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A synthetic route to 11-(1*H*-pyrrol-1-yl)-11*H*-indeno[1,2-*b*]quinoxaline derivatives exploiting a three-component coupling strategy under microwave irradiation

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Abstract—11*H*-Indeno[1,2-*b*]quinoxalin-11-ones generated in situ from ninhydrin and various 1,2-phenylenediamines, catalysed by montmorillonite K10 under microwave irradiation, condense with 4-hydroxyproline to produce 11-(1*H*-pyrrol-1-yl)-11*H*-indeno[1,2-*b*]quinoxaline derivatives in good yields.

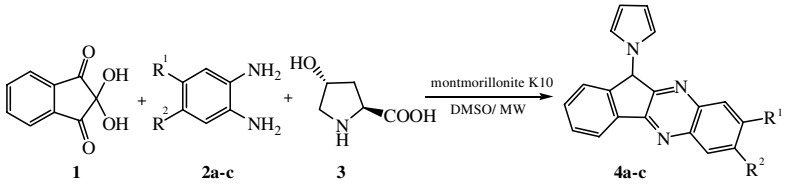
One-pot multicomponent processes have recently gained considerable and steadily increasing academic, economic and ecological interest because they address fundamental principles of synthetic efficiency and reaction design.[1] Additionally, the prospect of extending one-pot reactions into combinatorial and solid-phase synthesis[1,2] promises many opportunities for developing novel lead structures for pharmaceuticals, catalysts and even novel molecule based materials.

Since the pyrrole subunit occurs in many medicines, pesticides and natural products, the development of new methodologies[3–7] for the synthesis of pyrroles is of interest. Indenoquinoxaline[8] derivatives are an important class of intermediates in organic synthesis.

In the context of our general interest in multiple component reactions[9] and as part of our ongoing research programmes in the area of pyrrole synthesis,[9c,10] herein we report a novel, efficient and three-component method for the construction of 11-(1*H*-pyrrol-1-yl)-11*H*-indeno-[1,2-*b*]quinoxalines, via condensation of ninhydrin, 1,2-phenylenediamine and 4-hydroxyproline catalysed by montmorillonite K10 under microwave irradiation.

The multicomponent diversity elements are introduced by simple addition of 1 equiv of a 1,2-phenylenediamine to 1 equiv of ninhydrin on montmorillonite K10, then five drops of DMSO were added followed by 4-hydroxyproline (1 equiv) and the mixture exposed to MW to afford the corresponding 11-(1*H*-pyrrol-1-yl)-11*H*-indeno[1,2-*b*]quinoxalines **4** (Scheme 1).

The results were excellent in terms of yields and product purity in the presence of montmorillonite K10, while without it, only the 11*H*-indeno[1,2-*b*]quinoxalin-11-one **5** and 4-hydroxyproline were recovered (Table 1). This indicates that a catalyst is needed for this reaction.



1 2a-c 3 4a-c

Scheme 1.

Keywords: Three-component reaction; Pyrroles; Microwave irradiation.
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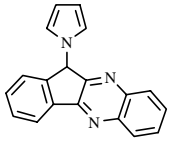
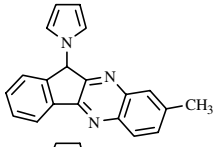
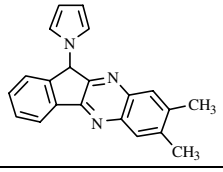
Table 1.

K 10	Time (min)	Products **4**	Yield (%)	MP (°C)
0.5 g	2	 **4a**	82	180
—	6		—	
0.2 g	2	 **4b**	78	192
—	6		—	
0.5 g	2	 **4c**	80	231
—	6		—	

The ^{1}H NMR spectrum of **4a** exhibited one single sharp line at (δ 6.21) readily recognised as arising from a methine proton along with multiplets (δ 7.58–8.29) for the aromatic protons. Two triplets (δ 6.23 and 6.74) were identified as pyrrole ring protons because of the small coupling constants of the protons characteristic of five-membered pyrrole rings (J = 2.10 Hz). The ^{1}H decoupled ^{13}C NMR spectrum of **4a** showed 17 distinct resonances in agreement with the proposed structure. The signal at 61.63 ppm corresponds to the methine carbon. The signals at 109.30 and 120.40 ppm are consistent with the presence of a pyrrole ring.[11]

We have not yet established a mechanism for the formation of **4a**–**c**, but a reasonable possibility is indicated in Scheme 2.

First, condensation of ninhydrin and 1,2-phenylenediamine would give 11*H*-indeno[1,2-*b*]quinoxalin-11-one **5**. This would undergo condensation with 4-hydroxyproline to form azomethine ylide **7** by thermal decarboxylation of **6**. The azomethine ylide **7** would dehydrate spontaneously to produce the conjugated azomethine ylide **8**, catalysed by montmorillonite K10. Proton transfers could then give azomethine ylide **9**, that is, **4a** (Scheme 2).

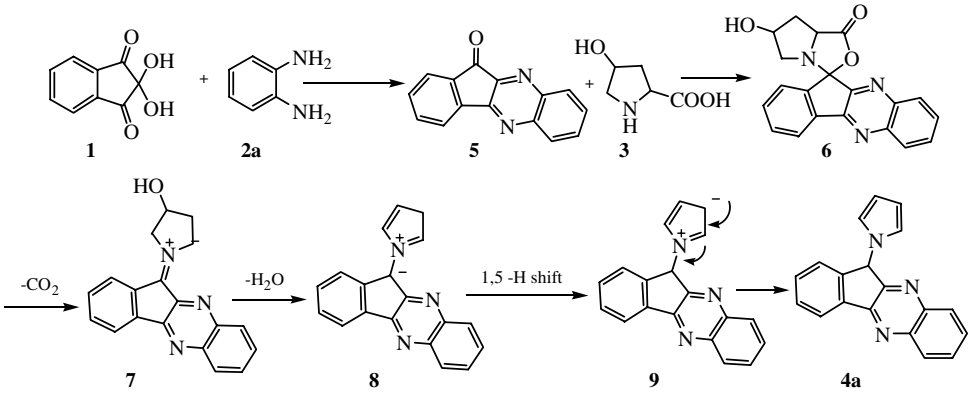
In order to prove the presence of the intermediate **5** in the proposed mechanism, compound **5** was synthesised separately by condensation of ninhydrin **1** and 1,2-phenylenediamine **2a**, and then the reaction of **5** and **3** was examined. The resulting product was identical to that formed in the three-component procedure.

In summary, the multicomponent reaction described herein provides a simple and direct entry into a number of interesting novel pyrroles.

General procedure: Montmorillonite K10 (0.2 g) was placed in a mortar followed by ninhydrin (0.178 g, 1 mmol) and 1,2-phenylenediamine (0.108 g, 1 mmol) to which was added five drops of DMSO. The reactants were mixed for 5 min. To this mixture was then added 4-hydroxyproline (0.130 g, 1 mmol). These materials were then mixed using a pestle for ca. 5 min. The homogenised mixture was placed in a pyrex test tube and inserted into a microwave oven and irradiated for 2 min. The contents were cooled to room temperature and mixed thoroughly with 10 mL of acetone. The solid inorganic material was filtered off, water was added and the separated solid was filtered off and dried under high vacuum and recrystallised from ethanol to give the pure crystalline solid **4a** (0.235 g).

References and notes

1. (a) Posner, G. H. *Chem. Rev.* **1986**, *86*, 831–844; (b) Domling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3167–3210; (c) Ugi, I.; Domling, A.; Werner, B. *J. Heterocycl. Chem.* **2000**, *37*, 647–658; (d) Bienayme', H.; Hulme, C.; Oddon, G.; Schmitt, P. *Chem. Eur. J.* **2000**, *6*, 3321–3329; (e) Ugi, I.; Heck, S. *Comb. Chem. High Throughput Screen.* **2001**, *4*, 1–34; (f) Nair, V.; Rajesh, C.; Vinod, A. U.; Bindu, S.; Sreekanth, A. R.; Mathen, J. S.; Balagopala, L. *Acc. Chem. Res.* **2003**, *36*, 899–907.
2. Kobayashi, S. *Chem. Soc. Rev.* **1999**, *28*, 1–15.
3. For a review on the synthesis of pyrroles, see: Ferreira, V. F.; Souza, M. C. B. V.; Cunha, A. C.; Pereira, L. O. R.;



Scheme 2.

Ferreira, M. L. G. *Org. Prep. Proced. Int.* **2001**, *33*, 411–454.
4. Adamczyk, M.; Reddy, R. E. *Tetrahedron Lett.* **1996**, *37*, 2325–2326.
5. Braun, R. U.; Muller, T. J. J. *Synthesis* **2004**, 2391–2406.
6. Arcadi, A.; Anacardio, R.; D'Anniball, G.; Gentile, M. *Synlett* **1997**, *11*, 1315–1317.
7. Tsutsuzi, H.; Kitamura, M.; Narasaka, K. *Bull. Chem. Soc. Jpn.* **2002**, *74*, 1451–1460.
8. Joshi, K. C.; Jain, R.; Chand, P. *Heterocycles* **1985**, *23*, 957.
9. (a) Azizian, J.; Mohammadi, A. A.; Karimi, A. R.; Mohammadizadeh, M. R. *J. Org. Chem.* **2005**, *70*, 350–352; (b) Azizian, J.; Karimi, A. R.; Mohammadi, A. A. *Synth. Commun.* **2003**, *33*, 383–387; (c) Azizian, J.; Karimi, A. R.; Arefrad, H.; Mohammadi, A. A.; Mohammadizadeh, M. R. *Mol. Diversity* **2003**, *6*, 223–226; (d) Azizian, J.; Mohammadi, A. A.; Karimi, A. R. *Synth. Commun.* **2003**, *33*, 415–420.
10. Azizian, J.; Karimi, A. R.; Kazemizadeh, Z.; Mohammadi, A. A.; Mohammadizadeh, M. R. *J. Org. Chem.* **2005**, *70*, 1471–1473.
11. *Spectral data for products*: 11-(1*H*-Pyrrol-1-yl)-11*H*-indeno[1,2-*b*]quinoxaline **4a**: mp: 180 °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). $MS_{(EI)}$ (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.
8-Methyl-11-(1*H*-pyrrol-1-yl)-11*H*-indeno[1,2-*b*]quinoxaline **4b**: mp: 192 °C, IR (KBr) (ν_{max}, cm^{-1}): 3098, 2918, 1483; ^1H NMR ($CDCl_3$, 300 MHz) δ_H: 2.66 (3H, s, CH_3), 6.25 (1H, s, CH), 6.27 (2H, br s, $CH_{pyrrole}$), 6.74 (2H, t, J = 2.00 Hz, $CH_{pyrrole}$), 7.62–8.23 (7H, m, arom); ^{13}C NMR ($CDCl_3$, 75 MHz) δ_C: 22.08 (CH_3), 62.13 (CH), 109.55, 120.44 ($2CH_{pyrrole}$), 122.58, 124.70, 128.69, 130.45, 131.13, 132.55, 136.70, 141.14, 141.38, 142.88, 143.88, 148.42, 153.17, 158.16 (arom). $MS_{(EI)}$ (m/z, %): 297 (M^+, 30), 246 (100), 231 (55), 218 (60), 190 (15), 130 (15), 89 (30). Anal. Calcd for $C_{20}H_{15}N_3$: C, 80.78; H, 5.08; N, 14.13. Found: C, 80.77; H, 5.05; N, 14.11.
7,8-Dimethyl-11-(1*H*-pyrrol-1-yl)-11*H*-indeno[1,2-*b*]quinoxaline **4c**: mp: 231 °C, IR (KBr) (ν_{max}, cm^{-1}): 3120, 2915, 1486, 1329; ^1H NMR ($CDCl_3$, 500 MHz) δ_H: 2.44 and 2.47 (6H, 2s, $2CH_3$), 6.12 (1H, s, CH), 6.23 (2H, t, J = 1.50 Hz, $CH_{pyrrole}$), 6.73 (2H, t, J = 1.56 Hz, $CH_{pyrrole}$), 7.50–8.19 (6H, m, arom); ^{13}C NMR ($CDCl_3$, 125 MHz) δ_C: 20.23 and 20.35 ($2CH_3$), 61.66 (CH), 109.17, 120.37 ($2CH_{pyrrole}$), 122.29, 125.83, 128.33, 129.00, 130.16, 131.54, 137.67, 139.72, 140.50, 140.65, 141.60, 143.56, 152.37, 157.14 (arom). $MS_{(EI)}$ (m/z, %): 311 (M^+, 100), 245 (90), 229 (30), 103 (15), 77 (15), 39 (45). Anal. Calcd for $C_{21}H_{17}N_3$: C, 81.00; H, 5.50; N, 13.49. Found: C, 79.88; H, 5.55; N, 13.51.