Eschenmoser-Coupling Reaction Furnishes Diazenyl-1,2,4-triazole-5(4H)-thione Derivatives

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Eschenmoser-Coupling Reaction Furnishes Diazenyl-1,2,4-triazole-5(4*H*)-thione Derivatives

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Abstract: Diazenyl 1,2,4-triazol-5(4*H*)-thione derivatives were synthesized in good yields *via* Eschenmoser-coupling reaction and nucleophilic attack between 1,4-disubstituted thiosemicarbazides and 2,3,5,6-tetrachloro-1,4-benzoquinone (*p*-CHL). The structure of the synthesized compounds was confirmed by IR, NMR and mass spectral data as well as single crystal X-ray analysis.

Introduction

The 1,2,4-triazole ring system belong to the most biologically active heterocyclic compounds. For example, 1,2,4-triazole derivatives exhibit pharmacological activities such as anticonvulsant,[1] antifungal,[2] antitumor,[3] antimicrobial[4] and antiviral[5] activities.

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Mercapto-substituted 1,2,4-triazole are very interesting compounds as they play an important role in chemopreventive and chemotherapeutic effect on cancer.[6-10] Cyclization of 1-acyl-4-alkylthiosemicarbazides in basic medium afforded 4-alkyl-1,2,4-triazol-3-thiones,[1] which screened for their anticonvulsant activity.[1]

5-Substituted (1,2,4-triazol-4-yl-diazenyl)naphthalen-2-ols were synthesized from benzaldehyde and hydrazine hydrate, followed by heating with CS_2/NaOH and hydrazine hydrate during five steps.[11] Trifluoroacetic acid reacted with thiocarbohydrazide in refluxing water to give 4-amino-5-(trifluoromethyl-4*H*-1,2,4-triazol-3-thiole).[2]

Intramolecular cyclization of substituted thiosemi-carbazides afforded 1,2,4-triazole derivatives. A variety of alkyl/aryl-5-(2-furyl)-1,2,4-triazol-3-thiones have been synthesized.[12] The synthesis of spiro-1,2,4-triazol-3-thiones *via* oxidative cyclization of *N*-cycloalkylidenehydrazinecarbo-thioamides and 1,4-benzoquinones has been reported.[13]

Mesoionic 1,2,4-triazolium-3-thiolate derivatives have been synthesized during the reaction of *N*-substituted 2-phenyl-hydrazinecarbothioamides with tetracyanoethylene (TCNE) *via* nucleophilic attack of R*N*^{4}H on C=C with elimination HCN, followed by cyclization.[14]

Addition of nucleophilic nitrogen groups to benzo- and naphthoquinones afforded many fused heterocyclic rings. [15-18]

One of the most important methods in carbon-carbon bond formation is the Eschenmoser-coupling reaction.[19] The reaction of thioamides with mono-haloketones and preparation several heterocyclic rings as well as natural products *via* Eschenmoser method has been reviewed by Hussaini et al. [20].

The reaction of *N*-substituted 2-tosylhydrazinecarbo-thioamides *via* nucleophilic attack of hydrazinecarbothioamide-

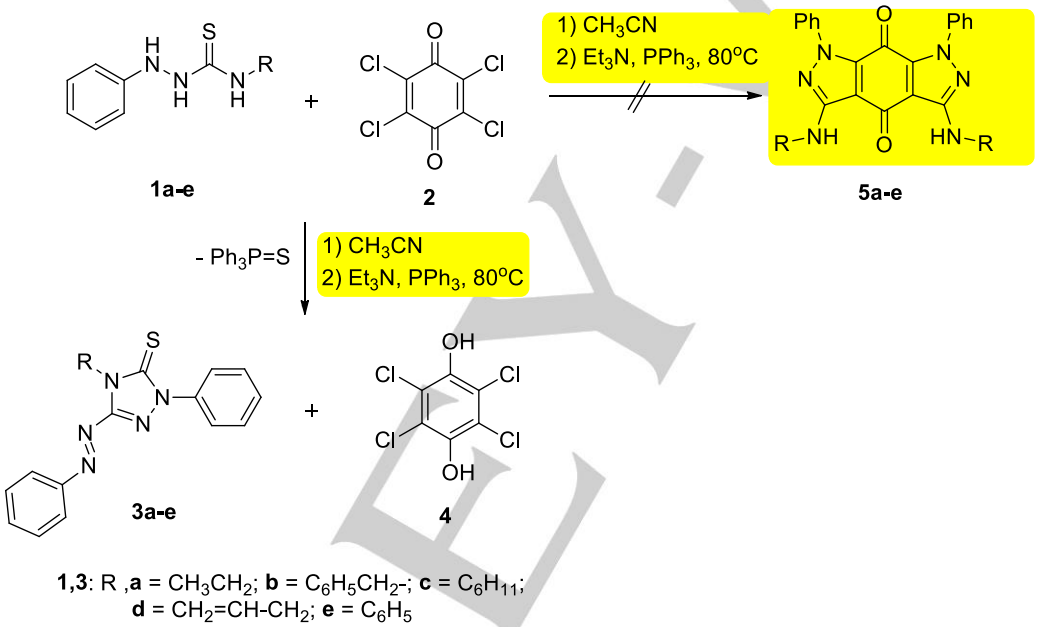
SH on 2,3-dichloro-1,4-naphthoquin-one to give (*Z*)-*N*-[3-(tosylamino)-4,9-dioxo-4,9-dihydronaphtho[2,3-*d*]thiazol-2(3*H*)-ylidene] substituted aminium chloride and (*Z*)-*N*-[(2-imino)-4,9-dioxo-4,9-dihydronaphtho[2,3-*d*]thiazol-3(2*H*)-yl-4-toluenesulfonamide hydrates has been reported.[21]

Recently, our group reported the synthesis of diazenylthiazoles by reaction of arylthiosemicarbazides with *ω*-bromoacetophenones via Eschenmoser-coupling reaction.[22]

So far, no analogous reactions with 2,3,5,6-tetrachloro-1,4-benzoquinone (*p*-CHL) in reaction with compounds **1a-e** have been described to design and synthesis new derivatives of pyrazoloindazoles **5a-e** or 1,2,4-triazol-5(4*H*)-thiones **3a-e** (Scheme 1).

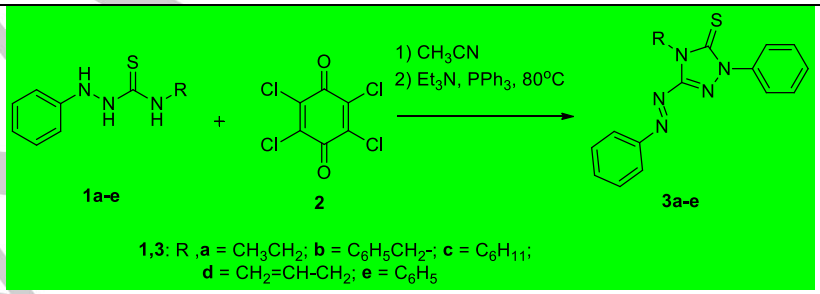
Results and Discussion

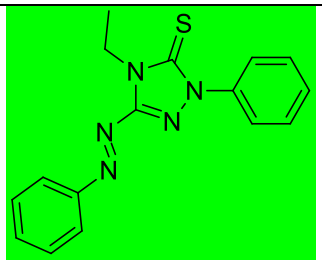
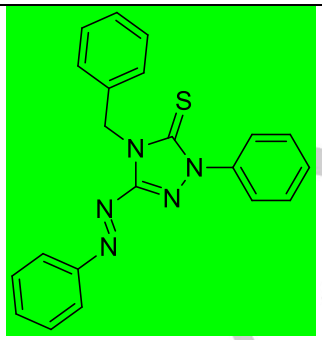
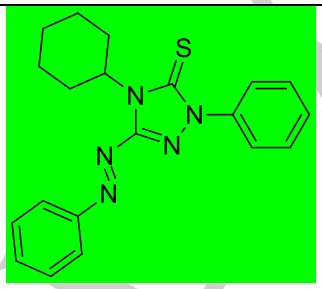
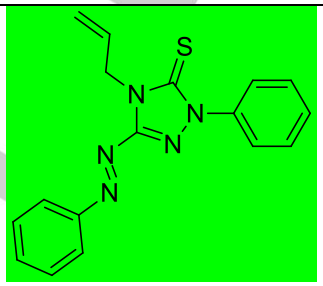
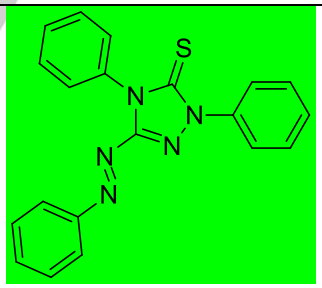
Herein we reported the results of our investigation on the reactions of *N*-substituted 2-phenylhydrazinecarbothioamides **1a-e** and 2,3,5,6-tetrachloro-1,4-benzoquinone (*p*-CHL, **2**) using the Eschenmoser-contraction method [19,20] (Scheme 1) to yield 1,2,4-triazol-5(4H)-thione which might have biological activity as demonstrated by related derivatives..



Scheme 1. Synthesis of diazenyl-1,2,4-triazol-3-thione derivatives **3a-e**

Table 1: Yields of the synthetic products **3a-e** (diazenyl-1,2,4-triazol-5-thione derivatives).



Compound number	Structure	Yield [%]
3a		86
3b		84
3c		82
3d		85
3e		88

The structures of diazenyltriazolthione derivatives **3a-e** were established from their spectroscopic methods, IR, NMR and mass spectrometry fragmentation. The IR of **3a-e** showed strong absorption at 1378-1390 and 900-950 were assigned to C=S and C-N stretching.[23,24] The peaks at 1525-1538 and 1438-1479 cm^{-1} of compounds **3a-e** could be attributed to N=N group.

The ^{1}H NMR of **3d** as example showed signals at 7.48-7.92 ppm for H-aromatic protons. The peaks between δ = 5.90-5.93 ppm were corresponding to the protons of allyl-CH= group. The signals for the protons of allyl-CH_2= were found between 5.01 and 5.05, while the signals of allyl-CH_2N appeared at 4.32-4.42.

In ^{13}C NMR spectrum using DEPT at 100 MHz of **3d** showed the peaks resonated at δ = 168.62 assigned for C=S confirming the thione form of triazole ring, the upfield-shift of C=S carbon was attributed to the effect of the adjacent nitrogen atoms with their electron-releasing capability,[25] signals at δ = 153.88 C=N and 124.63, 127.92, 128.30, 129.36, 131.87, 134.08 Ar-CH. The ^{13}C NMR showed the signals of allyl group which resonating at 48.15 due to (allyl-CH_2N), at δ = 117.62 and 134.83 attributed to allyl-CH_2= and allyl-CH=.

In the mass spectrometry of compounds **3a-e** showed molecular ion peaks in their spectra and characterized by the presence of the following fragments, $[Ph\text{-}N{=}N]^{+}$ at *m/z* = 105 and phenylisothiocyanate fragment at *m/z* = 135. X-ray structure of **3a** and **3c** is given in Figure 1and Figure 2 respectively.

Compounds **1a-e** may react either with their *1N*H, *2N*H, *4N*H or sulfur atom as nucleophilic centers. Since the previous reactions do not take place without the addition of **2** to the solution of **1a-e** in CH_3CN. The presence of (*p*-CHL, **2**) is required for the cyclization of **1a-e** and formation of triazolethione ring **3a-e**.

It is probable that the products **3a-e** were formed from one of the three 1:1 adducts **A-C** (Scheme 2). Several alternative structures were ruled on the basis of ^{13}C NMR spectroscopy. Finally a triazole ring **3a-e** was confirmed by X-ray crystallographic analysis (Figure 1 and figure 2).

The formation of diazenyl-1,2,4-triazole-5(4*H*)-thiones is described in Scheme 2. It is conceivable that *p*-CHL-accelerates the process of a Lewis acid through the intermediate **5** (Scheme 2) activating the C=S bond toward nucleophilic addition by nother molecule of **1** and *p*-CHL is released with the formation of one the three 1:1 adducts **A-C** (Scheme 2). It is clear that adduct **B** serve a useful adduct in determining the structures of compounds **3a-e**. Elimination a molecule of substituted amine from **B**, followed by intermolecular transformation of RNH on C=S in presence of Et_3N, and the ring is opened with formation of intermediate **8**. The latter reacted with PPh_3/Et_3N with elimination $Ph_3P{=}S$ and formation of **10**. Compound **10** gave diazenyl-1,2,4-triazole-5-thiones *via* oxidation with *p*-CHL (Scheme 2).

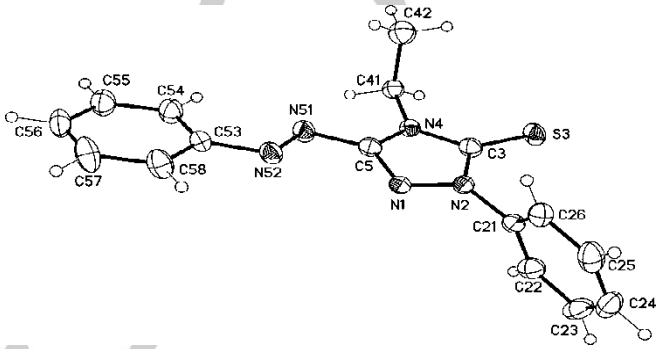


Figure 1. Molecular structure of compound **3a** in the crystal (minor disordered part omitted for clarity, displacement parameters are drawn at 50% probability level).

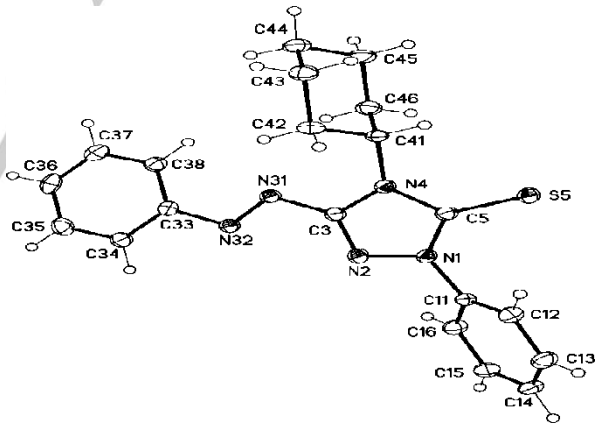
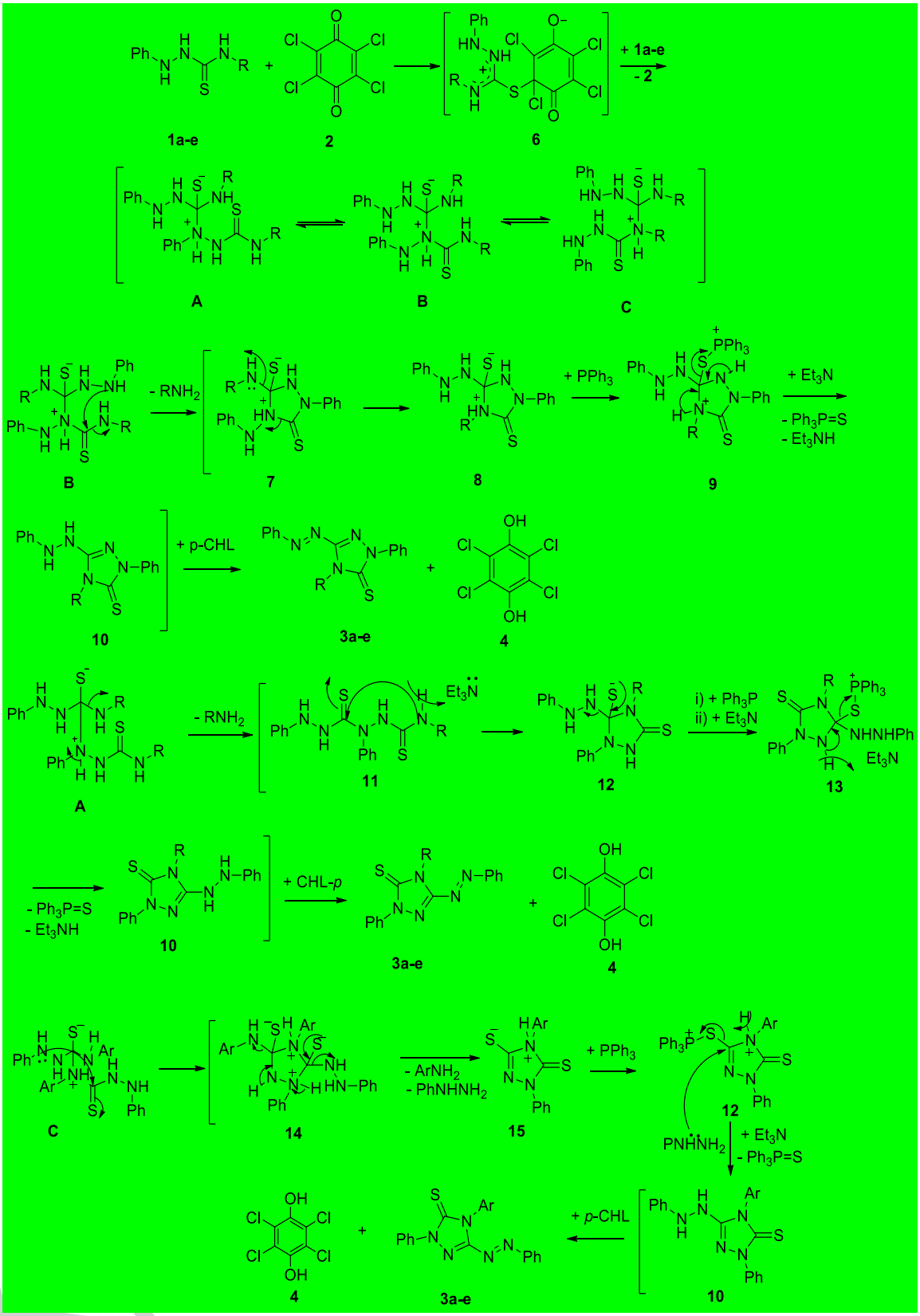


Figure 2. X-ray structure of compound **3c** (displacement parameters are drawn at 50% probability level).

With the optimized reaction conditions in hand, only one product class was isolated after preparative thin layer chromatography, namely diazenyltriazolthiones **3a-e**. Apparently, Ph_3P plays an important role on the reaction efficiency and product **3a-e** was formed *via* the intermediates **7-10**.



Scheme 2. The plausible mechanism for the formation of diazenyl-1,2,4-triazolthiones **3a-e**.

Without the addition of *p*-CHL, **2**) to the reaction mixture aforementioned steps do not take place. These cyclization reactions required the presence of *p*-CHL as a mediator and formation the products **3a-e**. The addition of sodium carbonate or sodium borate as bases instead of Et_3N and heating the mixture to reflux for 12-16 hrs, followed by extrusion with CH_2Cl_2 the starting materials **1** and **2** were separated without any reactions may be due to the insolubility in CH_3CN.

Conclusions

In conclusion, Eschenmoser-sulfide contraction was applied in the present investigation, followed by cyclization and oxidation using *p*-CHL (which react as a mediator) providing higher yields with lower costs of diazenyl-1,2,4-triazol-5(4*H*)-thione derivatives. It's conceivable that, the role of *p*-CHL in this reaction is used to activate the respective C=S bond toward nucleophilic addition.

Supporting Information

Supporting Information file includes the experimental procedure for diazenyl 1,2,4-triazol-5(4*H*)-thione derivatives, ^{1}H NMR, ^{13}C NMR and the supplementary data of the X-ray crystallographic structure of compound **3c**. CCDC 1823062 (**3a**) and 1856747 (**3c**) contain the supplementary crystallographic data for this paper.[26]

Acknowledgements

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Keywords: Eschenmoser-coupling reaction • Heterocyclization• Nucleophilic addition• Oxidation reaction• X-ray analyses.

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[26] These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

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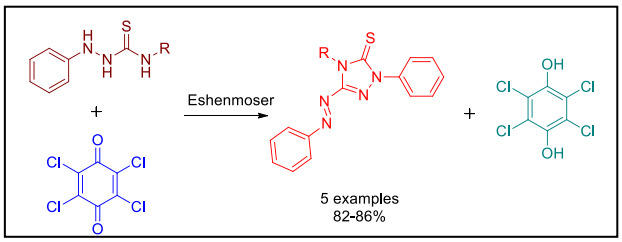

Nucleophilic attack of 1,4-disubstituted thiosemi-carbazides on 2,3,5,6-tetrachloro-1,4-benzoquinone (*p*-CHL), afforded the formation of heterocyclic triazolethione derivatives via multistep reaction. The cyclization reaction required the presence of *p*-CHL as a mediator and used to activate the C=S toward nucleophilic addition and elimination a molecule of substituted amine followed by cyclization and oxidation with *p*-CHL. The products were confirmed by X-ray analyses.