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Novel three-component synthesis of functionalized pyrrolidone: study antioxidant and antimicrobial activity

Maryam Ghazvini[a] and Narges Ghasemi[b*]

[a]*Department of Chemistry, Payame Noor university, P. O Box:3971189451, Tehran, Iran.*
[b]*National Petrochemical Company (NPC), petrochemical Research and Technology Company, Arak Center, Iran*

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Abstract: An efficient synthesis of functionalized pyrrolidone is described. This involves the three-component reaction of benzoyl isothiocyanates and secondary amines in the presence of activated acetylenes. We investigate antioxidant property of some synthesized compounds by diphenyl-picrylhydrazine (DPPH) radical trapping and power of ferric reduction experiment. Furthermore, the disk diffusion test on Gram positive and negative bacteria are utilized for investigation of antimicrobial activity of some pyrrolidones. The achieved outcomes of this experiment demonstrate that these synthesized compounds could prevent from growth of bacteria. Short time of reaction, high yields of product, easy separation of catalyst and products are some benefits of this process.

Keywords: Three-component reaction; Pyrrolidone; Activated acetylenes; Primary amines.

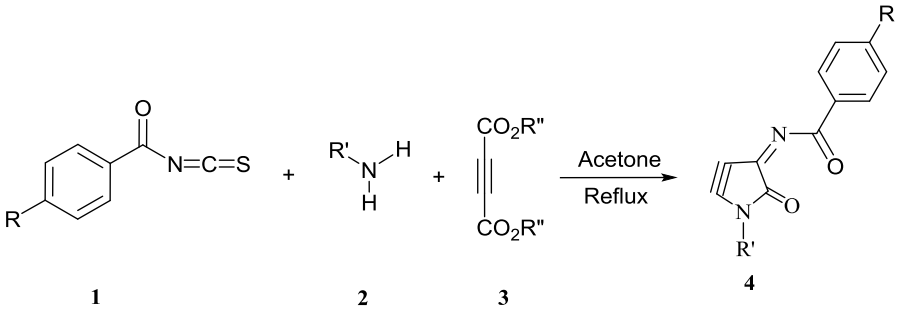
Introduction

N,*N*-Disubstituted-1-alkynylamines, the common name "Butynoates", are regarded as the alkynes activated through the interaction of the amino group linked directly to a triple bond, and thereby liable to undergoing the reaction with a variety of electrophiles [1-5]. During recent decades, the preparation and synthetic utility of butynoates in organic and related fields have been explored [6]. However, synthetic application of butynoates remained relatively limited because of the difficulty experienced in their preparation and handling, due to their high reactivity and sensitivity toward hydrolysis [6d]. Thus, modification to thermally stable butynoates without decreasing the reactivity afforded a challenging approach to improve their synthetic utility.

An important example of this approach includes functionalized acetylenes containing "push-pull' systems, with an electron-donating group at one end an electron-withdrawing group at the other end of the triple bond, as pioneered in Hsung [6c] and Ishihara [7]. As part of our current studies on the development of new routes in organic synthesis [8], we report an efficient synthesis of functionalized pyrrolidone. Evaluation of antioxidant power in synthesized compounds is another activity another topic in this research work. Commonly the compounds that have antioxidant property because of reductive property and chemical structure of them could be reduced or deleted negative effect of free radicals. Also the antioxidant compounds despite its antioxidant property could be avoid or decrease many sickness such as cardiovascular, inflammatory bowel syndrome, cancer, ageing, and Alzheimer. In recent times, new and

*Corresponding author. Fax: Tel: 0098-8633677201-9; Fax: 0098-8633677203, E-mail: naghasemi16@gmail.com

economical synthetic antioxidant compounds were discovered by biologists, medicinal and food chemist analysis and used for protecting of persons against these diseases. Presently, bacteria that is resisted against drug have produced considerable problems in the behaviour of many transmissible sickness. For this reason, finding out suitable and new methods to combat these pathogens are significant and recent investigation have focused on the evaluation of the synthesized compounds antibacterial effects. Thus, the reaction of benzoyl isothiocyanate **1** and primary amines **2** in the presence of dialkyl acetylenicdicarboxylates **3** led to pyrrolidone **4** in 87-94% yields (Scheme **1**).



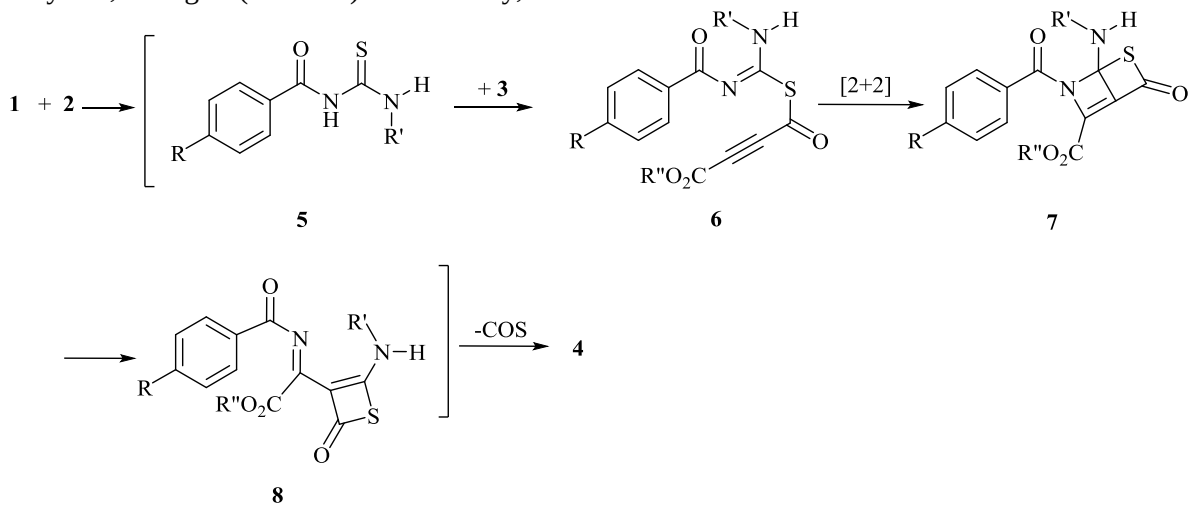
1 **2** **3** **4**

1, 2, 3, 4,	R	R'	R"	Yield (%) of **4**
a	H	$(CH_2)_5$	Me	94
b	H	$(CH_2)_5$	Et	87
c	Me	$(CH_2)_5$	Me	85
d	NO_2	$(CH_2)_5$	Me	85

Scheme 1: Synthesis of pyrrolidone derivatives

Result and Discussion

Structures of compounds **4a-4d** were assigned by IR, ^{1}H-NMR, ^{13}C-NMR and mass spectral data. For example, the ^{1}H-NMR spectrum of **4a** exhibited two broad multiplets (δ = 1.73 and 3.61) for pentamethylene, a singlet (δ = 3.76) for methoxy, and characteristic multiplets (δ = 7.39-7.76) for the aromatic protons. The ^{13}C NMR spectrum of **4a** shows carbonyl (δ = 162.4 and 170.8), imine (δ = 160.2), and acetylenic (δ = 59.5 and 109.1) carbons, in agreement with the butynoate structure.



5 **6** **7** **8** **4**

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

Mechanistically, the reaction starts with addition of amine **2** to benzoyl isothiocyanate **1**, and generates the benzoylthiourea derivative **5** [9]. Subsequent nucleophilic attack of **5** to acetylenic compound **3** yields the 1:1 adducts **6**, which undergoes an intramolecular [2+2] cycloaddition [10] to produce the strained intermediate **7**. Electrocyclic ring opening [11] of **7** leads to **8**, which is finally converted to **4** by elimination of COS [13] (Scheme **2**).

Evalution of antioxidant ability employing diphenyl-2-picrylhydrazyl (DPPH):

For the confirmation of antioxidant ability or power of compounds to take free radicals of some synthezied compounds and antioxidant property of them in foods and biological structures, DPPH radical trapping experiment is widely used. In these evaluation, antioxidant capacity of synthesized compounds was determined by taking the hydrogen atom or one electron by DPPH radical and order of antioxidant ability of synthesized compounds are basis of percentage of DPPH radical free trapping. The electron or hydrogen donating power of compounds **4a-4d** to the radical of DPPH determined the antioxidant ability of them.The radical of DPPH absorption 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 pyrrolidone **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>**4c>4a>4b>4d**.

As seen in Figure **1**, in all concentrations of the new prepared compounds existed good difference relative to BHT and TBHQ. Compound **4c** in among experimented compounds displayed good activity for trapping of radical relative to BHT and TBHQ as standard antioxidant.

The potential of synthesized pyrrolidone via Ferric ions (Fe3+) reducing:

The reducing ferric ions (Fe^{3+}) ability of some synthesized compounds such as **4a-4d** are calculated based on the quantity reducing of Fe^{3+}/ferricyanide to the Fe^{2+}/ ferrous at 700 nm. Compound **4c** was shown good ability of reducing than to BHT and TBHQ as standard antioxidants. The reducing activity trend of the samples was as follows: TBHQ>BHT>**4c>4d>4a>4b**.

Investigation of antibacterial activity:

In this research work we investigated and compared the antimicrobial activity of synthesized compounds with two standard antibacterial drugs such as Streptomycin and Gentamicin. The outcomes of this research are exhibited in Table 1. The our evaluation displayed that the kind of bacteria and concentration of compounds are essential factor on the diameter of the inhibition zone. As shown in outcomes in Table 4, the antimicrobial ability of compounds **4a, 4c** and **4d** versus two Gram positive and negative bacteria was the maximum effect on Escherichia coli due to good diameter of the inhibition zone.

Table 1: The antibacterial activity of some synthesized compounds **4.**

Compounds	*Staphylococcus aureus* (+)	*Bacillus cereus* (+)	*Escherichia coli*(-)	*Klebsiella pneumoniae* (-)
4a	**19**	**20**	**23**	**19**
4b	8	10	9	---
4c	**19**	**21**	**24**	**18**
4d	**16**	**20**	**24**	**21**
Streptomycin	16	24	25	23

Gentamicin	19	23	24	21

Conclusion

In conclusion, we have described a convenient route to functionalized butynoates from the three-component reaction of benzoyl isothiocyanates and primary amines in the presence of dialkyl acetylenedicarboxylates. 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 method for the preparation of functionalized pyrrolidone.

Experimental

Mp: Electrothermal-9100 apparatus; uncorrected. 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. All chemicals were used as-received from the appropriate suppliers.

General procedure:

To a stirred solution of benzoyl isothiocyanate (2 mmol) and methyl amine (2 mmol) in acetone (15 mL) dimethyl acetylenedicarboxylate (2 mmol) was added slowly and the reaction mixture was refluxed for 3 h. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (SiO_2; hexane/AcOEt) to afford **4a**.

Compound **4a**:

Yield: 0.39 g (65%); colorless crystals, mp 101-103ºC, IR (KBr): 1702, 1521, 1244 cm^{-1}. ^{1}H-NMR: δ = 1.73 (broad s, 3 CH_2), 3.61 (broad s, 2 CH_2), 3.76 (s, OCH_3), 7.39-7.45 (m, 3 CH), 7.76 (dd, ^{3}J = 9.5, ^{4}J = 2.4, 2 CH), ^{13}C-NMR: δ = 23.9 (CH_2), 25.1 (2 CH_2), 49.2 (2 CH_2), 51.5 (OMe), 59.5 (C), 109.1 (C), 127.5 (2 CH), 128.9 (CH), 129.8 (2 CH), 134.8 (C), 160.2 (C=N), 162.4, 170.8 (2 C=O). EI-MS: 298(M^+, 4); 137 (85); 105(30); 97 (40); 69 (45), 57 (100). Anal. Calcd for $C_{17}H_{18}N_2O_3$ (298.34): C, 68.44; H, 6.08; N, 9.39; found: C, 68.50; H, 6.10; N, 9.42%. Similarly, the following compounds were prepared. All compounds gave satisfactory analytical and spectroscopic data.

Compound **4b**:

Yield: 0.34 g (55%); yellow powder, mp 98-100ºC, IR (KBr): 1702, 1521, 1244 cm^{-1}. ^{1}H-NMR: δ = 1.25 (t, ^{3}J = 8.8, 3 CH), 1.69 (broad, 3 CH_2), 3.59 (broad, 2 CH_2), 4.24 (q, ^{3}J = 8.8, 2 CH), 7.36-7.42 (m, 3 CH), 7.74 (dd, ^{3}J = 9.4, ^{4}J = 2.1, 2 CH). ^{13}C-NMR: δ = 14.2 (Me), 22.9 (CH_2), 25.1 (2 CH_2), 49.2 (2 CH_2), 63.2 (OCH_2), 68.1, 109.7 (2 C), 127.4 (2 CH), 128.8 (CH), 129.8 (2 CH), 134.8 (C), 161.9 (C=N), 167.7, 170.7 (2 C=O).

Compound **4c**:

Yield: 0.42 g (67%); yellow powder; mp 85-86ºC. IR (KBr): 1703, 1695, 1539, 1239 cm^{-1}. ^{1}H-NMR: δ = 1.67 (broad, 3 CH_2), 2.37 (s, CH_3), 3.55 (broad, 2 CH_2), 3.72 (s, OCH_3), 7.19 (d, ^{3}J = 7.9, 2 CH), 7.64 (d, ^{3}J = 7.9, 2 CH). ^{13}C-NMR: δ = 21.4 (CH_3), 24.0 (CH_2), 25.1 (2 CH_2), 49.2 (2 CH_2), 51.5 (OMe), 60.1, 108.7 (2 C), 128.3 (2 CH), 129.7 (2 CH), 132.1, 133.6 (2 C), 160.6 (C=N), 162.5, 170.9 (2 C=O).

Compound **4d**:

Yield: 0.38 g (56%); Yellow powder; mp 115-117ºC. IR (KBr): 1690, 1607, 1550, 1240 cm^{-1}. ^{1}H-NMR: δ = 1.69 (broad s, 3 CH_2), 3.57 (broad s, 2 CH_2), 3.73 (s, OCH_3), 7.92 (d, ^{3}J = 8.7, 2 CH), 8.22 (d, ^{3}J = 8.7, 2 CH). ^{13}C-NMR: δ = 23.9 (CH_2), 25.1 (2 CH_2), 49.3 (2 CH_2), 51.8 (OMe), 59.6, 110.8 (2 C), 122.7 (2 CH), 130.9 (2 CH), 141.2, 147.8 (2 C), 157.4 (C=N), 162, 171.1 (2 C=O). EI-MS: 343 (M^+, 5); 152 (30); 137 (80); 97 (35); 71 (34), 69 (50), 57 (100). Anal. Calcd for $C_{17}H_{17}N_3O_5$ (343.34): C, 59.47; H, 4.99; N, 12.24; found: C, 59.37; H, 4.91; N, 12.30%.

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 **4b-4e** were added to DPPH methanolic solution (1 mmol/L) with an equal volume. The mixture was mixed for 30 min at ambient temperature and after this time putted in a gloomy space and the mixture absorbance was recorded at 517 nm. The compounds **4a-4d** was exchanged with methanol (3 mL) in the standard type. The standard antioxidants in this experiment are Butylated hydroxytoluene (BHT) and 2-tertbutylhydroquinone (TBHQ). By using Yen

and Duh [62] formula, the percentage of inhibition for the radical of DPPH was measured.

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), potassium ferricyanide ($K_3Fe(CN)_6$; 2.5 mL, 10g/L) and buffer of phosphate (2.5 mL, 0.2 mol/L, pH 6.6) were combined together and sustained for 30 min at 50 ^oC. Then, to the previous solution was added trichloroacetic acid (2.5 mL, 10% w/v) and centrifuged for 10 min. In the end, the supernatant (2.5 mL), distilled water (2.5 mL) and $FeCl_3$ (0.5 mL, 1 g/L) mixed together and at 700 nm the samples absorbance was measured. 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 by running one way study of variance (ANOVA) was used for data analyzing of compounds that confirmed variation of samples and control. Separation mean with the importance quantity of 95% ($P < 0.05$) was done by Duncan multiple range experiments.

Investigation of synthesized compounds antibacterial activity:

The disk diffusion method by using Gram-positive and Gram-negative bacteria was utilized for investigation of antibacterial effect of synthesized pyrrolidone against two bacteria. All of bacteria were produced from the Persian type culture collection (PTCC), Tehran, Iran. For getting ready bacteria to turbidity equivalent to McFarland Standard No. 0.5, they were cultured for 16 to 24 h at 37°C. Streptomycin and Gentamicin as two standards were utilized 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 compounds 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 with the standard.

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