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A Novel One-Pot Synthesis of Some New Interesting Pyrrole Derivatives

Javad Azizian,* Ali Reza Karimi, Zahra Kazemizadeh, Ali A. Mohammadi, and Mohammad R. Mohammadizadeh

Department of Chemistry, Faculty of Science, Shahid Beheshti University, P.O. Box 19395-4716, Tehran, Iran

j-azizian@cc.sbu.ac.ir

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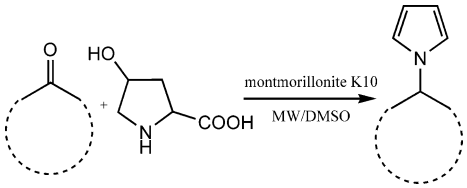

11-(1*H*-Pyrrol-1-yl)-11*H*-indeno[1,2-*b*]quinoxaline and 3-(1*H*-pyrrol-1-yl)indolin-2-one derivatives have been synthesized in good yields in a novel, one-pot, and efficient process by condensation of 11*H*-indeno[1,2-*b*]quinoxalin-11-one or isatin derivatives with 4-hydroxyproline on solid-support montmorillonite K10 under microwave irradiation.

Pyrroles are important heterocycles broadly used in material science[1] and found in naturally occurring and biologically important molecules.[2] Pyrroles can be found in a tremendous range of natural products[3] and bioactive molecules,[4] including the blockbuster drug atrovastatin calcium,[4a] as well as important antiflammatants,[4b] antitumor agents,[4c] and immunosuppressants.[4d] Accordingly, substantial attention has been paid to develop efficient methods for the synthesis of pyrroles.[1,2,5]

Quinoxaline[6] and indole[7] derivatives are important classes of nitrogen-containing heterocycles, and they constitute useful intermediates in organic synthesis.

Microwave-assisted organic synthesis is an increasingly popular field as indicated by numerous publications in the past few years.[8] The combination of solvent-free reaction conditions and microwave irradiation leads to large reductions in reaction times, enhancements in conversions, and sometimes in selectivity with several advantages of the ecofriendly approach, termed green chemistry.[9]

In the context of our ongoing studies on microwave-assisted synthesis of heterocyclic compounds,[10] and as a continuation of our previous work on the novel synthesis of some new pyrroles,[5c] herein, we wish to report a novel, efficient, and one-pot method for the construction of 11-(1*H*-pyrrol-1-yl)-11*H*-indeno[1,2-*b*]quinoxaline and 3-(1*H*-pyrrol-1-yl)indolin-2-one derivatives via condensation of 4-hydroxyproline with 11*H*-indeno[1,2-*b*]quinoxalin-11-one or isatin derivatives on solid support montmorillonite K10 under microwave irradiation.

To the best of our knowledge, there are no reports in the literature for the formation of pyrrole derivatives via condensation of 4-hydroxyproline with activated carbonyl compounds.

First, it was found that 11*H*-indeno[1,2-*b*]quinoxalin-11-ones **1a**−**c** in the presence of montmorillonite K10, as a solid support catalyst, under microwave irradiation underwent condensation with 4-hydroxyproline and then isomerization to give 11-(1*H*-pyrrol-1-yl)-11*H*-indeno[1,2-*b*]quinoxalines **3a**−**c** in 80% yield (Scheme 1).

This approach can be useful for synthesis of various types of *N*-substituted pyrroles using isatin derivatives. Thus, a number of isatin derivatives, such as isatin, 1-methylisatin, 1-benzylisatin, 5-methylisatin, and 5-bromoisatin, effectively participated in the condensation with 4-hydroxyproline to give the corresponding 3-(1*H*-pyrrol-1-yl)indolin-2-one compounds **5a**−**e** (Scheme 2).

The results were excellent in terms of yields and product purity in the presence of montmorillonite K10, while without it only starting material was recovered (Table 1). This indicates a catalyst is requiring for this reaction.

Under the same conditions, this reaction almost could not be observed when the tryptanthrine was used as a starting material (Scheme 3).

These compounds were characterized on the basis of their elemental analyses and IR, ^{1}H NMR, ^{13}C NMR, and MS spectra data. For example, the ^{1}H NMR spectrum of **3a** exhibited one single sharp line (δ 6.21) which was readily recognized as arising from methine proton along with multiplets (δ 7.58−8.29) for the aromatic protons.

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SCHEME 1. Synthesis of 11-(1*H*-Pyrrol-1-yl)-11*H*-indeno[1,2-*b*]quinoxalines 3a−c

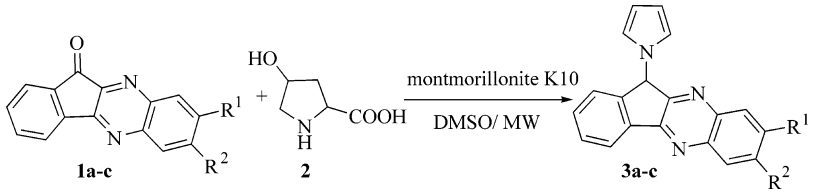
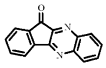
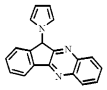
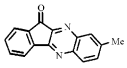
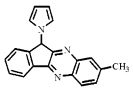
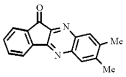
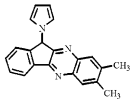
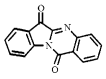
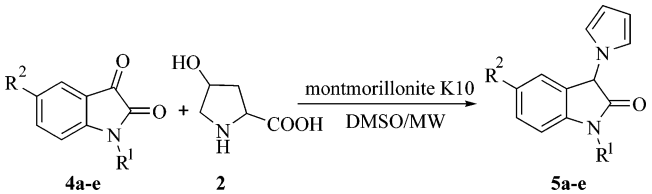


TABLE 1. Synthesis of 3a−c and 5a−e by Reaction of 4-Hydroxyproline with 1a−c or 4a−e under Microwave Irradiation[a]

Starting material	Montmorillonite K 10	Time	Product	Yield[b]	m. p.
 **1a**	0.5 g	2 min	 **3a**	83 %	
	-	6 min		-	180-181 °C
 **1b**	0.5 g	2 min	 **3b**	78 %	
	-	6 min		-	192-193 °C
 **1c**	0.5 g	2 min	 **3c**	80 %	
	-	6 min		-	231-232 °C
 **4a**	0.5 g	2 min	 **5a**	76 %	
	-	6 min		-	143-144 °C
 **4b**	0.5 g	2 min	 **5b**	78 %	
	-	6 min		-	133-134 °C
 **4c**	0.5 g	2 min	 **5c**	81 %	
	-	6 min		-	126-127 °C
 **4d**	0.5 g	2 min	 **5d**	75 %	
	-	6 min		-	163-164 °C
 **4e**	0.5 g	2 min	 **5e**	77 %	
	-	6 min		-	171-172 °C
	0.5 g	6 min		-	
	-	6 min	-	-	-

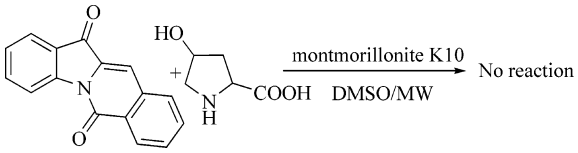
[a] With power of 900 W. [b] Isolated yield.

SCHEME 2. Synthesis of 3-(1*H*-Pyrrol-1-yl)indolin-2-ones 5a−e



Two triplets (δ 6.23 and 6.74) were identified as pyrrole ring protons because of small coupling constants of protons, characteristic for five-membered pyrrole rings (J = 2.12 Hz). The ^{1}H-decoupled ^{13}C NMR spectrum of **3a** showed 17 distinct resonances in agreement with the proposed structure. The signal at 61 ppm corresponds to methine carbon. The signals at 109 and 120 ppm indicate the presence of a pyrrole ring.

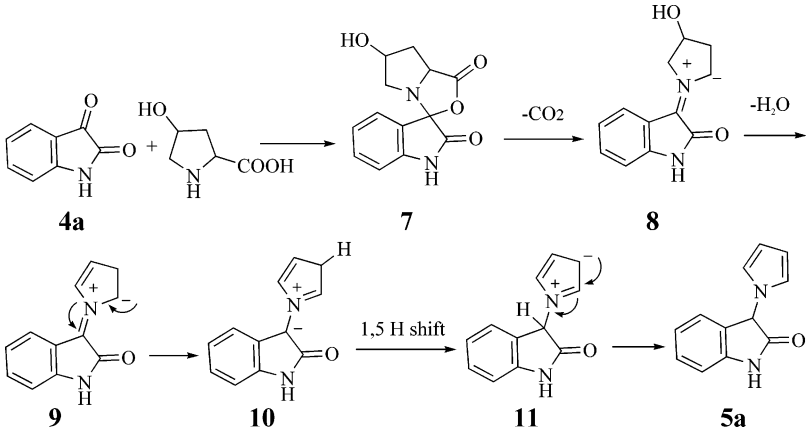
SCHEME 3. No Reaction Was Observed between Tryptanthrine and 4-Hydroxyproline



We have not yet established a mechanism for the formation of pyrrole derivatives **3a**−**c** and **5a**−**e**, but a reasonable possibility is suggested in Scheme 4.

First, 4-hydroxyproline would undergo a condensation with isatin to form azomthine ylide **8** by thermal decarboxylation of **7**. Initial azomethine ylide **8** dehydrated spontaneously to produce azomethine ylide **9**, because the new double bond can be in conjugation with the one that already exiss. The dehydrating agent in this reaction is montmorillonite K10. The next steps of this mechanism

SCHEME 4. Reasonable Mechanism for the Formation of Pyrrole Derivatives 3a−c and 5a−e



involve the resonance of azomethine ylide **9**, which brings the negative charge to the 3-position of the indolone ring and then the 1,5-proton-transfer reaction to afford the more stable zwitterion intermediate **11**, which would transform to **5a** (Scheme 4).

In conclusion, a novel, one-pot, and efficient method for the condensation of 4-hydroxy proline with 11*H*-indeno[1,2-*b*]quinoxalin-11-one or isatin derivatives into the 11-(1*H*-pyrrol-1-yl)-11*H*-indeno[1,2-*b*]quinoxaline and 3-(1*H*-pyrrol-1-yl)indolin-2-one compounds has been developed. The novelty and synthetic usefulness of this methodology was demonstrated in the efficient synthesis of some novel interesting pyrroles.

Experimental Section

Typical Procedure for Preparation of 11-(1*H*-Pyrrol-1-yl)-11*H*-indeno[1,2-*b*]quinoxaline 3a. Montmorillonite K10 (0.5 g) was placed in a mortar followed by addition of 11*H*-indeno[1,2-*b*]quinoxalin-11-one **1a** (0.232 g, 1 mmol) and 4-hydroxy proline **2** (0.131 g, 1 mmol) to which was added five drops of DMSO as a wet solvent. These materials were then mixed using a pestle for ca. 5 min. The homogenized mixture was placed in a Pyrex test tube and then loaded into a microwave oven and irradiated for 2 min with a power of 900 W. The contents were cooled to room temperature and mixed thoroughly with 10 mL of acetone. The solid inorganic material was filtered off. After separation of montmorillonite K10, water was added to the mixture and the separated solid was filtered off and dried under high vacuum and recrystallized in ethanol to give a pure crystalline solid **3a** (0.235 g): mp 180−181 °C; IR (KBr) (ν_{max}, cm^{-1}) 3095, 2920, 1478; ^1H NMR ($CDCl_3$, 500 MHz) δ_H 6.21(1H, s, CH), 6.23 (2H, t, J = 2.10 Hz, $CH_{pyrrole}$), 6.74 (2H, t, J = 2.09 Hz, $CH_{pyrrole}$), 7.58−8.29 (8H, m, arom); ^{13}C NMR ($CDCl_3$, 75 MHz) δ_C 61.63 (CH), 109.30, 120.40 ($2CH_{pyrrole}$), 122.78, 125.99, 128.99, 129.36, 129.81, 130.34, 130.38, 132.19, 137.19, 141.67, 142.59, 143.80, 153.17, 158.16 (arom); MS (*m/z*) 283 (M^+, 100), 217 (85), 190 (60), 141 (15), 114 (15), 89 (45), 63 (16), 39 (50). Anal. Calcd for $C_{19}H_{13}N_3$: C, 80.54; H, 4.62; N, 14.83. Found: C, 80.58; H, 4.63; N, 14.81.

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Supporting Information Available: General experimental procedures; ^1H NMR, ^{13}C NMR, and MS spectra for compounds **3a**,**c** and **5c**,**d**; and other characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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