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Catalyst free reaction of dialkoxycarbonate, propiolates and pyridines: Synthesis and study of antioxidant activity of indolizines

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Abstract: Pyridine reacts smoothly with dialkoxycarbonate in the presence of propiolate to produce indolizines. Also, in this research, DPPH radical trapping and reducing potential of ferric ion experiments was used for determining antioxidant activity of some newly synthesized compounds and comparing results with synthetic antioxidants (TBHQ and BHT). As a result, some of synthesized compounds display good DPPH radical trapping and excellent reducing power of ferric ion. The present procedure has the advantages such as clean reaction, high yield and simple purification.

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

Introduction

The development of simple synthetic routes for widely used organic compounds from readily available reagents is one of the major tasks in organic synthesis [1]. Bridgehead *N*-heterocycles are of interest because they constitute an important class of natural and unnatural products, many of which exhibit useful biological activity [2, 3]. Synthetic indolizines are important as potential central nervous system depressants [4], calcium entry blockers [5], and novel dyes [6]. The reaction of nucleophiles, nitrogen-containing heterocycles in particular, with activated acetylenes has been the subject of significant research over the last decades [7]. Multicomponent reactions (MCRs), with three or more reactants join in a one-pot procedure to afford a single product [8-10].

They are economically and environmentally useful because multi-step synthesis produce large amounts of trash frequently because of complex isolation actions frequently involving comfortable, toxic, and hazardous solvents after each step [11-14]. MCRs are absolutely suited for combinatorial library synthesis and increased utilize in the finding procedure for new drugs and agrochemicals [15]. They supply a dominant tool toward the one-pot synthesis of diverse and complex compounds as well as small and drug-like heterocycles [16]. Green chemistry move towards hold out significant potential not only for reduction of byproducts, waste produced, and lowering of energy but also in the expansion of new methodologies toward before exclusive materials, using existing technologies [17]. Between existing part of chemistry, medicinal and pharmaceutical chemistry are possibly developed for greening [18]. It should be mentioned, heterocyclic compounds are a highly valuable and unique class of compounds. These compounds demonstrate a broad spectrum of physical, chemical and biological characteristics [19, 20]. In nature, heterocyclic compounds are widely distributed and display an important part in metabolism owing to their structural nucleus occurring in various natural products, including hormones, antibiotics, alkaloids, vitamins and many others [21, 22]. Another topic in this work is

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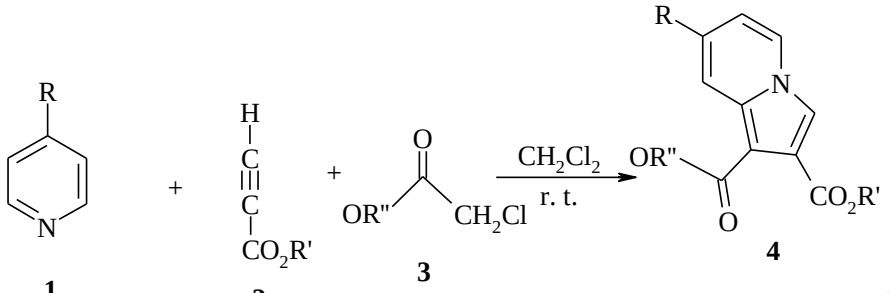
study of antioxidant activity of some synthesized compounds. Usually the compounds which because of their reductive properties and chemical structure have antioxidant activity employ as transitional metals chelators and removing the negative effect of free radicals. These compounds with antioxidant activity could be prevent or reduce many diseases such as cardiovascular, inflammatory bowel syndrome, cancer, ageing, and Alzheimer.

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 indolizines. The reaction of pyridine **1** and dialkyl acetylenedicarboxylates **2** in the presence of chloroacetate **3** proceeds smoothly in CH_2Cl_2 at ambient temperature to produce indolizines **4** in 95% yields (Scheme **1**).



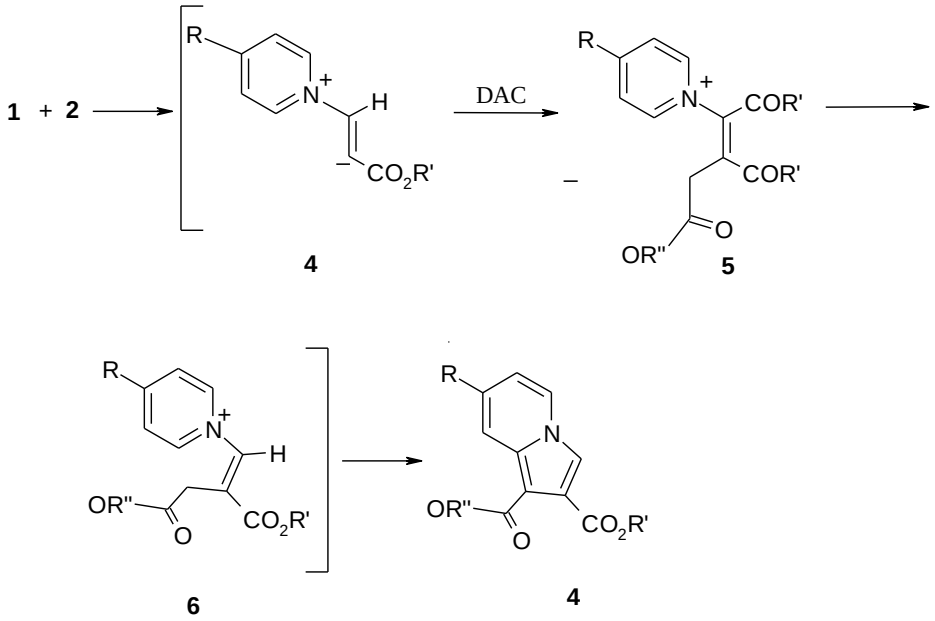
4	R	R'	Yield (%)
a	H	OMe	95
b	H	OEt	93
c	Me	OMe	97
d	Et	OMe	95
e	H	Ph	90

Scheme 1: Synthesis of indolizine **4.**

The reactions proceed spontaneously in CH2Cl2, and were complete within 24 hr. The structures of compounds **4a-4e** were deduced from their elemental analyses and their IR, ^{1}H-NMR and ^{13}C-NMR spectra. The ^{1}H-NMR spectrum of **3a** exhibited singlets (3.93 and 4.02 ppm) readily recognized as arising from methoxy protons. The proton-decoupled ^{13}C-NMR spectrum of **4a** 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 **5** from pyridine and the acetylenic compound, which is subsequently attacked by chloroacetate **3** to produce the salt **6**. Intermediate **6** undergoes cyclization/elimination reactions to generate **4**.

Study of antioxidant activity employing Diphenyl-2-picrylhydrazyl (DPPH):

For determination of antioxidant activity of some synthezied compounds and their antioxidant property in foods and biological systems as well as power of compounds to take free radicals, diphenyl-2-picrylhydrazyl (DPPH) radical trapping experiment is widely used. In these experiment, the DPPH radical takes the hydrogen atom (or one electron) of synthezied compounds **4a-4d** and gives an evaluation of antioxidant activity basis of free radical trapping. The absorption of DPPH radical was observed area 517 nm but when DPPH radical is reduced by an antioxidant or a radical species its absorption decreases. As shown from the results, free radical trapping activity of compounds **4a-4d** is weaker than to BHT and TBHQ. Therefore, concentration and structure were key factor on the DPPH trapping activity (P<0.05) (Figure **1**). The free radical trapping power had been enhanced from 200 to 1000 ppm. So, by rising concentration in all samples, the free radical activity was raised. For instance, compound **4c** with a concentration of 1000 ppm had 25.40% inhibition while a concentration of 200 ppm of compound **4c** was exhibited 20.50% free radical inhibition.



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

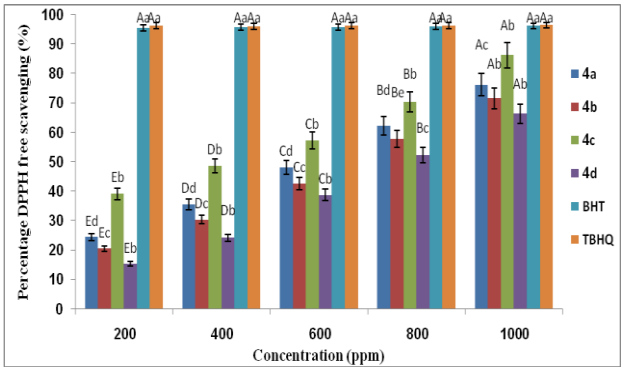


Figure 1: Radical trapping activity (RSA) of compounds **4a-4d.**

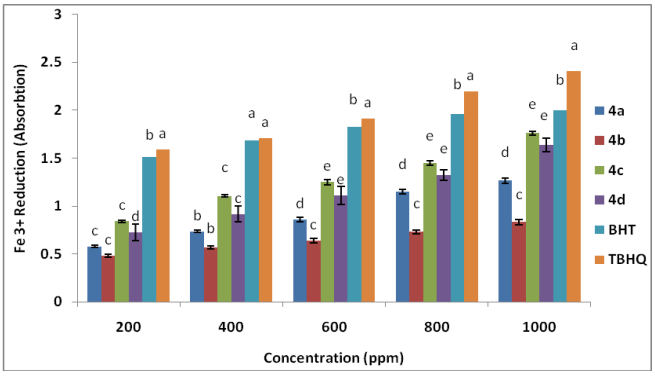


Figure 2. Ferric ions (Fe^{3+}) reducing antioxidant power (FRAP) of compounds **4a-4d**.

Ferric ions (Fe^{3+}) reducing potential (FRAP):

Reducing power of the synthesized compounds was determined by calculating of the exchange amount of Fe^{3+}/ferricyanide complex to the Fe^{2+}/ferrous form at 700 nm. The reducing power of compounds **4a-4d** compared with synthetic antioxidants (BHT and TBHQ) are showed in Figure **2**. The bigger reducing power means higher absorbance of the compounds. In all them, the increasing concentration was enhanced ferric ions reducing power. Compounds **4c** show very good reducing activity compared to standards (BHT and TBHQ).

Conclusion

In conclusion, we have described a convenient route to indolizines from N-heterocycles and activated acetylenes in the presence of chloroacetate. 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.

Representative Procedure for the Preparation of Dimethyl 1-(2,2,2-Trichloroacetyl)-2,3-indolizinedicarboxylate (4a).

To a stirred solution of 0.28 g of DMAD (2 mmol) and 0.52 g of HCA (2 mmol) in 10 ml of CH_2Cl_2 was added 0.16 g of pyridine (2 mmol) at room temperature. The reaction mixture was then stirred for 24 h. The solvent was removed under reduced pressure and the viscous residue was purified by preparative TLC on silica gel (Merck 230-400 mesh) using hexane-EtOAc as eluent to give **4a**. 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%. Similarly, the following compounds were prepared. All compounds gave satisfactory analytical and spectroscopic data. Selected physical and spectroscopic data are as follows. Compound **4b**: 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 **4c**: 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 **4d**: 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 **4e**: 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). Compound **9**: Yield 0.79 g (74%). Yellow crystals. Mp 178-179° (dec.). IR (KBr): 1733, 1706 **(**2 C=O**)**, 1274, 1225. ^{1}H-NMR: 3.79 and 3.93 (2 *s*, 2 CH_3); 5.87 (*d*, ^3J = 8, CH); 6.31 (*d*, ^3J = 8, CH); 6.70 (*s*, CH); 7.15 (*t*, ^3J = 7, CH); 7.32 (*t*, ^3J = 7, CH); 7.38 (*d*, ^3J = 7, CH); 7.77 (*d*, ^3J = 7, CH). ^{13}C-NMR: 52.5 and 53.5 (2 MeO); 74.1 and 79.9 (2 CCl_3); 87.7 and 104.6 (2 C); 105.9, 111.3 and 123.8 (3 CH); 125.1 (C); 125.5, 127.6 and 128.4 (3 CH); 129.6 (C); 130.1 (CH); 143.8 (C); 162.7 and 164.6 (2 C=O). MS: 537 ($M^{+\bullet}$+1, 5), 536 ($M^{+\bullet}$, 70), 463 (100), 130 (86), 91 (100). Anal. calc. for $C_{18}H_{13}Cl_6NO_5$ (536.0): C 40.33, H 2.44, N 2.61; found: C, 40.39; H, 2.43; N, 2.64%.

Evaluation of DPPH radical trapping:

By employing of DPPH (2,2-Diphenyl-1-picrylhydrazyl) radical trapping experiment, antioxidant activity of some synthesized compounds **4a-4d** was measured. In this experiment different concentrations of **4a-4d** (200-1000 ppm) were added to a same volume of methanolic solution of DPPH (1 mM) and the mixtures were mixed and then put in a dark room. The maximum absorbance of the mixture was 517 nm after 30 min at room temperature. The synthesized compounds **4a-4d** was exchanged with 3 ml methanol in the control sample and butylated

hydroxytoluene (BHT) and 2-tert-butylhydroquinone (TBHQ) were used as standard controls. The DPPH performance is calculated by the following formula.

$I = [(AB-AS)/AB] \times 100$

Where, I=DPPH inhibition (%), AB=absorbance of control sample (0 min) and AS=absorbance of an examined sample at the end of the reaction (after 30 min).

The power of reducing experiment:

By the procedure of Yildirim et. al., the power of **4a-4d** to reduce iron (III) was measured. The compounds **4a-4d** (1 ml) were combined with 2.5 ml of potassium ferricyanide ($K_3Fe(CN)_6$; 10 g/L) and 2.5 ml of phosphate buffer (0.2 M, pH 6.6) and stirred for 30 min at 50 °C. Then, 2.5 mL of trichloroacetic acid (10 % w/v) were added to the previous mixture and centrifuged for 10 min. Finally, supernatant (2.5 mL) and 0.5 ml $FeCl_3$ (1 g/L) was combined together in 2.5 ml of distilled water. The absorbance of samples was measured at 700 nm and higher absorbance attributed to higher reducing power.

Statistical investigation:

In this study, each measurement was carried out three times and data were examined by running one way analysis of variance (ANOVA) applying SPSS software version 18.0. A one way ANOVA was employed to evaluate difference in the mean value of samples and control. All mean separations were carried out with Duncan multiple range examination performing the importance level of 95% ($p<0.05$).

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