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RESEARCH ARTICLE

SYNTHESIS OF PYRAZOLE DERIVATIVES

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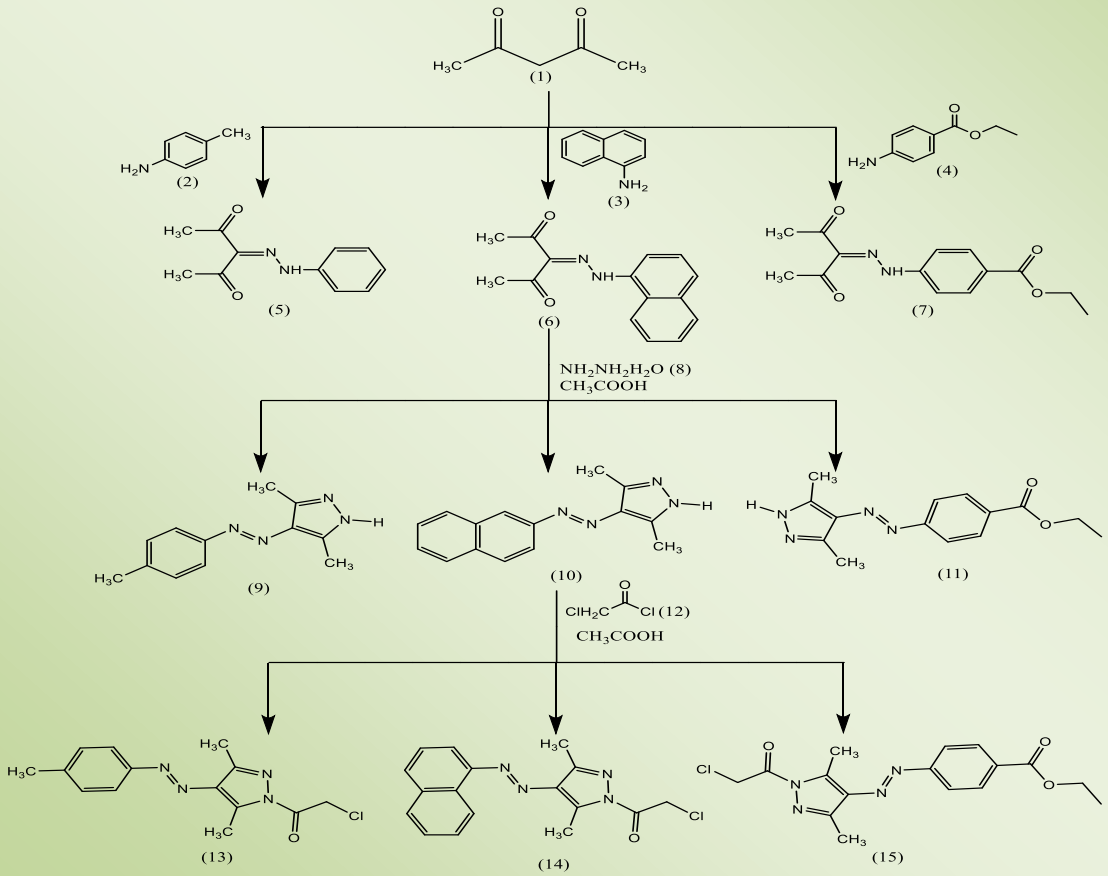
Abstract

In this study, some of the hydrazono compounds (5), (6), and (7) were formed when aromatic amines such as P-toluidine (2), Naphthyl amine (3), and ethyl-4-aminobenzoate (4) reacted with acetylacetone (1) in presence of sodium nitrite and sodium acetate. Theses hydrazono derivatives (5), (6), and (7) were refluxed with hydrazine hydrate (8) in glacial acetic acid gave pyrazolyldiazenes compounds (9), (10), and (11) which were further reacted with chloroacetyl chloride (12) afforded compounds (13), (14), and (15). In addition, All the synthesized compounds were identified on the basis m.p, TLC, IR, H^1-NMR, D_2O Exchange, C^{13}-NMR, DEPT spectroscopy.



Key Words: pyrazole**;** acetylacetone**;** hydrazine hydrate; cyclization; chloroacetyl chloride; acetic acid.

INTRODUCTION

pyrazole is an important class of heterocyclic compounds that plays an important role in medicinal chemistry, various substituted pyrazoles, and their derivatives containing two Nitrogen-atoms in five-membered parent ring. For a very long time the usefulness and great therapeutic value of the pyrazole nucleus have been recognized and the wide range of biological activities (Karthikeyan et al. 2007 & Parmar et al. 2005). Pyrazole ring has a fairly developing area of synthetic chemistry (Pareek et al. 2010).

pyrazole derivatives have a long history of applications in agrochemicals and pharmaceutical industries as herbicides and active pharmaceuticals. Being so composed and having pharmacological effects on humans, they are classified as alkaloids, although they are rare in nature. Pyrazoles derivatives are test for their anti-inflammatory (Tewari & Mishra 2001), antimicrobial (Pimerova & Voronina 2001), antiviral (Janus et al. 1999), antitumour (Park et al. 2005 & Bouabdallah et al. 2006), anticonvulsant (Michon et al. 1995), antibacterial activity (Shastri et al. 2007), and cytotoxic activity (Ahasan & Islam 2007 & VishnuvardanRao et al. 2011). Pyrazoles are widely distributed in nature and it is possible to obtain them by extractive techniques, also homogenous and heterogeneous synthesis procedures are frequently employed[12]. The wide range of biological activities associated with pyrazoles has made them popular synthetic targets.

MATERIALS and METHODS

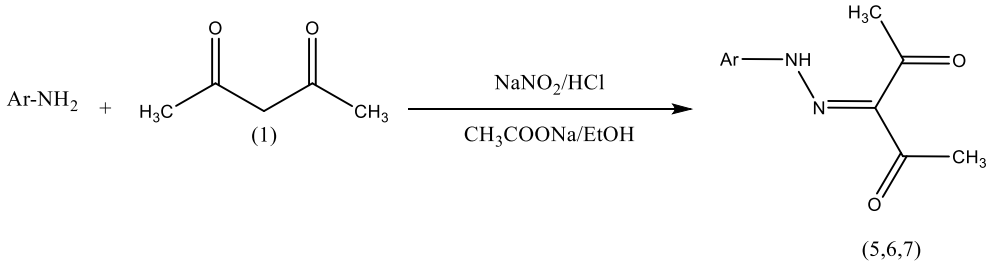
MATERIALS

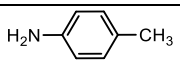
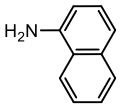
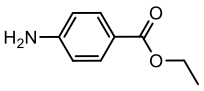
All chemicals were purchased from Sigma-Aldrich (St. Louis, Mo, USA) and were used as received. Reactions were monitored on TLC (petroleum ether/chloroform). All spectroscopic analysis of prepared compounds was conducted in the microanalytical unit at the research center of the science faculty, Alexandria University. H^1-NMR spectra were carried out on Bruker 500 MHz with chemical shift (δ) expressed in ppm downfield from tetramethylsilane as an internal stander (δ MS=0) using CDCl3 as a solvent. The multiplicity of the signal is as followis: s (Singlet), d (Doublet), t(Triplet), q(Quartet), m(Multiplet). C^{13}-NMR were measured on Bruker 125 MHz with internal reference TMS δ=0. Infrared spectra were recorded on a Buck Scientific IR spectrophotometer model 500, where the positions of absorptions have been expressed in wavenumber units (cm^{-1}). Melting points (m.p) of the synthesized compounds were measured in capillary tubes using the Griffin apparatus and are uncorrected.

METHODS

The reaction of diazonium salts with acetyl acetone

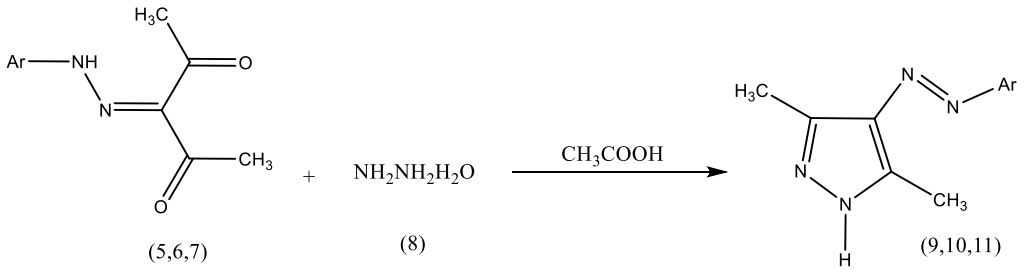
Aromatic amine was dissolved in a mixture of concentrated hydrochloric acid (8 ml) and water (6 ml) and then cooled to 0°C in an ice bath. A cold aqueous solution of sodium nitrite (0.02 mole) was added to the first solution to afford diazonium salt then a cold solution of acetylacetone (0.01 mole), sodium nitrite (0.01 mole), and sodium acetate (0.05 mole) in 20 ml ethanol was added to diazonium salt and stirred for two hours. The resulting solid was filtered off, dried, and purified by recrystallization from ethanol gave hydrazono derivative.

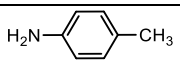
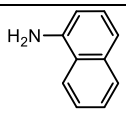
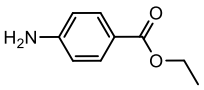


Compound no.	Ar-NH_2	(%) Yield	m.p (°C)
5		78	88-90
6		89	135-137
7		87	123-126

The reaction of hydrazono derivatives with hydrazine hydrate

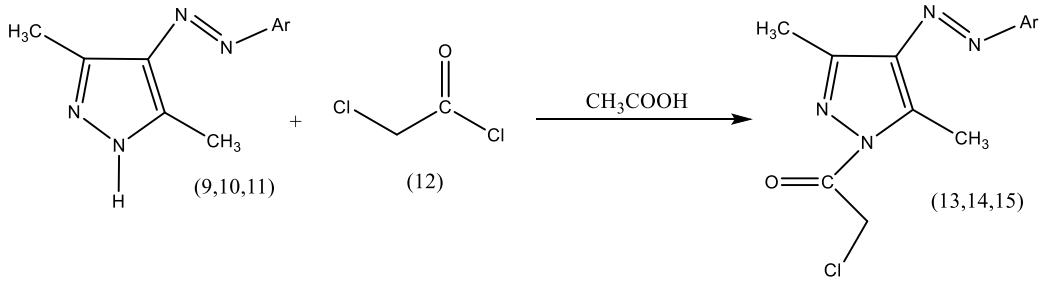
A hydrazono derivative (0.01 mole) was refluxed for 4-5 hours with hydrazine hydrate (0.015 mole) in glacial acetic acid (15 ml). the resulting mixture was concentrated and allowed to cool, then the resulting solid was filtered, washed, dried, and finally recrystallized from ethanol afforded pyrazolyldiazene.

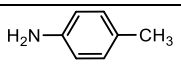
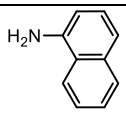
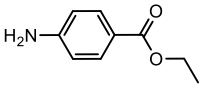


Compound no.	Ar-NH_2	(%) Yield	m.p (°C)
9		63	127-130
10		68	168-170
11		83	149-150

The reaction of pyrazolyldiazenes with chloroacetyl chloride

Pyrazolyldiazene (0.0025 mole) was dissolved in glacial acetic acid. The reaction mixture was cooled in an ice bath, chloroacetyl chloride (0.0025 mole) was cold then added drop wise with continuous stirring for 15 minutes in an ice bath. The stirring was continued for 30 minutes at room temperature, the mixture was poured into crushed ice forming precipitate, which was filtered, dried, and recrystallized from methanol.



Compound no.	Ar-NH_2	(%) Yield	m.p (°C)
13		47	137-140
14		47	120-122
15		43	153-155

RESULTS and DISCUSION

RESULTS

3-(2-(p-tolyl)hydrazono)pentane-2,4-dione (5): IR (KBr) ν =1666 cm^{-1} (C=O), 1624 cm^{-1} (C=O), 1587cm^{-1}(C=N). H^1-NMR ($CDCl_3$): δ = 2.35 (s, 3H, CH_3), 2.47(s ,3H, CH_3), 2.58(s, 3H, CH_3), 7.18(d, 2H, Ar-H), 7.31(d, 2H, Ar-H), 14.80(s, 1H, D_2O exchangeable NH). C^{13}-NMR ($CDCl_3$): δ =21.11(CH_3, 1C), 26.47(CH_3, 1C), 31.72(CH_3-Ar, 1C) ,116.34 (C-Ar, 2C), 130.31 (C-Ar, 2C), 132.98 (1C), 136.07(1C), 139.31(1C), 197.21(C=O, 1C), 197.86(C=O, 1C).

3-(2-(naphthalen-1-yl)hydrazono)pentane-2,4-dione (6): IR (KBr) ν =1663 cm^{-1} (C=O), 1618 cm^{-1} (C=O). H^1-NMR ($CDCl_3$): δ =2.55 (s, 3H, CH_3), 2.67(s ,3H, CH_3), 7.71, 7.80, 7.89, 7.90, 7.91 (m, 7H, Ar-H), 7.88 (s, 1H, D2O exchangeable NH) . C^{13}-NMR ($CDCl_3$): δ =26.84(CH_3, 1C), 31.83(CH_3, 1C), 123.48(C=N, 1C) ,197.32 (C=O, 1C), 198.32 (C=O, 1C), 112.05, 119.64, 126.11, 126.15, 126.68, 127.12, 128.92, 134.14, 134.41, 136.60 (C-Ar, 10C).

ethyl 4-(2-(2,4-dioxopentan-3-ylidene)hydrazinyl)benzoate (7): IR (KBr) ν =1670 cm^{-1} (C=O), 1630 cm^{-1} (C=O). H^1-NMR ($CDCl_3$): δ = 1.37 (t, 3H, CH_3), 2.50(s ,3H, CH_3), 2.60 (s, 3H, CH_3), 4.36 (q, 2H, CH_2), 7.41 (d, 2H, Ar-H), 8.08 (d, 2H, Ar-H), 14.58 (s, 1H, D_2O exchangeable NH). C^{13}-NMR ($CDCl_3$): δ =14.44 (CH_3, 1C), 26.74 (CH_3, 1C), 31.87 (CH_3, 1C) ,61.17 (CH_2, 1C), 115.62 (C-Ar, 2C), 131.45 (C-Ar, 2C), 127.45 (C-Ar, 1C), 134.16 (C-Ar, 1C), 145.13 (C=N, 1C), 165.96 (O-C=O, 1C), 197.15 (C=O, 1C), 198.45 (C=O, 1C).

3,5-dimethyl-4-(p-tolyldiazenyl)-1H-pyrazole (9): IR (KBr) ν = 3312 cm^{-1} (N-H), 850 cm^{-1} (*p*-CH_3). H^1-NMR (CDCl3): δ = 2.41 (s, 6H, 2CH_3), 2.61(s ,3H, CH_3), 7.26 (d, 2H, Ar-H), 7.68 (s, 1H, D_2O exchangeable NH), 7.70 (d, 2H, Ar-H). C^{13}-NMR (CDCl3): δ =12.05 (CH_3, 2C), 21.49 (CH_3, 1C), 121.95 (C-Ar, 2C) ,122.37 (C-N, 1C), 129.68 (C-Ar, 2C), 140.21 (2C), 141.11 (C-Ar, 1C), 151.56 (C-Ar, 1C).

3,5-dimethyl-4-(naphthalen-1-yldiazenyl)-1H-pyrazole (10): IR (KBr) ν = 3500 cm^{-1} (N-H). H^1-NMR (CDCl3): δ = 2.76 (s, 6H, $2CH_3$), 7.56-8.77 (m, 7H, Ar-H), 9.06 (s, 1H, D_2O exchangeable NH). C^{13}-NMR (CDCl3): δ =12.28 (CH3, 2C), 110.49, 111.29. 125.81, 126.31, 126.62, 128.00, 129.94 (C-Ar, 7C), 130.46 (C-Ar, 1C), 131.07 (C-Ar, 1C), 134.41 (C-Ar, 1C), 141.33 (C-CH_3, 2C), 148.45 (C-N, 1C).

ethyl 4-((3,5-dimethyl-1H-pyrazol-4-yl)diazenyl)benzoate (11): IR (KBr) ν = 3254 cm^{-1} (N-H), 1687 cm^{-1} (C=O). H^1-NMR (CDCl3): δ = 1.41 (t, 3H, CH_3), 2.64 (s, 6H, $2CH_3$), 4.41 (q, 2H, CH_2), 7.81 (d, 2H, Ar-H), 8.14 (d, 2H, Ar-H), 8.37 (s, 1H, D_2O exchangeable NH). C^{13}-NMR (CDCl3): δ = 12.15 (CH_3, 1C), 14.44 (CH_3, 2C), 61.29 (CH_2, 1C), 121.82 (C-Ar, 2C), 130.59 (C-Ar, 2C), 131.15 (C-CH_3, 2C), 141 (C-N, 1C), 141.91 (C-Ar, 1C), 156.02 (C-Ar, 1C), 166.34 (C=O, 1C).

2-chloro-1-(3,5-dimethyl-4-(p-tolyldiazenyl)-1H-pyrazol-1-yl)ethan-1-one (13): IR (KBr) ν = 1749 cm^{-1}(C=O). H^1-NMR (CDCl3): δ = 2.42 (s, 3H, CH_3), 2.48 (s, 3H, CH_3), 2.93 (s, 3H, CH_3), 4.95 (s, 2H, CH_2), 7.28 (d, 2H, Ar-H), 7.72 (d, 2H, Ar-H). C^{13}-NMR (CDCl3): δ = 12.11 (CH_3, 1C), 15.24 (CH_3, 1C), 21.57 (CH_3, 1C), 43.62 (CH_2, 1C), 122.35 (C-Ar, 2C), 129.81 (C-Ar, 2C), 137.92 (1C), 141.45 (1C), 144.58 (1C), 146.89 (C-Ar, 1C), 151.27 (C-Ar, 1C), 166.78 (C=O, 1C).

2-chloro-1-(3,5-dimethyl-4-(naphthalen-1-yldiazenyl)-1H-pyrazol-1-yl)ethan-1-one (14): H^1-NMR (CDCl3): δ = 2.73 (s, 3H, CH_3), 3.01 (s, 3H, CH_3), 4.97 (s, 2H, CH_2), 7.56-8.75 (m, 7H, Ar-H). C^{13}-NMR (CDCl3): δ = 12.22 (CH_3, 1C), 15.77 (CH_3, 1C), 43.64 (CH_2, 1C), 111.25, 123.31, 125.69, 126.53, 127.06, 128.13, 131.28 (C-Ar, 7C), 131.74, 134.43, 138.84, 145.59, 146.45, 148.28 (C-Ar, 6C), 166.80 (C=O, 1C).

ethyl 4-((1-(2-chloroacetyl)-3,5-dimethyl-1H-pyrazol-4-yl)diazenyl)benzoate (15): IR (KBr) ν = 1713 cm^{-1}, 1757 cm^{-1} (2C=O). H^1-NMR (CDCl3): δ = 1.41 (s, 3H, CH_3), 2.49 (s, 3H, CH_3), 2.96 (s, 3H, CH_3), 4.39 (q, 2H, CH_2), 4.96 (s, 2H, CH_2), 7.85 (d, 2H, Ar-H), 8.16 (d, 2H, Ar-H). C^{13}-NMR (CDCl3): δ = 12.20 (CH_3, 1C), 14.44 (CH_3, 1C), 15.33 (CH_3, 1C), 43.60 (CH_2, 1C), 61.38 (CH_2, 1C), 122.16 (C-Ar, 2C), 130.63(C-Ar, 2C), 132.01 (1C), 138.17 (1C), 146.26 (1C), 146.54 (1C), 155.57 (1C), 166.11(C=O, 1C), 166.82 (C=O, 1C).

DISCUSION

Both nucleophilic and electrophilic reactions were used during this research in order to obtain a heterocyclic system which widely used in medicine [10]. The reactions were made by the addition of freshly prepared diazonium salt of p-toluidine (2), naphthyl amine (3), and ethyl 4-aminobenzoate (4) to the active methylene in acetylacetone compound (1), obtaining the desired compounds 3-(2-(p-tolyl)hydrazono)pentane-2,4-dione (5), 3-(2-(naphthalen-1-yl)hydrazono)pentane-2,4-dione (6), and ethyl 4-(2-(2,4-dioxopentan-3-ylidene)hydrazinyl)benzoate (7). The obtained products were proved by spectroscopic tools, definitely the IR spectrum of compound (5), (6), and (7) showed peaks at about 1670 cm^{-1}, 1630 cm^{-1}, and 1587 cm^{-1} indicated the frequency of two carbonyl groups and cyano groups, respectively. Which were very low when compared with ketone group IR value which ranging from 1705-1725 cm^{-1} due to the conjugation of the carbonyl groups with the C=N bond, Also, a peak appeared at 3316 cm^{-1} was evidence of the existence of tautomer for the N-H group. H^1-NMR spectra for compounds (5), (6), and (7) showed the same peaks appeared at about 2.47 and 2.58 ppm which is characteristic of $2CH_3$-CO groups and signals at 14.08 and 14.58 ppm belonged to N-H groups for compound (5), and (7), respectively which were indicated by D_2O exchange. Whereas, N-

H peak for compound (6) detected at 7.88 ppm. C^{13}-NMR for compound (5) showed peaks at 21.11ppm and 26.74 ppm which is characteristic of 2 CH_3-CO also signals appeared at 139.31 ppm, 197.21 ppm, and 197.86 due to C=N and 2C=O groups, respectively. In addition to the peaks of 2 CH_3-CO groups and 2C=O groups, other peaks appeared in the C^{13}-NMR spectrum of compound (6) between (112.05-136.60 ppm) for naphthyl ring carbons as well as for signals belonged to quaternary carbons which proved by the disappearance in DEPT technique. Finally, C^{13}-NMR spectra confirmed the presence of 12, 15, and 14 carbon atoms in compound (5), (6), and (7) which indicates that these compounds were prepared successfully.

Compounds (9), (10), and (11) were prepared by reaction of hydrazine hydrate (8) with compounds (5), (6), and (7) in the presence of acetic acid to give Pyrazol ring. IR analysis of compounds (9), (10), and (11) indicated the presence of N-H stretching signals at 3312 cm^{-1}, 3500 cm^{-1}, and 3254 cm^{-1}. The H^1-ĩNMR and C^{13}-NMR spectra showed clear signals in agreement with the proposed structures for compounds (9), (10), and (11).

On the other hand, reaction of pyrazolyldiazenes compounds (9), (10), and (11) with chloroacetyl chloride (12) using acetic acid as catalyst afforded 2-chloro-1-(3,5-dimethyl-4-(p-tolyldiazenyl)-1H-pyrazol-1-yl)ethan-1-one (13), 2-chloro-1-(3,5-dimethyl-4-(naphthalen-1-yldiazenyl)-1H-pyrazol-1-yl)ethan-1-one (14), and ethyl 4-((1-(2-chloroacetyl)-3,5-dimethyl-1H-pyrazol-4-yl)diazenyl)benzoate (15). The appearance of the carbonyl group at 1749 cm^{-1} and the disappearance of the N-H band (3200-3550) cm^{-1} in the IR spectrum for compounds (13), (14), and (15) evidence of their successful preparation. The structures of compounds (13), (14), and (15) were also confirmed using H^1-NMR where the absorptions due to 2CH_3 groups attached to pyrazol ring detected at 2.42 ppm and 2.48 ppm for compound (13), 2.63 ppm and 3.1 ppm for compound (14), and 2.55 ppm and 2.96 ppm for compound (15) as well as signals appeared at 4.96 ppm belonged to CH_2-Cl, but the acidic protons in compounds (13), (14), and (15) were lost according to D_2O-exchange spectra which proved the correct preparation of these compounds. In addition to the carbons for two methyl groups attached to pyrazole ring and CH_2-Cl which detected at 12.11 ppm, 15.24 ppm, and 43.62 ppm C^{13}-NMR spectra for compounds (13), (14), and (15) confirmed the presence of six quaternary carbon atoms in compound (13) and seven quaternary carbon atoms in compound (14), and (15) that proved by disappearance when DEPT technique was used.

CONCLUSION

Hydrazono derivatives (5), (6), and (7) were successfully synthesized with high percentage yield (> 70%) using aromatic amines p-toluidine (2), naphthyl amine (3), and ethyl 4- aminobenzoate (4) with acetylacetone (1) which reacted with hydrazine hydrate (8) and gave pyrazolyldiazenes compounds (9), (10), and (11) with good percentage yield (> 63%). Further reaction of pyrazolyldiazenes compounds (9), (10), and (11) with chloroacetyl chloride (12) produced compounds (13), (14), and (15) with moderate percentage yield (> 43%). The structures of the synthesized compounds were established on the basis of the IR, H^1-NMR, C^{13}-NMR, D_2O Exchange, DEPT spectroscopy. All procedures for the synthesis of these compounds are very convenient due to the simple procedures, mild conditions, and moderate to high yields.

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