Iranian Journal of Organic Chemistry Vol. 6, No. 4 (2014) 1379-1382

An efficient synthesis of a new class of spiro heterocycles: Synthesis of {3-spiro (1,3- Dimethyl barbitoric) (4-hydroxy-6-aryl-1,11b-dihydro-2*H*-pyrido[2,1-*a*] isoquinolin-1-yl)}

Anvar Mirzaei*

Department of Chemistry, Faculty of Science, Sanandaj Branch, Islamic Azad University, Sanandaj, Iran.

Received: September 2014; Revised: September 2014; Accepted: September 2014

Abstract: The 1:1 intermediate generated by the addition of isoquinolin to Phenylpropargyl aldehyde is trapped by 1,3 Dimethyl barbitoric to yield a new class of spiroheterocycles in good yields. The structures of these products were confirmed by NMR.

Keywords: Spiro compound, MCRs, Phenylpropargyl aldehyde, Activated acetylenes Isoquinolin.

Introduction

The always increasing demand for large libraries of compounds readily available for High Throughput Screening assays in the discovery process of new drugs is allowing more and more the development of new and faster methodologies for the rapid construction of novel chemical entities [1].

Organic synthesis like any other human activity aims at achieving ideality. An ideal synthesis is one that can be performed in the most efficient and facile manner with maximum conversion. In this respect multicomponent reactions (MCRs) come very close to the concept of an ideal synthesis [2-3]. MCRs are ordered pot reactions, where three or more starting materials react in a sequence of steps, until a final one, to give a final product which contains most of the portions of all the initial components [4-5] a MCR is thus a domino process by definition [6-7]. The development of novel MCRs is an intellectually challenging task since one has to consider not only the reactivity match of the starting materials but also the reactivities of the intermediate molecules generated *in situ*, their compatibility and their compartmentalization [8-9]

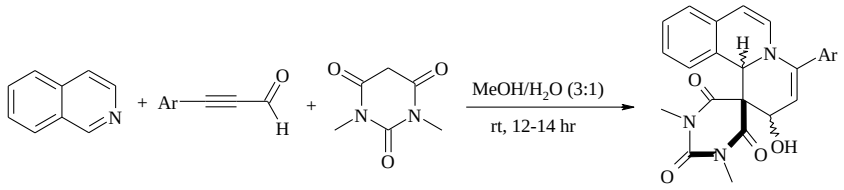
In other hand, the rich and fascinating chemistry that stems from the addition of nucleophiles to activated acetylenic compounds has evoked considerable interest. Isoquinolin is known to form zwitterions with activated acetylene compounds [10-12]. These zwitterions can be trapped by a variety of electrophiles and proton donors, which is a novel protocol for the synthesis of new heterocyclic compounds [13-14]

As part of our continuing interest in the construction of novel heterocycles [15-17], we now report the results of our studies involving the reactions of zwitterions derived from Isoquinoline (**1**) and Phenylpropargyl aldehyde (**2**) in the presence of 1,3 Dimethyl barbitoric acid (**3**), which constitutes a synthesis of {3-spiro (1,3- Dimethyl barbitoric) (4-hydroxy-6-aryl-1,11b-dihydro-2*H*-pyrido[2,1-*a*] isoquinolin-1-yl)} (**4**) (Scheme **1**).

*Corresponding author. Tel: (+98) 8713288661, Fax: (+98) 8713288662, E-mail: mirzaei.anvar@gmail.com

Results and discussion

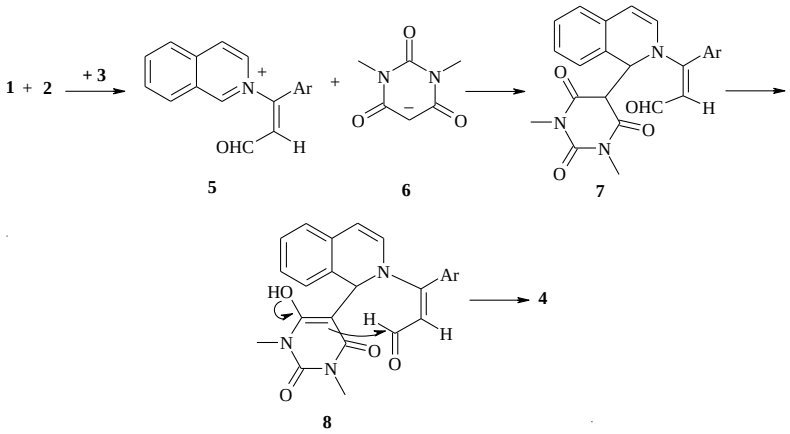
The structures of compounds **4a–b** were deduced from their elemental analyses and their IR, ^{1}H NMR and ^{13}C NMR spectra. For example, the ^{1}H NMR spectrum of **4a** exhibited six singlets identified as N-methyl (δ 3.27 and 3.35 ppm), OH (δ 3.24 ppm), methine (δ 3.43 and 6.08 ppm) and vinylic (δ 6.12 ppm) protons, along with multiplets for the aromatic region. The ^{1}Hdecoupled ^{13}C NMR spectrum of **4a** showed 22 distinct resonances, which confirmed the proposed structure. The IR spectrum of **4a** displayed characteristic hydroxy and aromatic bands. The ^{1}H NMR and ^{13}C NMR spectra of **4b** were similar to those for **4a** except for the aromatic moieties, which exhibited characteristic resonances in appropriate regions of the spectrum.



2, 4	Ar	Yield%
a	Ph	85
b	4-Me-Ph	64

Scheme 1: Synthesis of new spiro compounds **4**.

Although the mechanistic details of the reaction are not known, a plausible rationalization may be advanced to explain the product formation (Scheme **2**). Presumably, the zwitterionic intermediate [10-12], formed from isoquinoline and the arylpropargyl aldehyde is protonated by **3** to furnish intermediate **5**, which is attacked by carbanion **6** to produce **7**. This intermediate is converted to **8** by 1,3- hydrogen shift. Then the aldehyde group is attacked by the enol to produce final product **4**.



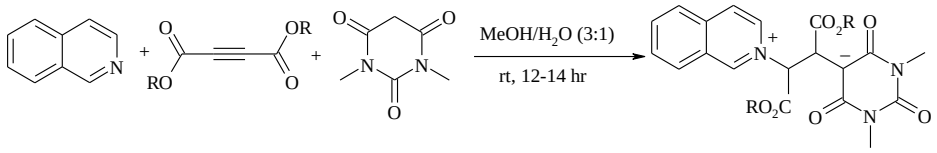
Scheme 2: Proposed mechanism for the formation of the compounds 4.

Under similar reaction conditions, dialkyl acetylenedicarboxylates produced 1,4 zwitterionic [18-19], compounds **9 a-b** (Scheme **3**). The ^{1}H NMR spectrum of **9a** exhibited four singlets identified as N-methyl (δ 3.00 ppm), methoxy (δ 3.67 and 3.87 ppm) and N–CH=N (δ 8.25 ppm) protons, and two doublets (δ 4.98 and 6.09 ppm) for the vicinal aliphatic methine protons, along with multiplets for the aromatic region. The ^{1}Hdecoupled ^{13}C NMR spectrum of **9a** showed 19 distinct resonances, which confirmed the proposed structure. The ^{1}H NMR and ^{13}C NMR spectra of **9b** were similar to those for **9a** except for the aliphatic moiety, which exhibited characteristic resonances in appropriate regions of the spectrum. Observation of a two resonance for the three carbonyl groups of the 1,3 Dimethyl barbitoric acid residue supports the open-chain structures for **9a** and **9b**.

Conclusion

In summary, we have reported a transformation involving isoquinolin and phenylpropargyl aldehyde in the presence of 1,3- Dimethyl barbitoric, which affords

a new route to the synthesis of completely new spiro compounds. In contrast three component reaction of isoquinolin, dialkyl acetylenedicarboxylates and 1,3-Dimethyl barbitoric leads to 1,4 zwitterionic compounds. The present procedure has the advantage that not only is the reaction performed under neutral conditions, but also the reactants can be mixed without any prior activation or modification.



1 **9** **3**

9, 10	R	Yield%
a	Me	96
b	Et	90

Scheme 3: Structures of compounds **9** and **10**.

Experimental

General procedure:

All compounds were obtained from Fluka, Merck or Sigma Aldrich. Tolylpropargyl aldehyde was prepared according to the literature procedure [25]. M.p.: Electrothermal-9100 apparatus. IR Spectra: Shimadzu IR-460 spectrometer. ^{1}H-, ^{13}C- NMR spectra: Bruker DRX-500 AVANCE instrument; in $CDCl_3$ or DMSO (*d6*) at 500, 125 MHz, respectively; δ in ppm. Elemental analyses (C, H, N) were performed with a Heraeus CHNS-O-Rapid analyzer.

Typical procedure for preparation of **4a**:

A solution of 0.28 g of isoquinoline (2.2 mmol) in 3 mL of solvent ($MeOH/H_2O$, 3:1) was added to a stirred solution of the Phenylpropargyl aldehyde (2 mmol) and 0.31 g of 1,3- Dimethyl barbitoric (2 mmol) in 5 mL of solvent ($MeOH/H_2O$, 3:1) at room temperature. The reaction mixture was then allowed to stir for 12 h. The precipitate was filtered off and washed with ether to get pure product **4a**.

Typical procedure for the synthesis of compounds **10a**:

A solution of isoquinoline (2.2 mmol) in 3 mL of solvent ($MeOH/H_2O$, 3:1) was added to a stirred solution of dialkyl acetylenedicarboxylates (2 mmol) and 0.31 g of 1,3- Dimethyl barbitoric (2 mmol) 5 mL of solvent ($MeOH/H_2O$, 3:1) at room temperature. The reaction mixture was then allowed to stir for 18 h. The precipitate was filtered off and washed with ether to get pure product **10a**.

{3-spiro (1,3- Dimethyl barbitoric) (4-hydroxy-6-phenyl-1,11b-dihydro-2H-pyrido[2,1-a] isoquinolin-1-yl)} 4a:

Pale yellow powder, mp 181–183 °C, 0.353 g, yield 85%. IR (KBr) (ν_{max}/cm^{-1}): 3300, 2930, 1690, 1680, 1653, 1455, 1215, 1010. Anal. Calcd for $C_{24}H_{21}N_3O_4$ (415.45): C, 69.39; H, 5.10; N, 10.11 %. Found: C, 69.55; H, 5.35; N, 10.27 %. ^{1}H NMR (in $CDCl_3$) : δ 3.24 (1 H, br s. OH), 3.27 (3 H, s. N-CH_3), 3.35 (3 H, s. N-CH_3), 3.43 (1H, s. N-CH), 6.08 (1H, s, O-CH), 6.12 (1H, s, CH), 6.43 (1H, br s, CH), 7.29-7.45 (5H, m, 5CH), 7.48-752 (2H, m, 2CH), 7.54 (1H, d, $^{3}J_{=}$ 6.0, CH), 7.88 (1H, d, $^{3}J_{=}$ 8.2, CH), 8.24 (1H, br s, CH) ppm. ^{13}C NMR: δ 27.8 (N-CH_3), 28.2 (N-CH_3), 52.4 (N-CH), 67.2 (C), 85.5(O-CH), 107.8 (CH), 108.0 (CH), 125.4 (CH), 126.6 (C), 127.2 (CH), 128.0 (CH), 128.9 (2 CH), 129.0 (CH), 129.6 (CH), 130.2 (C), 131.2 (2 CH), 132.3 (C), 152.0 (C), 156.7 (CH), 162.7 (C=O), 163.1 (C=O), 166.0 (C=O) ppm.

{3-spiro (1,3- Dimethyl barbitoric) (4-hydroxy-6-tolyl-1,11b-dihydro-2H-pyrido[2,1-a] isoquinolin-1-yl)} 4b:

Yellow powder, mp 185–187 °C, 0.27 g, yield 64%. IR (KBr) (ν_{max}/cm^{-1}): 3200, 2935, 1670, 1665, 1653, 1455, 1219, 1025. Anal. Calcd for $C_{25}H_{23}N_3O_4$ (429.48): C, 69.92; H, 5.40; N, 9.78 %. Found: C, 69.84; H, 5.48; N, 9.89 %. ^{1}H NMR (in $CDCl_3$) : δ 2.24 (CH_3), 3.320 (1 H, br s. OH), 3.33 (3 H, s. N-CH_3), 3.39 (3 H, s. N-CH_3), 3.43 (1H, s. N-CH), 5.88 (1H, s, O-CH), 6.23 (1H, s, CH), 6.438 (1H, br s, CH), 7.29-7.45 (4H, m, 4CH), 7.50-7.53 (2H, m, 2CH), 7.56 (1H, d, $^{3}J_{=}$ 6.2, CH), 7.80 (1H, d, $^{3}J_{=}$ 7.9, CH), 8.26 (1H, br s, CH) ppm. ^{13}C NMR: δ 20.5 (CH_3), 26.6 (N-CH_3), 28.0 (N-CH_3), 51.3 (N-CH), 64.5 (C), 86.2 (O-CH), 107.8 (CH), 108.1 (CH), 125.5 (CH), 126.7 (C), 127.0 (CH), 128.0 (CH), 128.7 (2 CH), 129.2 (C), 129.6 (CH), 130.5 (C), 131.1 (2 CH), 132.8 (C), 152.1 (C), 156.6 (CH), 162.1 (C=O), 163.0 (C=O), 166.3 (C=O) ppm.

Dimethyl-2-(N,N'-dimethylbarbitoric acid-5-yl-5-ylide)-3-isoquinolinium-1,4-butanedioate 10a:

Yellow powder; 165–167 °C (decomp.), yield: 0.41 g (96%). IR (KBr) (ν_{max}/cm^{-1}): 2935, 1733, 1724, 1703, 1692, 1631, 1416, 1175. Anal. Calcd for $C_{21}H_{21}N_3O_7$ (427.4): C, 59.01; H, 4.95; N, 9.83. Found: C, 59.21; H, 5.10; N, 9.78. ^{1}H NMR (in DMSO): δ 3.00 (6H, s, 2 N-Me), 3.67 (3H, s, OMe), 3.87 (3H, s, OMe), 4.98 (1H, d, ^3J = 7.1 Hz, CH), 6.09 (1H, d, ^3J = 7.0 Hz, CH), 7.01 (1H, d, ^3J = 6.7 Hz, CH), 7.59–7.83 (5H, m, 5 CH), 8.25 (1H, s, CH). ^{13}C NMR: δ 27.7 (2 N-Me), 47.2 (CH), 52.7 (O-Me), 53.6 (O-Me), 70.0 (CH), 75.9 (C-), 114.0 (CH), 125.4 (CH), 126.2 (CH), 126.5 (CH), 128.8 (CH), 129.0 (CH), 134.7 (C), 135.8 (C), 136.2 (CH), 152.2 (C=O), 164.3 (2 C=O), 169.3 (C=O), 171.9 (2 C=O).

Diethyl-2-(N,N'-dimethylbarbitoric acid-5-yl-5-ylide)-3-isoquinolinium-1,4-butanedioate 10b:

Yellow powder; 180–183 °C (decomp.), yield: 0.41 g (90%). IR (KBr) (ν_{max}/cm^{-1}): 2925, 1726, 1720, 1700, 1690, 1635, 1415, 1180. Anal. Calcd for $C_{23}H_{25}N_3O_7$ (455.46): C, 60.65; H, 5.53; N, 9.23. Found: C, 60.59; H, 5.60; N, 9.38. ^{1}H NMR (in DMSO): δ 1.16 (3H, t, ^3J = 7.4 Hz, CH_3), 1.36 (3H, t, ^3J = 7.1 Hz, CH_3), 2.97 (6H, s, 2 N-Me), 4.30 (3H, q., ^3J = 7.4 Hz, O-CH_2), 4.41 (3H, q., ^3J = 7.4 Hz, O-CH_2), 4.79 (1H, d, ^3J = 6.9 Hz, CH), 6.12 (1H, d, ^3J = 7.1 Hz, CH), 7.06 (1H, d, ^3J = 6.9 Hz, CH), 7.61–7.87 (5H, m, 5 CH), 8.45 (1H, s, CH). ^{13}C NMR: δ 13.8 (CH_3), 14.5 (CH_3), 28.1 (2 N-Me), 47.4 (CH), 61.4 (O-CH_2), 62.3 (O-CH_2), 71.3 (CH), 79.7 (C-), 114.1 (CH), 125.6 (CH), 126.4 (CH), 126.1 (CH), 128.6 (CH), 129.0 (CH), 134.4 (C), 135.9 (C), 136.0 (CH), 149.1 (C=O), 164.4 (C=O), 169.6 (C=O), 172.5 (2 C=O).

References

[1] Bio M. M.; Javadi, G.; Song Z. J. *Synthesis* **2005**, 19.
[2] Nair, V.; Menon, R. S.; Ani Deepthi; Rema B. *Tetrahedron Lett.* **2005**, *46*, l337.
[3] Nair, V.; Beneesh, P. B. *Synthesis* **2006**, 443.
[4] Aller, E.; Molina, P.; Lorenzo, A. *Synthesis* **2000**, 526.
[5] Souldozi, A.; Ramazani, A. *Tetrahedron Lett.* **2007**, *48*, 1549
[6] Adib, M.; Kesheh, M. R.; Ansari, S.; Bijanzadeh, H. R. *Syntlett* **2009**, 1575.
[7] Palacios, F.; Aparicio, D.; Rubiales, G.; Alonso, D. *Curr. Org. Chem.* **2009**, *13*, 810.
[8] Sun, X.; Janvier, P.; Zhao, G.; Bienaymé, H.; Zhu, J. *Org. Lett.* **2001**, *3*, 877.
[9] Janvier, P.; Sun, X.; Bienaymé, H.; Zhu, J. *J. Am. Chem. Soc.* **2002**, *124*, 2560.
[10] Huisgen, R.; Morikawa, M.; Herbig, K.; Brunn, E. *Chem. Ber*. **1967**, *100*, 1094.
[11] Winterfeldt, E.; Schumann, D.; Dillinger, H. J. *Chem. Ber*. **1969**, *102*, 1656.
[12] Dillinger, J.; Fengler, G.; Schumann, D.; Winterfeldt, E. *Tetrahedron* **1974**, *30*, 2553.
[13] Yavari, I.; Moradi, L. *Tetrahedron Lett*. **2006**, *47*, 1627.
[14] Yavari, I.; Mokhtarporyani-Sanandaj, A.; Moradi, L. *Tetrahedron Lett*. **2007**, *48*, 6709.
[15] Yavari, I.; Mirzaei, A.; Moradi, L. *Helv. Chim. Acta* **2006**, *89*, 2825.
[16] Yavari, I.; Moradi, L.; Mirzaei, A. *Helv. Chim. Acta* **2007**, *90*, 392.
[17] Mirzaei, A. *Iran. J. Org. Chem.* **2013**, *5*, 971.
[18] Yavari, I.; Maghsoodlou, M. T. *Tetrahedron Lett*. **1998**, *39*, 4579.
[19] Yavari, I.; Islami, M. R.; Bijanzadeh, H. R. *Tetrahedron* **1999**, *55*, 5547.
[20] Allen C. F. H.; Edens, J. C. *Organic Syntheses*, **1955**, *3*, 731.