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Synthesis of isoquinoline derivatives using activated acetylenic compounds

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Abstract: In this work, synthesis of isoquinolines derivatives in excellent yield using multicomponent reaction of phthalaldehyde, ammonium actate, propiolate and alkyl chloride in the presense of catalytic amount of Fe_3O_4-MNPs in water at room temperature were investigated. The reduction of ferric chloride solution with *orange peel* water extract caused to synthesis of magnetic iron oxide nanoparticles (Fe_3O_4-NPs) as a green method. These compounds have biological potential because of isoquinoline or quinoline core. For this reason, the antimicrobial activity of some synthesized compounds was studied employing the disk diffusion test on Gram-positive bacteria and Gram-negative bacteria. The results of disk diffusion test showed that compound prevented the bacterial growth.

Keywords: Three-component reaction, Isoquinoline, Bridgehead N-heterocycles, Activated acetylenes.

Introduction

Green chemistry is chemical procedure that decrease or remove application and production of hazardous chemicals from the environment. Organic solvents that are needed for performing some organic reactions are often toxic and expensive. For this reason, elimination of these solvents is a suitable work for nature. Therefore, performing organic reactions in water as solvent has received wonderful notice in recent years [1]. For synthesis of heterocyclic compounds using multi-component reactions, design of new procedures has more attention in the last decade. In multi-component reactions (MCRs), organic compounds were generated in a few steps or in a one-pot procedure [2-4]. Isoquinoline or isoquinoline derivatives is one of the important heterocyclic compounds that have outstanding moiety in medicinal chemistry and display a broad variety of biological and pharmacological properties [5-11]. Isoqunoline derivatives are as a main group of heterocycle compounds because of their existence in nature [12-13] and their pharmacological activities including antifungal [14] antibacterial [15], antitumor [16], anti-inflammatory [17] anticonvulsant [18], analgesic [19] and antitubercular [20] activities. Furthermore, isoquinoline derivatives are as a new group of cancer chemotherapeutic agents alongwith considerable therapeutic performance anti solid tumor [21]. As well, isoquinoline derivatives have a chief location in asymmetric catalysis and photochemistry as ligands [30]. For first time, isoquinoline was separated in 1885 by Hoogewerf and van Dorp from coal tar [22]. A number of procedures exist for the synthesis of isoquinoline ring which can be well modified to generate some of different functionalized isoquinolines. Conventional methods for the preparation of isoquinoline such as Bischer−Napieralski, Pictet−Spengler, and Pomeranz−Fritsch reactions often have disadvantages such as low yields, a limited substrate scope and hard reaction conditions. Recently, organic chemists show a much attention to nano catalysis. These compounds display enhanced catalytic activity compared to their bulk sized types. Another topic in this work is investigation of synthesized compounds power in term

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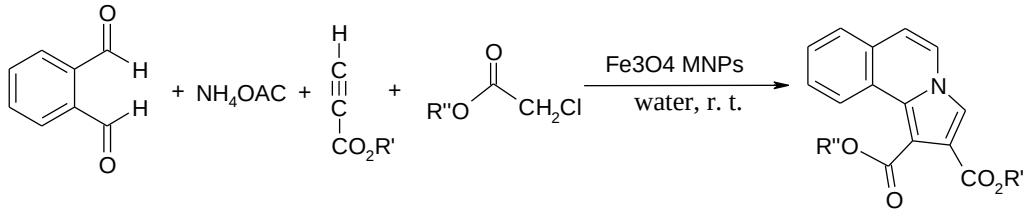
of antioxidant activity. Usually the compounds which have antioxidant activity because of their reductive properties and chemical structure employ as transitional metals chelators and negative effect of free radicals could be eliminate via these compounds. At present, bacteria that is stable in the presence of drug have created substantial problems in the performance of many communicable diseases. Therefore, discovering new ways to fight against these pathogens are important. For this reason, recent studies have focused on the study of the antibacterial effects of new synthesized compounds. At present, bacteria that is stable in the presence of drug have created substantial problems in the performance of many communicable diseases. Therefore, discovering new ways to fight against these pathogens are important. For this reason, recent studies have focused on the study of the antibacterial effects of new synthesized compounds. Herein, in continuation of our studies for discovering new procedure for synthesis of important organic compounds with biological activity [37-45], in this research we carry out the synthesis of new derivatives of isoquinoline *via* the reaction of phthalaldehyde **1**, ammonium acetate **2**, Propiolate **3** and alkyl chloride **4** in the presence of Fe3O4-MNPs in good yields (Scheme **1**).

Results and discussion

As part of our current studies on the development of new routes in heterocyclic systems, in this letter we describe a simple synthesis of functionalized isoquinolines. The reaction of phthalaldehyde **1**, ammonium acetate **2**, Propiolate **3** and alkyl chloride **4** in the presence of Fe_3O_4-MNPs in good yields (Scheme **1**).

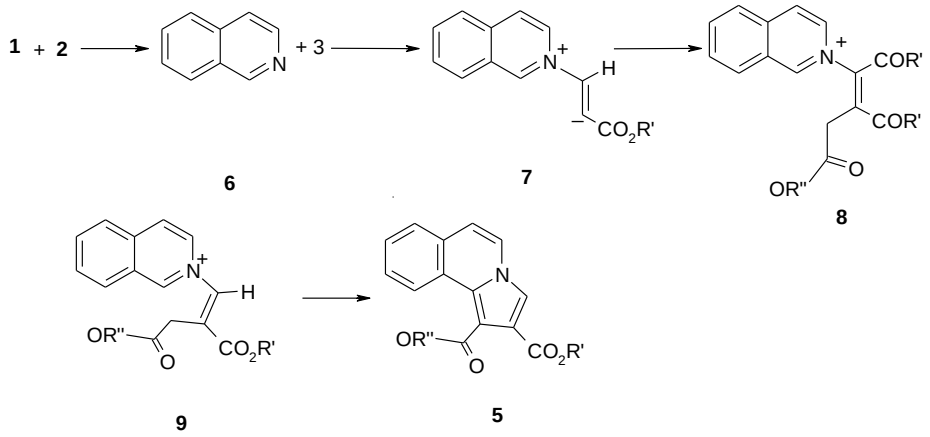


1 **2** **3** **4** **5**

5	R	R'	Yield (%)
a	H	OMe	95
b	H	OEt	93
c	Me	OMe	97
d	Et	OMe	95
e	H	Ph	90

Scheme 1: Synthesis of isoquinoline derivatives **5**

The reactions proceed spontaneously in H_2O and were complete within 2 h. The structures of compounds **5a-5e** were deduced from their elemental analyses and their IR, ^{1}H-NMR and ^{13}C-NMR spectra. The ^{1}H-NMR spectrum of **5a** exhibited singlets (3.93 and 4.02 ppm) readily recognized as arising from methoxy protons. The proton-decoupled ^{13}C-NMR spectrum of **5a** showed fourteen distinct resonances in agreement with the proposed structure. A tentative mechanism for this transformation is proposed in Scheme **2**. It is conceivable that, the initial event is the formation of 1,3-dipolar intermediate **6** from isoquinoline that is produced from the reaction of phthalaldehyde **1** and the ammonium acetate **2** with propiolate **3**, which is subsequently attacked by alkyl chloride **4** to produce the salt **9**. Intermediate **9** undergoes cyclization/elimination reactions to generate **5**.



Scheme 2: Proposed mechanism for the formation of **5**.

Analysis of the antibacterial activity of synthesized compounds

Also, a comparison between the activity of our synthesized compounds with Streptomycin and Gentamicin as standard drug was discussed. The results of the antimicrobial activity of some synthezized compounds on bacterial species are investigated. The present study indicated that the type of bacteria and concentration of compounds are effective on the diameter of the inhibition zone. It is apparent from the obtained data, the antimicrobial activity of the most synthesized compounds **5a, 5b, 5d,** and **5c** were good active against Gram positive bacteria and Gram negative bacteria So that the diameter of the inhibition zone of compounds has the maximum effect on Escherichia coli.

Conclusion

In conclusion, we have described a convenient route to isoquinoline from phthalaldehyde, ammonium acetate, activated acetylenic compounds and alkyl chloride in the presence of Fe_3O_4-MNPs. The functionalized bridgehead N-heterocycles reported in this work may be considered as potentially useful synthetic intermediates because they possess atoms with different oxidation states. The advantage of the present procedure is that the reaction is performed under neutral conditions by simple mixing of the starting materials. The simplicity of the present procedure makes it an interesting alternative to other approaches. The procedure described here provides an acceptable one-pot method for the preparation of functionalized heterocyclic compounds.

Experimental

General. Melting points were measured on an *Electrothermal 9100* aparatus. Further purification. 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, resp; δ in ppm, *j* in Hz. EI-MS (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 for preparation of compounds 5

Phthalaldehyde **1** (2 mmol) and ammonium acetate **2** (2 mmol) stirred in water (5 mL) as solvent for 20 min at 80 ^{o}C in the presence Fe_3O_4 MNPs (10 mol%). In this stage isoquinoline was prepared and for confirmation of it we checked with isoquinoline that are prepared from company by TLC. Then activated acetylenic compounds **3** (2 mmol) was added slowly and mixture was stirred for 15 min. then alkyl chloride **4** was added and mixture was stirred for 2 h in the presence of Fe_3O_4-MNPs (10 mol%) at r.t. for 45 min. After completion of the reaction (2 h; TLC control (hexane–AcOEt, 6:1), the Fe_3O_4 MNPs were separated by external magnet from mixture of reaction. After removing solvent, the residue was purified by column chromatography (6:1 hexane/EtOAc) to afforded pure title compounds.

Representative Procedure for the Preparation of Dimethyl 1-(2,2,2-Trichloroacetyl)-2,3-indolizinedicarboxylate (5a).

Yield: 0.62 g (82%). Colorless crystals. Mp 173-176° (dec.). IR (KBr): 1730, 1697, 1651 (3 C=O), 1218. ^{1}H-NMR: 3.93, 4.02 (*s*, 2 MeO); 7.14 (*t*, ^3J = 7, CH); 7.50 (*t*, ^3J = 9, CH); 8.42 (*d*, ^3J = 9, CH); 9.67 (*d*, ^3J = 7, CH). ^{13}C-NMR: 52.3 and 53.0 (2 MeO); 96.3 (CCl_3); 105.0 and 114.2 (2 C); 115.7, 121.9, 127.8 and 128.6 (4 CH); 134.3 and 136.1 (2 C); 160.2, 165.9 and 176.0 (3 C=O). MS: *m/z* (%) = 378 ($M^{+\bullet}$, 2), 231 (10), 261 (20), 260 (100), 143 (28), 115 (20). Anal. Calc. for $C_{14}H_{10}Cl_3NO_5$ (378.6): C 44.42, H 2.66, N 3.70; found: C, 44.28; H, 2.72; N, 3.74%.

Compound 5b:

Yield: 0.65 g (80%). White powder. Mp 112-114° (dec.). IR (KBr): 1726, 1697, 1647 **(**3 C=O**)**, 1209. ^{1}H-NMR: 1.43 (*t*, ^3J = 7, CH_3); 1.48 (*t*, ^3J = 7, CH_3); 4.44 (*q*, ^3J = 7, CH_2O); 4.54 (*q*, ^3J = 7, CH_2O); 7.17 (*t*, ^3J = 7, CH); 7.54 (*t*, ^3J = 9, CH); 8.46 (*d*, ^3J = 9, CH); 9.74 (*d*, ^3J = 7, CH). ^{13}C-NMR: 14.4 and 14.5 (2 CH_3); 61.8 and 62.5 (2 MeO); 96.7 (CCl_3); 105.3 and 114.6 (2 C); 116.0, 122.3, 128.2 and 129.0 (4 CH); 135.0 and 136.4 (2 C); 160.3, 165.9 and 176.1 (3 C=O).

Compound 5c:

Yield: 0.62 g (79%). Yellow powders. Mp 233-235° (dec.). IR (KBr): 1730, 1694, 1649 **(**3 C=O**)**, 1216. ^{1}H-NMR: 2.55 (*s*, CH_3); 3.96 and 4.06 (*s*, 2 MeO); 7.01 (*dd*, ^3J = 7, ^4J = 1, CH); 8.24 (*s*, CH); 9.57 (*d*, ^3J = 7, CH). ^{13}C-NMR: 22.4 (CH_3); 52.7 and 53.4 (2 MeO); 96.4 (CCl_3); 105.3 and 114.1 (2 C); 118.1, 121.2 and 128.3 (3 CH); 134.7(C); 136.4 and 140.2 (2 C); 160.6, 166.5, and 177.0 (3 C=O). MS: 392 ($M^{+\bullet}$, 5), 278 (20), 274 (100), 244 (10), 157 (57), 103 (30), 77 (37), 57 (28), 84 (70), 59 (18). Anal. calc. for $C_{15}H_{12}Cl_3NO_5$ (392.6): C 45.89, H 3.08, N 3.57; found: C, 45.82; H, 3.10; N, 3.61%.

Compound 5d:

Yield: 0.63 g (78%). Yellow powder, Mp 125-127°. IR (KBr): 1730, 1697, 1651 **(**3 C=O**)**, 1218. ^{1}H-NMR: 1.38 (*t*, ^3J = 7, CH_3); 2.85 (*q*, ^3J = 7, CH_2); 3.96 and 4.06 (*s*, 2 MeO); 7.01 (*dd*, ^3J = 7, ^4J = 1, CH); 8.28 (*s*, CH); 9.58 (*d*, ^3J = 7, CH). ^{13}C-NMR: 14.3 (CH_2); 29.1 (CH_3); 52.7 and 53.4 (2 MeO); 96.9 (CCl_3); 104.4 and 114.1 (2 C); 117.7, 119.8 and 128.4 (3 CH); 137.2 (C); 137.2 and 145.9 (2 C); 160.6, 166.5, and 176.2 (3 C=O). MS: 407 ($M^{+\bullet}$+1, 40), 406 ($M^{+\bullet}$, 20), 348 (38), 289 (85), 288 (100), 171 (62), 117 (62), 115 (62), 84 (70), 59 (58). Anal. calc. for $C_{16}H_{14}Cl_3NO_5$ (406.64): C 47.26, H 3.47, N 3.44; found: C, 47.32; H, 3.43; N, 3.48%.

Compound 5e:

Yield: 0.70 g (75%). Dark yellow oil. IR (KBr): 1730, 1697, 1651**(**3 C=O**)**, 1218. ^{1}H-NMR: 7.12 (*t*, ^3J = 8, 2 CH); 7.23-7.36 (*m*, 5 CH); 7.44 (*d*, ^3J = 7, 2 CH); 7.45 (*d*, ^3J = 7, 2 CH); 7.51 (*t*, ^3J = 7, CH); 8.40 (*d*, ^3J = 9, CH); 9.60 (*d*, ^3J = 7, CH). ^{13}C-NMR: 96.3 (CCl_3); 108.6 (C); 116.3 and 121.5 (2 CH); 126.1 (C); 128.3 and 128.6 (4 CH); 128.7 (CH), 129.1 (2 CH); 129.2 (CH), 129.5 (2 CH); 130.6 (C); 132.7, 133.4 (2 CH); 138.2, 139.6 and 140.3 (3 C); 180.0, 187.9 and 192.2 (3 C=O).

Investigation of antibacterial activity for some of the synthesized compounds

Gram-positive and Gram-negative bacteria were utilized for investigation of antibacterial effect of synthesized isoquinoline derivatives utilizing the disk diffusion method. All of bacteria were prepared from the Persian type culture collection (PTCC), Tehran, Iran. The two kinds of bacteria were cultured for 16 to 24 h at 37°C for preparing bacteria to turbidity equivalent to McFarland Standard No. 0.5. Streptomycin and Gentamicin as two standards were employed against bacteria with a concentration 40 μg/mL. The bacterial suspension was produced according to the turbidity of the 0.5 McFarland (About 1.5 × 108 CFU/mL) standards and cultured with a sterile swab on Mueller Hinton agar. The synthesized isoquinoline and quinoline derivatives with concentration of 25 µg/ml were poured on sterile blank disks for evaluation of their antibacterial activity. The plates were incubated in an incubator at 37 °C for 24 h. The diameter of the inhibition zone was measured and compared to the standard.

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