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Green synthesis of isoquinoline derivatives using mlticomponent reaction of ninhydrin

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Abstract: In this work, The 1,3-dipolar intermediates generated by addition of isoquinoline to dialkyl acetylenedicaboxylates are trapped by ninhydrin to produce spiro compounds in excellent yields. In addition, for investigation of antioxidant ability radical trapping by DPPH and reducing power of ferric ion experiments was performed. As a result, synthesized compounds show excellent radical trapping by DPPH and good reducing ability of ferric ion. The current procedure has the benefits for instance excellent yield of reaction, green media and easy separation of product and catalyst.

Keywords: Spiro compounds; Acetylenedicarboxylates; Ninhydrin; *N*-Heterocycles.

Introduction

The basic principles of dipolar cycloaddition reactions were provided by the work of *Huisgen* and co-workers [1]. An interesting example of this type is the dipole generated from isoquinoline and dimethyl acetylenedicarboxylate (*DMAD*), whose existence was established by *Huisgen* [2]. Spiro compounds having cyclic structures fused at a central carbon are of interest due to their interesting conformational features and their structural implications on biological systems [3]. The asymmetric characteristic of the molecule due to the chiral spiro carbon is one of the important criteria of the biological activities. The presence of the sterically constrained spiro structure in various natural products also adds to the interest in the investigations of spiro compounds [4]. 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.

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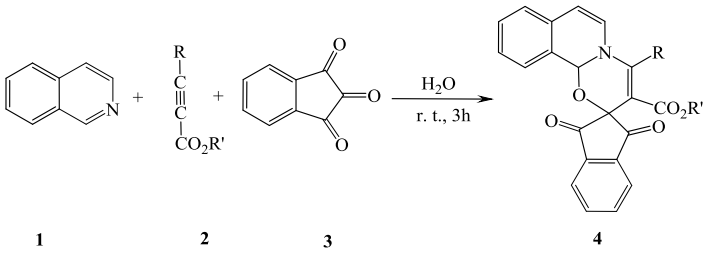
In this research investigation of antioxidant ability for some of the synthesized compounds is performed. Frequently compounds with antioxidant ability, eliminate the negative property of free radicals and utilize as transitional metals chelators. This result is due to their reducing properties and chemical structure. Also, these compounds could be avoid or decrease many sicknesses such as cardiovascular, inflammatory bowel syndrome, cancer, ageing, and alzheimer. Herein, in continuation of our studies for discovering new procedure for synthesis of important organic compounds with biological activity, in this research we carry out the synthesis of new derivatives of spiro compounds **4** *via* the reaction of isoquinoline **1**, activated acetylenic compounds **2** and ninhydrine **3** 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 the reaction of isoquinoline **1**, activated acetylenic compounds **2** and ninhydrine **3** in water in good yields (Scheme **1**).

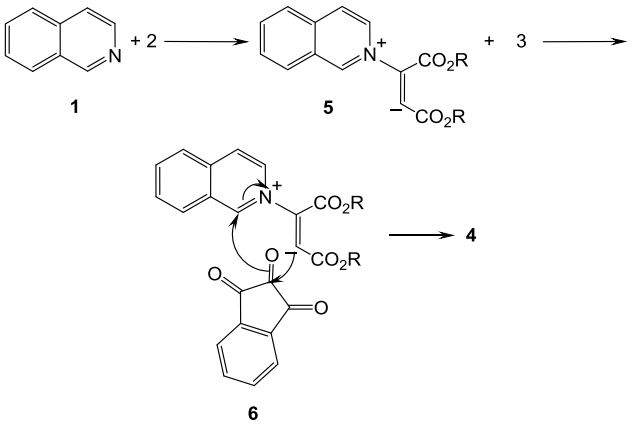


1 2 3 4

4	R	R'	Yield % of **4**
a	CO_2Me	Me	95
b	H	Me	90
c	CO_2Et	Et	87
d	H	Et	85

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

The structures of compounds **4a**–**4d** were deduced from their elemental analyses and their IR, ^{1}H-NMR, and ^{13}C-NMR spectra. For example, in the ^{1}H-NMR spectrum for the major isomer of **4a**, signals due to the two methoxy groups were visible at δ = 3.29 and 3.98; the corresponding signals for minor isomer of **4a** were observed at δ = 3.25 and 3.96. The ring junction proton of the major isomer of **4a** was discernible as a singlet at δ = 7.08; the corresponding signal for minor isomer of **5a** was seen as a singlet at δ = 6.52. In ^{13}C-NMR spectrum, the signals corresponding to ester and amide carbonyl groups of the major isomer of **4a** were observed at δ = 163.5, 163.9, and 174.5. Those for the minor isomer were visible at δ = 163.6, 163.7, and 174.6. The mass spectrum of **4a** displayed the molecular ion peak at *m*/*z* = 432, which is consistent with the 1:1:1 adduct of isoquinoline, *DMAD* and ninhydrin. Mechanistically, it is conceivable that the reaction involves the initial formation of intermediate 5 from the reaction of acetylenic compounds 2 react with isoquinoline 1 and reacts with the carbonyl group of ninhydrin to produce **6**. Cyclization of this zwitterionic intermediate leads to the spiro compound **4** (Scheme 2).



1 5 6

Scheme 2: Proposed mechanism for the formation of **4**

Diphenyl-2-picrylhydrazyl (DPPH) utilizing for evaluation of antioxidant ability

DPPH radical trapping experiment is generally employed for the approval of antioxidant ability or power of compounds to get free radicals of some synthezied compounds and antioxidant property of them in foods and biological structures. In these experiment, taking one electron or the hydrogen atom of synthezied compounds was performed by DPPH radical and show an valuation of antioxidant capacity basis of free radical trapping. The electron or hydrogen

donating power of compounds **4a-4d** to the DPPH radical determined the antioxidant ability of them. The absorption of DPPH radical was decreased from 517 nm when give one electron or hydrogen from antioxidant or a radical typs. In this research, the antioxidant ability or power of compounds **4a-4d** for taking free radicals was compared to synthesized antioxidant such as BHT and TBHQ at different concentrations. Overall, the power of DPPH trapping was obtained TBHQ>BHT>**4b**>**4c**>**4a**>**4d** (Figure 1).

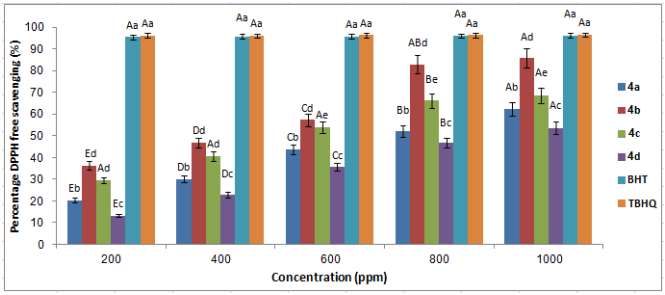


Figure 1. Order of antioxidant activity **of 4a-4d** using DPPH

As shown in Figure 1, the new synthesized compounds in all concentrations have moderate distinctions than to BHT and TBHQ. Among selected synthezied compounds, **4b** was shown excellent radical trapping activity relative to standards (BHT and TBHQ).

The potential of synthesized compounds by Ferric ions (Fe^{3+}) reducing

The ability of reducing ferric ions (Fe^{3+}) by some synthesized compounds such as **4a-4d** are calculated by the quantity of Fe^{3+}/ferricyanide reduced to the Fe^{2+}/ferrous at 700 nm [61]. As shown in Figure 8 in this test, compound **4b** was shown good reducing ability than to standard antioxidants such as BHT and TBHQ. The reducing activity trend of the samples was as follows: TBHQ>BHT>**4b**>**4a**>**4d**>**4c**. The outcomes are displayed in Figure 2.

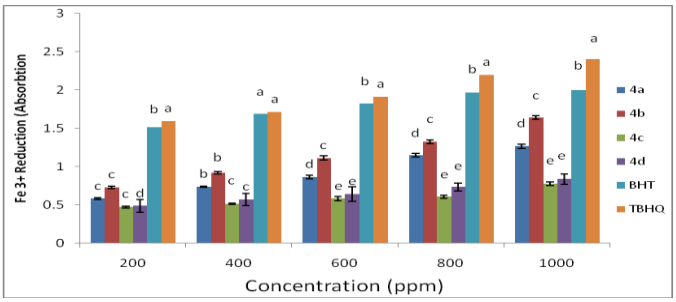


Figure 2. Ferric ions (Fe^{3+}) decreasing antioxidant ability (FRAP) of compounds **4a-4d**

Conclusion

In conclusion, we have described a convenient route to spiro compounds from *insitue* produced isoquinoline and react with dialkyl acetylene dicarboxylates in the presence of *N*-alkylisatins. The advantage of the present procedure is that the reaction is performed under neutral conditions by simply mixing the starting materials. The procedure described here provides an acceptable one-pot method for the preparation of spiro 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 4

Isoquinoline **1** (2 mmol) and activated acetylenic compounds **2** (2 mmol) stirred in water (5 mL) as solvent for 20 min at r.t. Then ninhydrin **3** was added and mixture was stirred for 2 h at r.t. for 45 min. After completion of the reaction (2 h; TLC control (hexane–AcOEt, 6:1) andr removing solvent, the residue was purified by column chromatography (4:1 hexane/EtOAc) to afforded pure title compounds.

Dimethyl 1,2-Dihydro-2-oxo-1-methyl-spiro[3H-indole-3,2'-[2H,11bH] [1,3]oxazino[2,3-a]isoquinoline]-3',4'-dicarboxylate (4a):

Yellow crystals. M.p. 210-212°C, Yield 0.84 g, 97%. IR (KBr): ν = 1742, 1721, 1647, 1593, 1566 cm^{-1}; EI-MS: 432 (M^+, 5); 401 (25); 302 (78); 161 (86); 129 (48); 104 (100); 76 (44); 59 (18); NMR data for the major isomer (67%); ^{1}H-NMR: 3.29 (*s*, O*Me*); 3.46 (*s*, *Me*); 3.98 (*s*, O*Me*); 5.83 (*d*, ^{3}J = 7.3, CH); 6.41 (*d*, ^{3}J = 7.2, CH); 6.80 (*d*, ^{3}J = 7.7, CH); 6.96 (*t*, ^{3}J = 7.4, CH); 7.08 (*s*, CH); 7.11 (*t*, ^{3}J = 7.6, CH); 7.16-7.26 (*m*, 4 CH); 7.36 (*d*, ^{3}J = 7.5, CH) ppm; ^{13}C-NMR: 26.3 (N*Me*); 51.7, 53.4 (2 O*Me*); 77.5 (CH); 79.7, 105.8 (2 C); 105.3, 108.3 (2 CH); 122.6, 122.9 (2 C); 123.2, 123.3, 125.2, 126.2, 127.1, 128.3, 129.5, 129.8 (8 CH); 130.2, 145.2, 145.3 (3 C); 163.5, 163.9, 174.5 (3 C=O) ppm.

Diethyl 1,2-Dihydro-2-oxo-1-methyl-spiro[3H-indole-3,2'-[2H,11bH] [1,3]oxazino[2,3-a]isoquinoline]-3',4'-dicarboxylate (4b):

Yellow crystals. M.p. 215-217°, Yield: 0.87 g, 95%. IR (KBr): ν = 1740, 1719, 1650, 1590, 1560 cm^{-1}; EI-MS: 460 (M^+, 12); 415 (48); 370 (78); 331 (96); 161 (48); 129 (56); 76 (44); 45 (100); NMR data for the major isomer (65%); ^{1}H-NMR: δ = 0.91, 1.41 (2 *t*, ^3J = 7.1, 2 *Me*); 3.27 (*s*, N*Me*); 3.87, 4.39 (2 *q*, ^3J = 7.1, 2 OCH_2); 5.80 (*d*, ^3J = 8.7, CH); 6.41 (*d*, ^3J = 7.1, CH); 6.48 (*d*, ^3J = 8.7, CH); 6.81 (*t*, ^3J = 7.4, CH); 7.04 (*s*, CH); 7.10 (*t*, ^3J = 7.6, CH); 7.11-7.26 (*m*, 4 CH); 7.36 (*d*, ^3J = 7.5, CH) ppm; ^{13}C-NMR: δ = 13.6, 14.0 (2 *Me*); 26.3 (N*Me*); 60.4, 62.7 (2 OCH_2); 77.5 (C); 79.6 (CH); 104.9 (C); 105.2, 108.2 (2 CH); 122.6, 123.0 (2 C); 123.2, 123.4, 125.2, 126.2, 127.1, 128.3, 129.5, 129.9 (8 CH); 130.1, 145.3, 145.6 (3 C); 163.1, 163.2, 174.7 (3 C=O) ppm.

Dimethyl 1,2-Dihydro-2-oxo-1-benzyl-spiro[3H-indole-3,2'-[2H,11bH] [1,3]oxazino[2,3-a]isoquinoline]-3',4'-dicarboxylate (4c):

Yellow crystals. M.p. 235-237°C, Yield 0.99 g, 98%. IR (KBr): ν = 1738, 1719, 1647, 1560, 1572 cm^{-1}; EI-MS: 508 (M^+, 10); 477 (65); 446 (25); 417 (86); 129 (48); 91 (100); 76 (44); 31 (100); NMR data for the major isomer (67%); ^{1}H-NMR: 3.33 (*s*, O*Me*); 4.0 (*s*, O*Me*); 5.11 (*AB* system, $^2J_{AB}$ = 15.4, CH_2); 5.82 (*d*, ^3J = 6.2, CH); 6.42 (*d*, ^3J = 6.2, CH); 6.74 (*d*, ^3J = 7.7, CH); 6.80 (*d*, ^3J = 7.6, CH); 6.94 (*t*, ^3J = 7.3, CH); 7.44 (*s*, CH); 7.03-7.44 (*m*, 10 CH) ppm;. ^{13}C-NMR: 44.9 (CH_2); 51.6 (O*Me*); 53.4 (O*Me*); 77.5 (C); 79.5 (CH); 105.2 (C); 109.3 (CH); 123.1 (CH); 123.2 (CH); 123.4 (CH); 125.3 (CH); 126.3 (C); 127.1 (CH); 127.6 (2 CH); 127.7 (CH); 128.1 (CH); 128.7 (C); 128.8 (3 CH); 129.6 (CH); 129.8 (CH); 130.1 (CH); 135.8 (C); 144.3 (C); 145.5 (C); 163.6 (C=O); 163.7 (C=O); 174.7 (C=O) ppm.

Diethyl 1,2-Dihydro-2-oxo-1-benzyl-spiro[3H-indole-3,2'-[2H,11bH] [1,3]oxazino[2,3-a]isoquinoline]-3',4'-dicarboxylate (4d):

Yellow crystals. M.p. 240-242°C, Yield 1.03 g, 96%. IR (KBr): ν = 1742, 1721, 1647, 1593, 1566 cm^{-1}; EI-MS: 536 (M^+, 12); 491 (55); 446 (78); 238 (86); 129 (48); 91 (100); 76 (44); 45 (98); NMR data for the major isomer (60%); ^{1}H-NMR: δ = 0.73, 1.42 (2 *t*, ^3J = 7.1, 2 *Me*); 3.73, 3.98 (2 *q*, ^3J = 7.1, 2 OCH_2); 4.90 (*AB* system, $^2J_{AB}$ = 13.2, CH_2); 5.82 (*d*, ^3J = 7.8, CH); 6.44 (*d*, ^3J = 7.7, CH); 6.78 (*d*, ^3J = 7.8, CH); 7.31 (*s*, CH); 7.02-7.45 (*m*, 12 CH) ppm;. ^{13}C-NMR: δ = 13.5, 13.9 (2 *Me*); 44.5 (CH_2); 60.6, 62.8 (2 OCH_2); 78.2 (C); 80.1 (CH); 104.2 (C); 109.4 (CH); 122.6 (CH); 123.2 (CH); 123.8 (CH); 125.9 (CH); 126.9 (C); 127.5 (CH); 127.7 (2 CH); 127.8 (CH); 128.7 (CH); 128.8 (C); 128.9 (3 CH); 129.8 (CH); 130.1 (CH); 130.2 (CH); 135.7 (C); 143.2 (C); 145.3 (C); 163.0 (C=O); 163.4 (C=O); 173.9 (C=O) ppm.

Determination of antioxidant activity using radical trapping test by (DPPH):

The radical trapping experiment by DPPH was employed for valuation of antioxidant ability for some generated compounds such as **4a-4d** as indicated by Shimada et al procedure. For achieving to this purpose, different concentrations (200–1000 ppm) of compounds **4a-4d** were added to DPPH methanolic solution (1 mmol/L) with an equal volume. The mixtures were mixed for 30 min at ambient temperature and after this time puted in a dark room. Then, the mixture absorbance was calculated and recorded at 517 nm. The compounds **4a-4d** was exchanged with methanol (3 mL) in the standard type. The standard antioxidant such as Butylated hydroxytoluene (BHT) and 2-tertbutylhydroquinone (TBHQ) were employed as standard control sample. The percentage inhibition of the DPPH radical was measured using Yen and Duh formula.

Evaluation of reducing ability for synthesized compounds:

The ability of reducing iron (III) was evaluated for the compounds **4a-4d** using Yildirim et al. method. For this purpose, the samples (1 mL), phosphate buffer (2.5 mL, 0.2 mol/L, pH 6.6) and potassium ferricyanide ($K_3Fe(CN)_6$; 2.5 mL, 10g/L) were combined together and sustained for 30 min at 50 ^oC. Then, trichloroacetic acid (2.5 mL, 10% w/v) was added to the previous solution and centrifuged for 10 min. In the end, the supernatant (2.5 mL) was mixed with distilled water (2.5 mL) and FeCl3 (0.5 mL, 1 g/L) and the samples absorbance was computed at 700 nm. The higher reducing power was attributed to higher absorbance. For accuracy of calculating, each calculation was performed in three times. The SPSS software version 18.0 was used for data analyzation of compounds by running one way analysis of variance (ANOVA) that confirmed variation in the mean value of samples and control. All removing were done by Duncan multiple range tests employing the importance level of 95% ($P < 0.05$).

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