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Green and Efficient Synthesis of Trialkyl (E)-3-(3-Oxo-2-3,4-dihydro-2-(1H)-quinoxalinylidene)-prop-1-ene-1,2,3- tricarboxylates using K_2CO_3-PEG-400 as robust catalytic system

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Abstract

An efficient synthesis of trialkyl (E)-3-(3-Oxo-2-3,4-dihydro-2-(1H)-quinoxalinylidene)-prop-1-ene-1,2,3-tricarboxylate derivatives via a simple three-component reaction between benzene-1,2-diamines with dialkyl acetylenedicarboxylates in the presence of K_2CO_3-PEG catalytic system at 100 ^oC was reported. The desired products were obtained in excellent yields (88-92%). Various benzene-1,2-diamines, and dialkyl acetylendicarboxylate were used in the traditional method.

Keywords: benzene-1,2-diamine, dialkyl acetylenedicarboxylates, trialkyl (E)-3-(3-Oxo-2-3,4-dihydro-2-(1H)-quinoxalinylidene)-prop-1-ene-1,2,3-tricarboxylates, Three-component reaction.

Introduction

Recently, replacement of hazardous solvents with environmentally benign solvents is one of the major focus areas of Green Chemistry. Polyethylene glycol (PEG) is being extensively used as a solvent in organic synthesis [1,2]. It is a thermally stable, recoverable, inexpensive, environmentally friendly, and non-toxic hydrophilic polymer, which can be replaced with hazardous organic solvents. The high solubility of PEGs in water and several organic solvents including dichloromethane, acetone, alcohol, and toluene - instead of insolubility of them in less polar solvents such as hexane, cyclohexane, and diethyl ether – cause their

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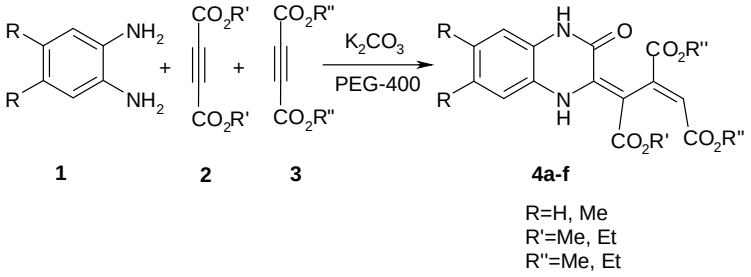
easy recovery and high performance in organic reactions[3,4].

Quinolines are major classes of hetero-cyclic compounds, which have attracted considerable attention from chemists for their large broad biological activities and amazing physical properties [5-9]. Furthermore, the synthesis of quinoxalines and their derivatives has received much attention from organic and medicinal chemists. Very recently, the synthesis of trialkyl (E)-3-(3-Oxo-2-3,4-dihydro-2-(1H)-quinoxalinylidene)-prop-1-ene-1,2,3-tricarboxylate derivatives was reported in toluene but it was in the presence of a stoichiometric amount of triphenyl phosphine (Ph_3P) and under reflux [10]. As part of our current studies on the development of new routes to synthesize quinoxaline systems [11-13], and also our continuous effort C-C bond formation in PEG-400 [14,15],We report that the readily available K_2CO_3 as the base, in combination with an eco-friendly solvent PEG-400 is an extremely effective catalytic system for the synthesis of trialkyl (E)-3-(3-Oxo-2-3,4-dihydro-2-(1H)-quinoxalinylidene)-prop-1-ene-1,2,3-tricarboxylates (Scheme 1).



Scheme 1. Three-component synthesis of quinolines **4**

Experimental

General

Commercially available materials were used without further purification. Melting points were measured on an Electrothermal 9100 apparatus. Mass spectra were recorded on Agilent-5975 C inert XL MSD mass spectrometer operating at an ionization potential of 70 eV. Elemental analyses were performed using a Heraeus CHN–O–Rapid analyzer. ^1H and ^{13}C NMR spectra were measured ($CDCl_3$ solution) with a Bruker DRX-400 Avance spectrometer at 400 and 100 MHz, respectively. IR spectra were recorded on a Shimadzu IR-460 spectrometer.

General Procedure for the Preparation of Compounds 4a

In a round bottom flask equipped with a magnetic stirrer, benzene-1,2-diamine (1 mmol), dimethyl acetylenedicarboxylate (1 mmol) in 2 mL of PEG-400 was stirred for 5 min at room temperature. Then, dimethyl acetylenedicarboxylate (1 mmol) and K_2CO_3 (15 mol%) were added to the mixture and the mixture was heated at 100 ^oC for 12 h, as indicated by TLC (AcOEt/hexane, 1:4), the reaction mixture was cooled to room temperature. Then, H_2O (5 mL) was added and the product was extracted with Et_2O (3 × 4 mL). The solvent was removed under reduced pressure to afford pure title compound.

(1E,3Z)-triethyl 3-(3-oxo-3,4-dihydroquinoxalin-2(1H)-ylidene)prop-1-ene-1,2,3-tricarboxylate (4d)

Pale yellow powder, yield 0.34 g (85%), mp: 168–170 ^oC. IR (KBr): ν = 3228 (NH), 3185 (NH), 1718 (C=O), 1712 (C=O), 1710 (C=O) cm^{-1}; ^1H NMR: 1.09-1.21 (m, 9H, 3 CH_3), 4.12-4.23 (m, 6 H, 3 OCH_2), 6.91 (s, CH), 6.96–7.11 (m, 4 CH), 10.91 (s, NH),12.41 (s, NH) ppm; ^{13}C NMR: 14.1 (CH_3), 14.2 (CH_3), 14.5 (CH_3), 60.6 (OCH_2), 61.0 (OCH_2), 61.2 (OCH_2), 95.7 (C), 115.1 (CH), 115.6 (CH), 122.8 (CH), 124.5 (CH), 125.3 (C), 126.1 (CH), 131.0 (C), 140.4 (C), 142.6 (C), 158.4 (C=O), 166.4 (C=O), 167.5 (C=O), and 169.0 (C=O) ppm. MS (EI, 70 eV): *m/z* (%): 402 (M^+, 1), 279 (7), 167 (31), 149 (100), 83 (29), 71 (35). Anal. calcd. for $C_{20}H_{22}N_2O_7$ (402.4): C, 59.70; H, 5.51; N, 6.69%. Found: C, 59.82; H, 5.57; N, 6.61%.

(1E,3Z)-trimethyl 3-(6,7-dimethyl-3-oxo-3,4-dihydroquinoxalin-2(1H)-ylidene)prop-1-ene-1,2,3-tricarboxylate (4e)

Pale yellow powder; yield: 0.37 g (92%), mp 203–205 ^oC. IR (KBr): ν = 3220 (NH), 3170 (NH), 1712 (C=O), 1716 (C=O), 1719 (C=O) cm^{-1}; ^1H NMR: (400.22 MHz, $CDCl_3$) δ = 2.08 (s, 3H, CH_3), 2.18 (s, 3H, CH_3), 3.66 (s, OCH_3), 3.70 (s, OCH_3), 3.74 (s, OCH_3), 6.98 (s, 1H, CH), 7.25 (s, 1H, CH), 10.35 (s, NH), 12.28 (s, NH) ppm; ^{13}C NMR: : (100.63 MHz, $CDCl_3$) δ = 19.5 (CH), 20.2 (CH), 51.5 (OCH_3), 51.9 (OCH_3), 53.1 (OCH_3), 95.5 (C), 115.0 (CH), 115.5 (CH), 123.0 (CH), 124.6 (C), 125.4 (C), 125.6 (C), 130.9 (C), 140.1 (C), 142.7 (C), 158.6 (C=O), 166.0 (C=O), 167.1 (C=O), 169.7 (C=O), ppm. MS (EI, 70 eV): *m/z* (%): 388 (M^+, 1), 307 (6), 195 (35), 177 (100), 157 (24). Anal. calcd. for $C_{19}H_{20}N_2O_7$ (388.4): C, 58.76; H, 5.19; N, 7.21%. Found: C, 58.68; H, 5.12; N, 7.16%.

(1E,3Z)-1,2-diethyl 3-methyl 3-(6,7-dimethyl-3-oxo-3,4-dihydroquinoxalin-2(1H)-ylidene)prop-1-ene-1,2,3-tricarboxylate (4f)

Pale yellow powder, yield 0.37 g (89%), mp: 194–196 °C. IR (KBr): ν = 3185 (NH), 3180 (NH), 1707 (C=O), 1709 (C=O), 1715 (C=O) cm^{-1}; ^1H NMR: (400.22 MHz, $CDCl_3$) δ = 1.25 (t, ^3J = 7.2 Hz, CH_3), 1.31 (t, ^3J = 7.2 Hz, CH_3), 2.03 (s, 3H, CH_3), 2.19 (s, 3H, CH_3), 3.72 (s, OCH_3), 4.15 (q, ^3J = 7.2 Hz, OCH_2), 4.24 (m, OCH_2), 6.94 (s, CH), 7.02 (s, CH), 7.23 (s, CH), 11.04 (s, NH), 12.41 (s, NH) ppm; ^{13}C NMR: : (100.63 MHz, $CDCl_3$) δ = 14.2 (CH_3), 14.6 (CH_3), 19.4 (CH_3), 20.2 (CH_3), 51.4 (OCH_3), 60.8 (OCH_2), 62.1 (OCH_2), 95.7 (C), 115.0 (CH), 115.4 (CH), 123.2 (CH), 124.4 (C), 124.6 (C), 125.6 (C), 131.3 (C), 140.1 (C), 142.7 (C), 158.8 (C=O), 165.7 (C=O), 166.2 (C=O), and 169.7 (C=O) ppm. MS (EI, 70 eV): *m/z* (%): 416 (M^+, 1), 269 (7), 194 (25), 177 (91), 119 (12), 57 (100). Anal. calcd. for $C_{21}H_{24}N_2O_7$ (416.4): C, 60.57; H, 5.81; N, 6.73%. Found: C, 60.62; H, 5.78; N, 6.65%.

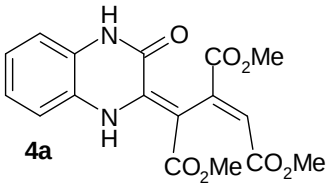
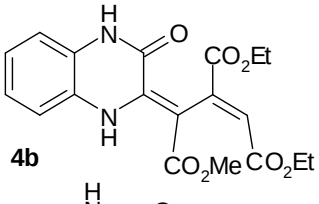
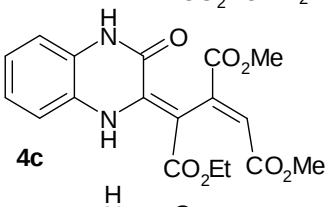
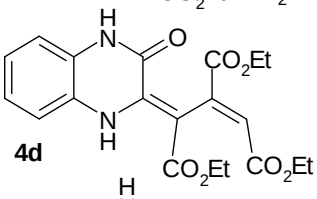
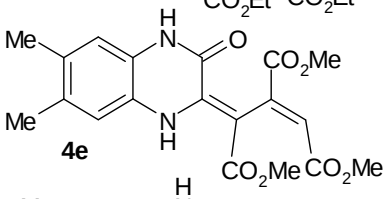
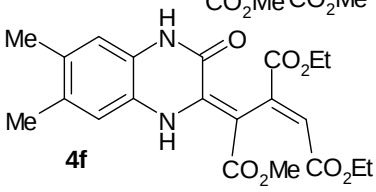
Results and discussion

Reaction of benzene-1,2-diamine **1** with dialkyl acetylenedicarboxylate **2** gave rise to the alkyl 2-[3-oxo-3,4-dihydro-2 (1H)-quinoxadinylidene]ethanoates [16]. The latter were then reacted with dialkyl acetylenedicarboxylate **3** in the presence of K_2CO_3-PEG system at 100 °C leads to trialkyl (E)-3-[3-oxo-2-3,4-dihydro-2-(1H)-quinoxalinylidene]-prop-1-ene-1,2,3-tricarboxylates **4** in excellent yields (Table 1). Our initial studies were focused on the reaction of methyl 2-[3-oxo-3,4-dihydro-2 (1H)-quinoxadinylidene]ethanoates and dimethyl acetylenedicarboxylate in order to optimize the reaction conditions with respect to temperature, time, and the molar ratio of K_2CO_3 to the substrates. We found that 15 mol% of K_2CO_3 was found to be most favorable to obtain the corresponding (1E,3Z)-trimethyl 3-(3-oxo-3,4-dihydroquinoxalin-2(1H)-ylidene)prop-1-ene-1,2,3-tricarboxylate **4a** in 91% yield within 12 h in PEG-400 at 100 °C. In the absence of K_2CO_3, **4a** was obtained in only 40% yield after 12 h in PEG-400 at 100 °C. With the optimized conditions in hand, the reaction of alkyl 2-[3-oxo-3,4-dihydro-2 (1H)-quinoxadinylidene]ethanoates and dialkylacetylenedicarboxylates for the synthesis of trialkyl (E)-3-(3-Oxo-2-3,4-dihydro-2-(1H)-quinoxalinylidene)-prop-1-ene-1,2,3-tricarboxylate derivatives were studied. The results are summarized in Table 1.

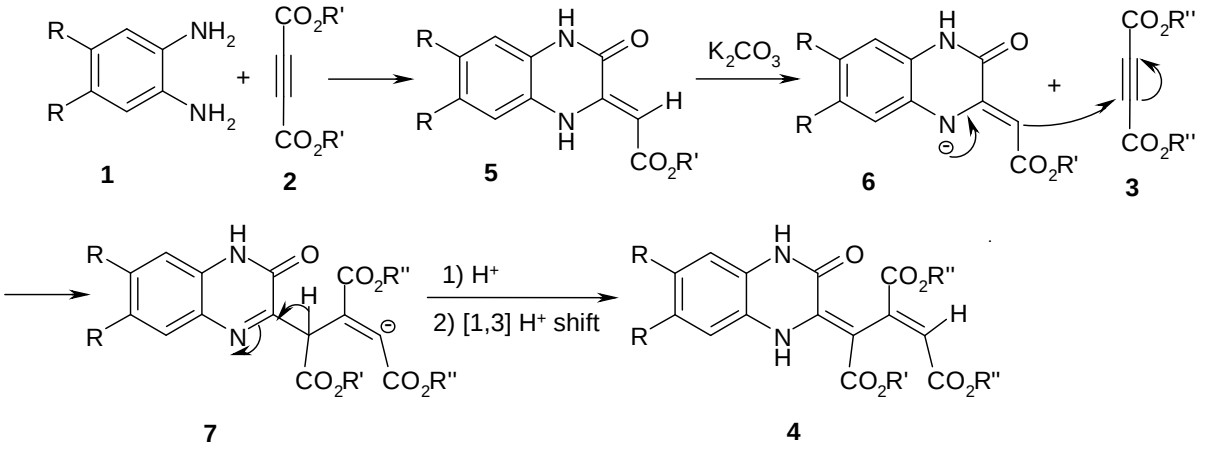
The products were characterized by comparison of their spectroscopic and physical data with authentic samples synthesized by the reported procedures. The ^1H-NMR spectrum of **4e** exhibited two singlets at 2.08 and 2.18 for the methyl

groups, and three singlets at 3.66, 370 and 3.74 ppm for the three methoxy groups. The vinyl proton was observed at 6.98 ppm, and NH groups resonances were observed at 10.35, and 12.28 ppm. The ^{1}H-decoupled ^{13}C-NMR spectrum of **4e** showed 19 distinct signals, in agreement with the proposed structure.

Table 1. Synthesis of compounds **4**

Entry	R	R'	R''	Product	Yield[%][a]	Mp(°C)[lit.]
1	H	Me	Me	 **4a**	91	186-188 [186-188][10]
2	H	Me	Et	 **4b**	89	171-173 [170-173][10]
3	H	Et	Me	 **4c**	88	180-182 [180-182][10]
4	H	Et	Et	 **4d**	85	168-170
5	Me	Me	Me	 **4e**	92	203-205
6	Me	Me	Et	 **4f**	89	194-196

[a]Isolated yield



Scheme 2. Proposed mechanism for the formation of quinoxalines **4**

Mechanistically, it is conceivable that the reaction leading to **5** involves the initial formation of 2-[3-oxo-3,4-dihydro-2 (1H)-quinoxadinylidene]ethanoates from benzene-1,2-diamines **1** and acetylenic esters **2** [15]. Then, in the presence of K_2CO_3 it has been converted to furnish intermediate **6**. In the next step, the latter acetylenic compound was attacked by the C-atom of the bidentate anion **6** to afford the yield **7**. This intermediate is converted to **4** by protonation and [1,3]-H^+ shift (Scheme 2).

Conclusion

In summary, the reaction between benzene-1,2-diamines and dialkyl acetylenedicarboxylates (2 eq) in the presence of K_2CO_3-PEG system at 100 ^oC provides a simple one-pot synthesis of trialkyl (E)-3-[3-oxo-2-3,4-dihydro-2-(1H)-quinoxalinylidene]-prop-1-ene-1,2,3-tricarboxylates of potential synthetic and pharmaceutical interest. The method enjoys the advantages that PEG endowed to the green organic synthesis. The catalysts are safe, and cheap without any need for the application of chromatographic methods in the work-up procedure.

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