[8c] and also act as dyes.[9] Furthermore they act as useful rigid subunits in macrocyclic receptors for molecular recognition[10] and chemically controllable switches.[11]

2,3-Disubstituted quinoxalines are usually synthesized by condensation of aryl-1,2-diamines with epoxides[12] or α-dicarbonyl compounds or their equivalents.[13] Difunctional quinoxalines can also be prepared by cyclization of α-aryliminooximes of α-dicarbonyl compounds[14] and by $POCl_3$ mediated hetero-annulation of α-nitroketene *N*,*S*-anilinoacetals.[15] Very recently, while this manuscript was being prepared, a report appeared describing an efficient protocol for the synthesis of quinoxaline derivatives at room temperature using cupric sulfate pentahydrate as catalyst in water.[16] However, many of these processes suffer from drawbacks, such as drastic reaction conditions, use of organic solvents (e.g., acetic acid, ethanol, DMSO) expensive and toxic catalysts and reagents [e.g., $Pd(OAc)_2$, $RuCl_2$–$(PPh_3)_3$–TEMPO,[17a] MnO_2,[17b,c] $POCl_3$] and tedious work-up procedures, which limit their use. Hence, there is still a need to develop improved methods for the synthesis of quinoxaline derivatives paying attention avoid toxic reagents and solvents, economic viability and operational simplicity.

In view of the recent trend towards the development of clean and environment friendly green chemical processes, investigations of solvent- and hazardous reagent-free reactions have become important in synthetic organic chemistry.

Although there have been numerous publications on both solution phase and solid phase[18] synthesis of quinoxaline derivatives, to the best of our knowledge, there is no report of the synthesis of quinoxalines under solvent-free conditions without using any commercial oxidants or catalysts. In continuation of our ongoing interest in novel classes of biologically active aza-heterocycles,[19] herein we describe a simple one-pot strategy to synthesize differently substituted quinoxalines from very simple starting materials at room temperature under solvent- and catalyst-free conditions.

In a model reaction, a 1:1 mixture of *ortho*-phenylenediamine **1a** and diethyl bromomalonate was kept under vacuum without solvent at room temperature. After 6 h the reaction was complete and furnished with ethyl 3-hydroxy-quinoxaline-2-carboxylate **2a.**

Keywords: Condensation; Oxidative aromatization; Quinoxaline; Solvent-free conditions.
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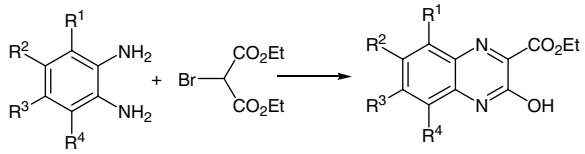


1 **2**

Scheme 1.

Subsequently, the reaction was extended to other substituted aryl-1,2-diamines **1** with a view to investigate the generality of the reaction for the synthesis of 2,3-disubstituted quinoxalines **2** (Scheme 1) and the results are depicted in Table 1. The key feature of this synthesis is in situ oxidative aromatization without using any commercial oxidants and catalyst.

For unsymmetrically substituted diaminobenzenes **1e–f** formation of quinoxaline isomers were observed but in the cases of **1c** and **1d**, 7-substituted isomers **2c** and **2d** were formed exclusively. We speculate that the regioselectivity depends on the different reactivity of the two amino groups being influenced by the highly electron-withdrawing nitro and benzoyl groups.

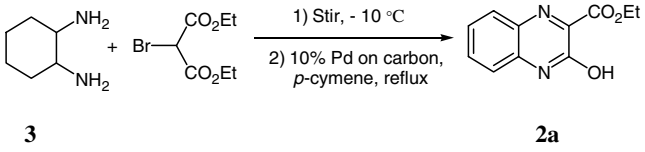
Mixing *cis* 1,2-cyclohexanediamine **3** with diethyl bromomalonate at −10 °C for 15 min, followed by treatment of the reaction mixture with 10% Pd on carbon in refluxing *p*-cymene, gave quinoxaline **2a** in 43% yield (Scheme 2).

All the compounds were characterized from spectroscopic data and the ratio of the isomers were calculated from ^{1}H NMR spectra.

In conclusion, we have developed a novel and simple one-pot (nucleophilic substitution, amide formation followed by in situ oxidative aromatization) procedure under solvent- and catalyst-free conditions for the synthesis of 2,3-disubstituted quinoxalines, amongst which compound **2a** is the key synthetic intermediate for the synthesis of a 5-HT$_3$ receptor antagonist.[8a,20] The operational simplicity, economic viability, commercial oxidant, toxic catalyst- and solvent-free conditions of this one-pot process make our methodology a useful contribution to existing processes for the synthesis of 2,3-disubstituted quinoxalines.

2. Typical experimental procedure[21]

A mixture of aryl-1,2-diamine (10 mmol) and diethyl bromomalonate (10 mmol) was stirred under vacuum for 6–8 h. The vacuum was released (to facilitate the aerial oxidative aromatization) and the solid mass (completion of the reaction was monitored by TLC) was purified by column chromatography over silica gel with hexane–ethyl acetate (2:1) as eluent.



3 **2a**

Scheme 2.

2.1. Spectral data of representative compounds

2.1.1. Ethyl 3-hydroxyquinoxaline-2-carboxylate 2a. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.44–1.51 (t, 3H, $J = 7.2$ Hz), 4.49–4.61 (q, 2H, $J = 7.2$ Hz), 7.41–7.47 (m, 2H), 7.59–7.64 (m, 1H), 7.94–7.98 (m, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.07, 62.43, 116.36, 124.84, 129.97, 131.84, 132.01, 132.64, 148.27, 154.46, 163.34. Anal. Calcd. for $C_{11}H_{10}N_2O_3$: C, 60.55; H, 4.62; N, 12.84. Found: C, 60.71, H, 4.57, N, 12.81. MS (EI, 70 eV): m/z (%) = 218 (M^+, 75.5), 146 (100).

2.1.2. Ethyl 6,7-dichloro-3-hydroxyquinoxaline-2-carboxylate 2b. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.43–1.50 (t, 3H, $J = 7.2$ Hz), 4.49–4.59 (q, 2H, $J = 7.2$ Hz), 7.60 (s, 1H), 8.05 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.12, 62.94, 117.81, 129.33, 130.97, 131.07, 131.56, 137.48, 148.61, 154.14, 163.45. Anal. Calcd. for $C_{11}H_8Cl_2N_2O_3$: C, 46.02; H, 2.81; N, 9.76. Found: C, 46.12, H, 2.77, N, 9.80.

2.1.3. Ethyl 7-benzoyl-3-hydroxyquinoxaline-2-carboxylate 2c. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.44–1.49 (t, 3H, $J = 7.09$ Hz), 4.51–4.58 (q, 2H, $J = 7.11$ Hz), 7.49–7.57 (m, 3H), 7.61–7.63 (m, 1H), 7.79–7.82 (m, 2H), 8.20–8.23 (m, 1H), 8.37 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.07, 62.74, 116.81, 128.45, 129.78, 130.72, 132.69, 132.96, 133.56, 133.96, 134.93, 136.87, 149.36, 154.27, 162.84, 194.53. Anal. Calcd. for $C_{18}H_{14}N_2O_4$: C, 67.08; H, 4.38; N, 8.69. Found: C, 67.17, H, 4.36, N, 8.65.

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Table 1.

Substrate	Product	Yield (%)
1a ($R^1 = R^2 = R^3 = R^4 = H$)	**2a** ($R^1 = R^2 = R^3 = R^4 = H$)	78
1b ($R^1 = R^4 = H$, $R^2 = R^3 = Cl$)	**2b** ($R^1 = R^4 = H$, $R^2 = R^3 = Cl$)	67
1c ($R^1 = R^3 = R^4 = H$, $R^2 = PhCO$)	**2c** ($R^1 = R^3 = R^4 = H$, $R^2 = PhCO$)	64
1d ($R^1 = R^3 = R^4 = H$, $R^2 = NO_2$)	**2d** ($R^1 = R^3 = R^4 = H$, $R^2 = NO_2$)	51
1e ($R^1 = R^3 = R^4 = H$, $R^2 = Me$)	**2e** ($R^1 = R^3 = R^4 = H$, $R^2 = Me$) and **2e′** ($R^1 = R^2 = R^4 = H$, $R^3 = Me$)	47, 23
1f ($R^1 = Me$, $R^2 = R^3 = R^4 = H$)	**2f** ($R^1 = Me$, $R^2 = R^3 = R^4 = H$) and **2f′** ($R^1 = R^2 = R^3 = H$, $R^4 = Me$)	44, 22

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21. This reaction could also be performed in the open air, but the yield of product was found to be nearly half that performed under vacuum. We found that the formation of arylaminomalonate[19] by the condensation of various arylamines and diethyl bromomalonates occurred only when the reaction was performed in vacuum. In the case of diamines, we speculate that under vacuum, the formation of diethyl 2-(2-aminophenylamino)malonate was aided, which was responsible for the higher yield of product than in the open air. Obviously the oxidative aromatization occurs with aerial oxygen on release of vacuum.