Iranian Journal of Organic Chemistry Vol. 12, No. 4 (2020) 2989-2992

Synthesis of isoquinoline derivatives using multicomponent reaction of isothiocyanates

Mahboubeh Ghasemian[*a], and Sanaz Souri[b]

[a]*Facualty of Chemistry, University of Mazandaran, Babolsar, Iran.*
[b]*Department of Chemistry, Tarbiat Modares University, Tehran, Iran.*

Received: August 2020; Revised: September 2020; Accepted: September 2020

Abstract: An efficient synthesis of isoquinoline derivatives *via* one-pot reactions between phthalaldehyde, ammonium acetate, acetylenic esters and isothiocyanates is described.

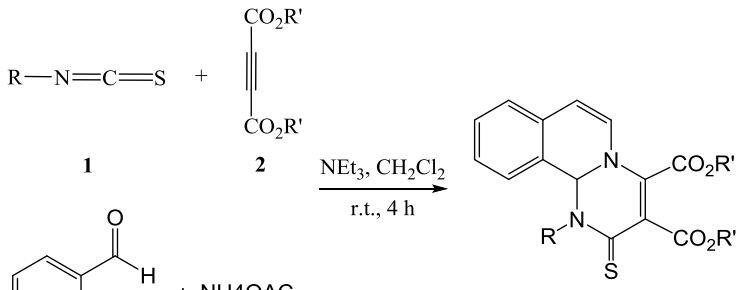
Keywords: Phthalaldehyde, Ammonium acetate, Isothiocyanate, Dialkyl acetylenedicarboxylate, Isoquinoline.

Introduction

The isoquinoline skeleton is found in a large number of naturally occurring and synthetic biologically active heterocyclic compounds [1]. In particular, 1,2-dihydroisoquinoline derivatives act as delivery systems that transport drugs through the otherwise highly impermeable blood–brain barrier [2]. These compounds also exhibit sedative [3], antidepressant [4], antitumor, and antimicrobial activities [5]. For the functionalization of quinoline, isoquinoline and related aromatic amines, the Reissert reaction has remained one of the most powerful tools [6]. This reaction can be considered as a multi-component reaction, where adducts are formed from an azine, an acyl chloride, and sodium cyanide via an *N*-acyliminium intermediate. Multi-component reactions (MCRs), due to their productivity, simple procedures, convergence, and facile execution, are one of the best tools in combinatorial chemistry [7]. Therefore, the design of novel MCRs has attracted great attention from research groups working in areas such as drug discovery, organic synthesis andmaterials science. As a result, the number of new MCRs has grown rapidly [8].

In this paper, as part of our ongoing studies on the multicomponent area [9-11], we present herein our results of a novel discovery involving synthesis of isoquinoline derivatives, using commercially available starting materials in excellent yields. Thus, the reaction of phthalaldehyde **1**, ammonium acetate **2**, acetylenic esters **3** and isothiocyanates **4**, in dichloromethane as the solvent, produced isoquinoline derivatives **5** in good yields (Scheme **1**).

* Corresponding author. Fax: +(98) 1232211647; Tel: +989112252650; E-mail: pghm49@yahoo.com

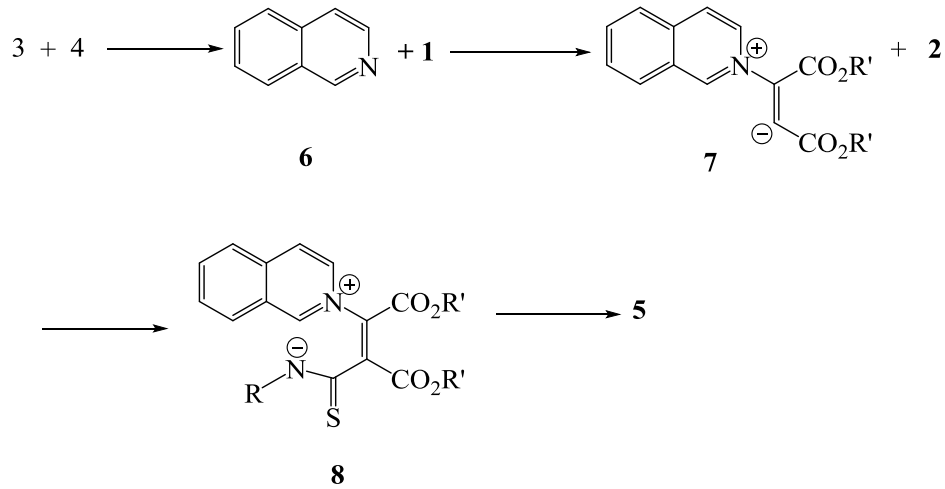


5	R	Ar	Yield % of **5**
a	Me	Phenyl	85
b	Me	4-nitrophenyl	94
c	Me	4-bromophenyl	92
d	Me	3-bromophenyl	92

Scheme 1: Synthesis of isoquinoline derivatives

As indicated in Scheme **1**, phthalaldehyde **1**, ammonium acetate **2**, acetylenic esters **3** and isothiocyanates **4** undergo a smooth 1:1:1:1 addition reaction in dichloromethane at room temperaure to produced isoquinoline **5** in 85–94% yields (Scheme **1**).

The data obtained from elemental analysis, IR, ^{1}H NMR, ^{13}C NMR, and mass spectra confirmed all of the proposed products. The mass spectrum of **5b** displayed a molecular ion peak at m/z 451 and more important, an ion peak at m/z 297 indicated that aryl group has been lost and thus the presence of this group on the structure was confirmed. Absorption bands at 1745 and 1732 cm^{-1} are due to the two carbonyl groups. The ^{1}HNMR spectrum of **5b** exhibited two sharp singlet signals recognized as arising from methoxy groups (δ_H = 3.81, 3.92 ppm). Two doublets at 6.98 (2 H, d, ^{3}J = 7.6 Hz, 2 CH), 8.28 (2 H, d, ^{3}J = 7.5 Hz, 2 CH) is attributed to aryl protons. The ^{1}H decoupled ^{13}C NMR spectrum of **5b** showed 23 distinct signals, which were in agreement with the proposed structure. Partial assignment of these resonances for compounds **5** is given in experimental section.



Scheme 2: Proposed mechanism for synthesis of **5**

Although we have not established the mechanism of our reaction in an experimental manner, a possible explanation is proposed in Scheme **2**. It is conceivable that, the reaction involves the initial formation of a 1,3-

dipolar intermediate **5** between isoquinoline and the acetylenic compounds, which reacts with the arylisothiocyanate to produce either **6**. Cyclization of zwitterionic intermediate **6** leads to the **5**.

Conclusion

In summary, we reported an efficient method for the synthesis of isoquinoline derivatives. The advantages of our work are as follows: (1) the reaction is performed under neutral and more important in water as a solvent. (2) No catalyst is required for this reaction. (3) The simplicity of the present procedure makes it an interesting alternative to the complex multistep approaches.

Experimental

All chemicals were obtained from *Fluka* and were used without further purification. Mp: Electrothermal-9100 apparatus. IR spectra: *Shimadzu IR-460* spectrometer. ^{1}H and ^{13}C NMR spectra: *Bruker DRX-500 Avance* instrument; in $CDCl_3$ at 500.1 and 125.7 MHz, respectively; δ in parts per million, J in hertz. EIMS (70 eV): *Finnigan-MAT-8430* mass spectrometer, in *m/z*. Elemental analyses (C, H, N) were performed with a *Heraeus CHN-O-Rapid* analyzer.

General procedure

To a magnetically stirred solution of phthalaldehyde 1 and ammonium acetate 2 in the presence of isothiocyanate **1** and dialkyl acetylenedicarboxylates **2** (2 mmol) in CH_2Cl_2 was added isoquinoline **3** (2 mmol) slowly and the reaction stirred for 8 h at room temperature. After completion of the reaction, as indicated by TLC (ethyl acetate/n-hexane, 5:1), the reaction mixture was purified by column chromatography to afford pure title compounds.

*Compound **4a**:*

Yellow powder, mp 135-137°C, yield 85%. IR (KBr) (ν_{max}/cm^{-1}): 1725, 1720, 1685, 1587, 1432 and 1129 cm^{-1}. ^{1}H-NMR: δ 3.65 (3 H, s, MeO), 3.82 (3 H, s, MeO), 7.25 (1 H, s, CH), 7.54 (1 H, d, ^3J = 7.6 Hz, CH), 7.53 (2 H, t, ^3J = 7.2, 2 CH), 7.61 (1 H, t, ^3J = 7.2, CH), 7.69 (1 H, t, ^3J = 7.2 Hz, CH), 7.73 (1 H, t, ^3J = 7.2 Hz, CH), 7.93 (1 H, d, ^3J = 7.5 Hz, CH), 8.02 (2 H, d, ^3J = 7.3, 2 CH), 8.69 (1 H, d, ^3J = 7.5 Hz, CH), 9.31 (1 H, d, ^3J = 7.6 Hz, CH) ppm. ^{13}C-NMR: δ 52.5 (MeO), 53.0 (MeO), 65.2 (CH), 103.4 (CH), 112.4 (C), 120.3 (2 CH), 122.3 (CH), 123.6 (CH), 125.4 (CH), 125.7 (CH), 128.7 (2 CH), 129.0 (CH), 138.2 (C), 133.5 (C), 139.7 (C), 140.1 (C), 148.7 (C-N), 157.4 (C=N), 160.7 (C=O), 161.5 (C=O) ppm. Anal. Calcd for $C_{23}H_{19}NO_4S$ (406.45): C, 65.01; H, 4.46; N, 6.89 found: C, 64.95; H, 4.38; N, 6.75.

*Compound **4b**:*

Pale yellow crystals, mp 153-155°C, yield 94%. IR (KBr) (ν_{max}/cm^{-1}): 1745, 1732,, 1658, 1587, 1489, 1365, 1258 and 1157 cm^{-1}. ^{1}H-NMR: δ 3.81 (3 H, s, MeO), 3.92 (3 H, s, MeO), 6.98 (2 H, d, ^3J = 7.6, 2 CH), 7.28 (1 H, s, CH), 7.49 (1 H, d, ^3J = 7.6 Hz, CH), 7.65 (1 H, t, ^3J = 7.3 Hz, CH), 7.68 (1 H, t, ^3J = 7.3 Hz, CH), 7.88 (1 H, d, ^3J =7.5 Hz, CH), 8.28 (2 H, d, ^3J = 7.5, 2 CH), 8.65 (1 H, d, ^3J = 7.5 Hz, CH), 9.27 (1 H, d, ^3J = 7.6 Hz, CH) ppm. ^{13}C-NMR: δ 53.2 (MeO), 53.8 (MeO), 65.4 (CH), 103.8 (CH), 111.4 (C), 120.0 (2 CH), 123.5 (CH), 126.1 (2 CH), 127.2 (CH), 127.8 (CH), 128.5 (CH), 130.8 (CH), 139.6 (C), 141.6 (C), 146.8 (C), 154.2 (C), 154.9 (C-N), 156.2 (C=N), 160.7 (C=O), 166.5 (C=O). Anal. Calcd for $C_{22}H_{17}N_3O_6S$ (451.45): C, 58.53; H, 3.80; N, 9.31 found: C, 58.48; H, 3.75; N, 9.28.

*Compound **4c**:*

Orange crystals, mp 165-167°C, yield 92%. IR (KBr) (ν_{max}/cm^{-1}): 1725, 1715, 1658, 1424. 1310, 1258 and 1100 cm^{-1}. ^{1}H-NMR: δ 3.81 (3 H, s, MeO), 3.91 (3 H, s, MeO), 6.76 (2 H, d, ^3J = 7.8, 2 CH), 7.19 (1 H, d, ^3J = 7.7 Hz, CH), 7.32 (1 H, s, CH), 7.51 (2 H, d, ^3J = 8.0, 2 CH), 7.54 (1 H, t, ^3J = 7.4 Hz, CH), 7.59 (1 H, t, ^3J = 7.4 Hz, CH), 7.70 (1 H, d, ^3J = 7.5 Hz, CH), 8.44 (1 H, d, ^3J = 7.5 Hz, CH), 9.23 (1 H, d, ^3J = 7.7 Hz, CH) ppm. ^{13}C-NMR: δ 52.6 (MeO), 53.2 (MeO), 64.3 (CH), 103.5 (CH), 112.0 (C), 121.2 (2 CH), 124.3 (CH), 126.7 (2 CH), 127.8 (CH), 128.2 (CH), 128.9 (CH), 131.2 (CH), 139.5 (C), 142.6 (C), 145.8 (C), 153.8 (C), 155.4 (C-N), 158.9 (C=N), 161.7 (C=O), 164.5 (C=O).

*Compound **4d**:*

White powder, yield: (92%); m.p. 169-171°C. IR(KBr)(ν_{max}/cm^{-1}): 1723, 1714, 1699, 1523, 1489, 1358 and 1124 cm^{-1}. ^{1}H-NMR: δ 3.81 (3 H, s, MeO), 3.91 (3 H, s, MeO), 6.81 (1 H, t, ^3J = 7.8, CH), 7.09 (1 H, d, ^3J = 7.8 Hz, CH), 7.25 (1 H, d, ^3J = 7.8 Hz, CH), 7.34 (1 H, s, CH), 7.50 (1 H, d, 3J = 7.7 Hz, CH), 7.71 (1 H, d, ^3J = 7.2 Hz, CH), 7.73 (1 H, t, ^3J = 7.2 Hz, CH), 7.93 (1 H, t, ^3J = 7.5 Hz, CH), 8.55 (1 H, d, ^3J = 7.5 Hz, CH), 9.21 (1 H, d, ^3J = 7.7 Hz, CH) ppm. ^{13}C-NMR: δ 53.2 (MeO), 53.7 (MeO), 62.7 (CH), 105.2 (CH), 112.5 (C), 121.8 (2 CH), 125.0 (CH), 126.8 (2 CH), 128.2 (CH), 128.7 (CH), 129.2 (CH), 131.8 (CH),

138.6 (C), 142.5 (C), 145.8 (C), 154.0 (C), 155.6 (C-N), 157.5 (C=N), 161.5 (C=O), 163.4 (C=O).

References

[1] (a) Bentley, K. W. *The Isoquinoline Alkaloids*; Pergamon Press: London, **1965**. (b) Bentley, K. W. *Nat. Prod. Rep.* **2001**, *18*, 148; (c) Michael, J. P. *Nat. Prod. Rep.* **2002**, *19*, 742; (d) Scott, J. D.; Williams, R. M. *Chem. Rev.* **2002**, *102*, 1669; (e) Hansch, C. P.; Sammes, G.; Taylor, J. B. Comprehensive Medicinal Chemistry; Pergamon Press: Oxford, **1990**.

[2] (a) Pop, E.; Wu, W. M.; Shek, E.; Bodor, N. *J. Med. Chem.* **1989**, *32*, 1774; (b) Sheha, M. M.; El-Koussi, N. A.; Farag, H. *Arch. Pharm. Pharm. Med. Chem*. **2003**, *336*, 47; (c) Mahmoud, S.; Aboul-Fadl, T.; Farag, H.; Mouhamed, A. M. I. *Arch. Pharm. Pharm. Med. Chem.* **2003**, *336*, 573; (d) Prokai, L.; Prokai-Tatrai, K.; Bodor, N. *Med. Res. Rev.* **2000**, *20*, 367.

[3] Lukevics, E.; Segal, I.; Zablotskaya, A.; Germane, S. *Molecules* **1997**, *2*, 180.

[4] (a) Maryanoff, B. E.; McComsey, D. F.; Gardocki, J. F.; Shank, R. P.; Costanzo, M. J.; Nortey, S. O.; Schneider, C. R.; Setler, P. E. *J. Med. Chem.* **1987**, *30*, 1433; (b) Sorgi, K. L.; Maryanoff, C. A.; McComsey, D. F.; Graden, D. W.; Maryanoff, B. E. J. *Am. Chem. Soc.* **1990**, *112*, 3567.

[5] (a) Tietze, L. F.; Rackehmann, N.; Miller, I. *Chem. Eur. J.* **2004**, *10*, 2722; (b) Knjlker, H. J.; Agarwal, S. *Tetrahedron Lett.* **2005**, *46*, 1173; (c) Scott, J. D.; Williams, R. M. *Chem. Rev.* **2002**, *102*, 1669.

[6] (a) Scriven, E. F. In Comprehensive Heterocyclic Chemistry; Katritzky, A. R., Rees, C. W., Eds.; Pergamon Press: Oxford, **1984**; Vol. 2, p 65. (b) Blasko, G.; Kerekes, P.; Makleit, S. Reissert Synthesis of Isoquinoline and Indole Alkaloids. In The Alkaloids; Brossi, A., Ed.; Academic Press: London, **1987**; Vol. 31, p 987. (c) Takamura, M.; Funabashi, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *122*, 6327.

[7] Terrett, N. K. Combinatorial Chemistry; Oxford University Press: New York, **1998**.

[8] (a) Orru, R. V. A.; Greef, M. *Synthesis* **2003**, 1471; (b) Domling, A. *Curr. Opin. Chem. Biol.* **2002**, *6*, 306; (c) Bienayme, H.; Hulme, C.; Oddon, G.; Schmitt, P. *Chem. Eur. J.* **2000**, *6*, 3321; (d) Do¨mling, A. *Chem. Rev.* **2006**, *106*, 17; (e) Zhu, J.; Bienayme´, H. Multicomponent Reactions; Wiley-VCH: Weinheim, **2005**.

[9] Yavari, I.; Hossaini, Z.; Sabbaghan, M.; ghazanfarpour-Darjani, M. *Tetrahedron* **2007**, *63*, 9423.

[10] Yavari, I.; Hossaini, Z.; Alizadeh, A. *Monatsch. Chem*. **2006**, *137*, 1083.

[11] Yavari, I.; Anary-Abbasinejad, M.; Hossaini, Z. *Org. Biomol. Chem*. **2003**, *1*, 560.