

## REACTION OF SOME X-PHENYLAZIDES DERIVATIVES WITH DIETHYL 1,3-ACETONEDICARBOXYLATE

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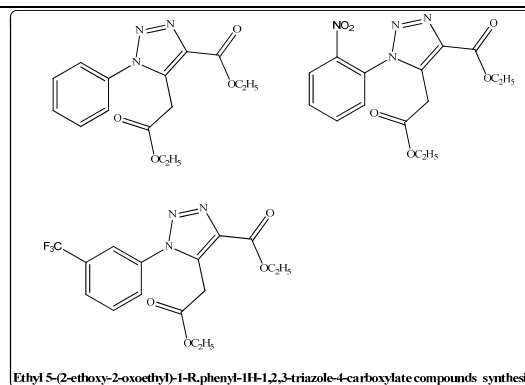
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A series of ethyl 5-(2-ethoxy-2-oxoethyl)-1-(X-phenyl)-1H-1,2,3-triazole-4-carboxylate was synthesized through a condensation reaction of some aryl azides and diethyl-1,3-acetonedicarboxylate (DEAD) in the presence of sodium ethoxide as a base. An unexpected heterocycle was isolated in the case of 2-trifluoromethylphenylazide. All the compounds are elucidated using FT-IR, NMR and MS spectroscopic techniques.



### INTRODUCTION

Azoles, are valuable five membered nitrogen heterocycles, mainly those with 1,2,3-triazoles nucleus.<sup>1</sup> Since their discovery 1,2,3-triazoles, have gained growing interest in medicinal chemistry and drug discovery field, due to its stability toward light, moisture, oxygen, and metabolism in the body.<sup>2</sup> Since they display intriguing pharmacological properties associated with a wide spectrum of biological activities like: anticancer,<sup>3</sup> antiviral,<sup>4</sup> antifungal,<sup>5</sup> anti-acetylcholinesterase,<sup>6</sup> anti-inflammatory,<sup>7</sup> antioxidant,<sup>8</sup> antidiabetic and anti-HIV.<sup>9-10</sup> They also found use in agrochemicals,<sup>11</sup> dyes,<sup>12</sup> photostabilizers<sup>13</sup> and corrosion inhibitors.<sup>14</sup> Owing to their importance,

numerous synthetic approaches, have been developed over the years for their preparation. Among these methods the most commonly used to access the triazole ring is the 1,3-dipolar cycloaddition of organic azides with alkynes.<sup>15</sup> Although this reaction requires strong conditions and affords a mixture of regioisomers, the cycloaddition proceeds smoothly when the alkyne is electron deficient.<sup>16</sup> In continuation of our interest in the synthesis of 1,2,3-triazoles derivatives,<sup>17,18</sup> we report in this study, an efficient and simple protocol for the preparation of 1,4,5-trisubstituted-1,2,3-triazole from the condensation of different aryl azides with diethyl-1,3-acetonedicarboxylate in the presence of sodium ethoxide in ethanol.

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## EXPERIMENTAL

### General

The chemicals were purchased from commercial suppliers, and they were used without any further purification. All melting points were determined on a Büchi melting point apparatus, and are uncorrected. IR, mass and  $^1\text{H}$  NMR spectra were measured on a Perkin-Elmer 1710 or 8000 Fourier transform Infrared spectrometer as KBr pellets, a Finnegan 4000 or a Shimadzu QP 2010 plus mass spectrometer, and a Bruker AC 300 MHz or a Bruker Avance DPX250 NMR spectrometer in  $\text{CDCl}_3$  solution, respectively. TLC was conducted on camlab polygram silica G/UV254.

### Procedure for aryl azides synthesis <sup>19</sup>

2- $\text{NO}_2$ / 2- $\text{CF}_3$  and 3- $\text{CF}_3$  aniline (1 mol) in concentrated hydrochloric acid solution 6M (150 mL) was heated at 45°C for 30 min. The mixture was cooled to (0–5°C) in ice bath. To this mixture was added a solution of sodium nitrite (1,1 mole) in (40 mL) of water. The resulting diazonium solution was kept cooled and added dropwise to a solution of sodium acetate (60 g) and sodium azide (1,1 mole) in water (150 mL), the resulting mixture was stirred for 30 min.

The solid was filtered off, washed with water (30 mL) and acidified to give the corresponding aryl azides 5, 6 and 8.

### Procedure for phenyl azide synthesis

To a mechanically stirred, and ice-cold solution of water (100 mL) and concentrated hydrochloric acid (18.5 mL), was added freshly distilled phenyl hydrazine (0.11 mol) dropwise over a period of 10 minutes. Phenyl hydrazine hydrochloride separates, as white plates. Diethyl ether (56 mL) was added when the temperature of the mixture is (0–3°C), then a solution of sodium nitrite (0.12 mol) in water (15 mL) was added dropwise while maintaining the temperature between 0–5°C. The stirring was continued for a further 10 min. The mixture was then suspended to a steam distillation under normal conditions until about 200 mL of distillate is obtained. Diethyl ether (100 mL) was added to the distillate, which was well shaken. The ether layer was separated, dried over anhydrous  $\text{Na}_2\text{SO}_4$  and then evaporated to dryness to yield a dark oil which was purified by column chromatography on  $\text{SiO}_2$ , using light petrol as eluent to give phenyl azide as a yellow liquid.

### General Procedure

To a solution of phenyl azide (11.28 mmol) and diethyl 1,3-acetonedicarboxylate (11.28 mmol) in absolute ethanol (20 mL) was added a solution of sodium (11.28 mmol) in absolute ethanol (10 mL) in one portion, and the mixture was brought to reflux for 3 hrs. It was then, cooled, solvent removed under reduced pressure, and water (50 mL) was added. The mixture was extracted with diethyl ether (3 × 50 mL), dried over anhydrous  $\text{Na}_2\text{SO}_4$  and evaporated to dryness to give a residue, which was purified by flash chromatography on  $\text{SiO}_2$  EtOAc: light petrol; (1:4) followed by (1:1), was used as eluent, to yield the pure product.

### Ethyl 5-(2-ethoxy-2-oxoethyl)-1-(2-nitrophenyl)-1H-1,2,3-triazole-4-carboxylate

White solid (from EtOH), m.p = 78–79°C. IR (film): 1738  $\text{cm}^{-1}$  (2 × CO).  $^1\text{H}$  (NMR):  $\delta$  = 1.18 (t, 3H,  $\text{CH}_3$ ); 1.44 (t, 3H,  $\text{CH}_3$ ); 3.97 (s, 2H,  $\text{CH}_2$ ); 4.09 (q, 2H,  $\text{CH}_2$ ); 4.44 (q, 2H,  $\text{CH}_2$ ); 7.77–7.85 (m, 2 $\text{H}_{\text{arom}}$ ), 8.19–8.22 (m, 2 $\text{H}_{\text{arom}}$ ). M.S: m/z (%) = 348 ( $\text{M}^+$ , 9); 99 (100).

### Ethyl 5-(2-ethoxy-2-oxoethyl)-1-phenyl-1H-1,2,3-triazole-4-carboxylate

75% as colorless viscous oil. IR (film): 1783 and 1699  $\text{cm}^{-1}$  (2 × CO).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ; 250MHz):  $\delta$  = 1.15 (t, 3H,  $\text{CH}_3$ ); 1.39 (t, 3H,  $\text{CH}_3$ ); 3.97 (s, 2H,  $\text{CH}_2$ ); 4.04 (q, 2H,  $\text{CH}_2$ ); 4.39 (q, 2H,  $\text{CH}_2$ ); 7.38–7.54 (m, 4 $\text{H}_{\text{arom}}$ ). M.S./ m/z (%) = 303 ( $\text{M}^+$ , 8); 77 (100).

### Pyrazole-3,5-dicarboxylate

Light grey cotton like solid (from EtOH), m.p = 104–106 °C. IR (film): 3380 (OH); 3205 (NH); 1712 and 1674  $\text{cm}^{-1}$  (2 × CO).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ; 250MHz):  $\delta$  = 1.40 (t, 6H, 2 $\text{CH}_3$ ); 4.45 (q, 4H, 2 $\text{CH}_2$ ); 4.78 (s, 1H). M.S: 288 ( $\text{M}^+$ , 45); 200 ( $\text{M}^+$ , 28, 16); 182 (100).

### Ethyl 5-(2-ethoxy-2-oxoethyl)-1-(3-(trifluoromethyl)phenyl)-1H-1,2,3-triazole-4-carboxylate

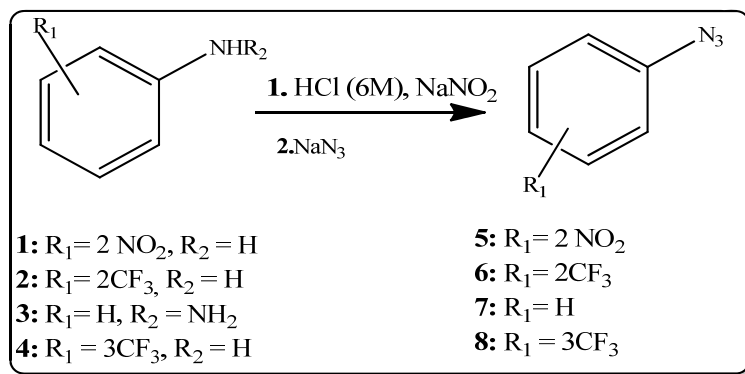
IR (film),  $\nu$ : 1701 and 1675.00  $\text{cm}^{-1}$  (2 x CO).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ; 250MHz):  $\delta$  = 1.21 (t, 6H, 2  $\text{CH}_3$ ), 3.68 (s, 2H,  $\text{CH}_2$ ), 4.25 (q, 2H,  $\text{CH}_2$ ), 4.50 (q, 2H,  $\text{CH}_2$ ), 7.30 (dd, 1 $\text{H}_{\text{arom}}$ ), 7.65 (m, 1 $\text{H}_{\text{arom}}$ ), 7.80 (dd, 2 $\text{H}_{\text{arom}}$ ) ppm. M.S: m/z (%) = 371 ( $\text{M}^+$ , 9), 242 (98), 145 (100).

## RESULTS AND DISCUSSION

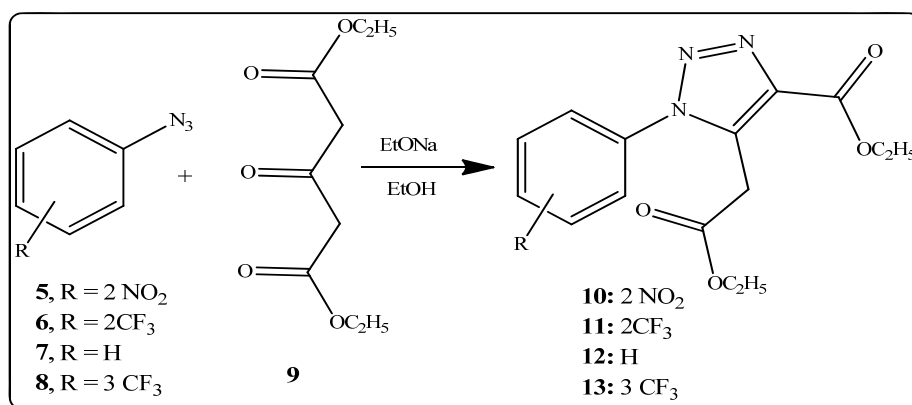
The general synthesis of the targeted compounds is outlined in Scheme 1. We first prepared the starting aryl azides 5–8. They were prepared from aniline derivatives and phenyl hydrazine (Scheme 1) in HCl (6M) solution at 0°C, via their diazonium salts, according to the literature procedure.<sup>10</sup> The yields thus obtained are quantitative, around 85%. The azide function was confirmed by their FTIR spectra, by the presence of a large band around 2120  $\text{cm}^{-1}$ .

When 2-nitrophenyl azide 1 reacts with DEAD 9 in absolute ethanol, in the presence of sodium ethoxide as a base, this latter was added dropwise into the solution mixture. The only isolated product in good yields, was 2-nitroaniline; its structure was confirmed by a comparative TLC with an authentic commercial 2-nitro aniline, and with mass spectroscopy with a molecular peak at 138 (100). This indicates that the initially formed triazole has decomposed.

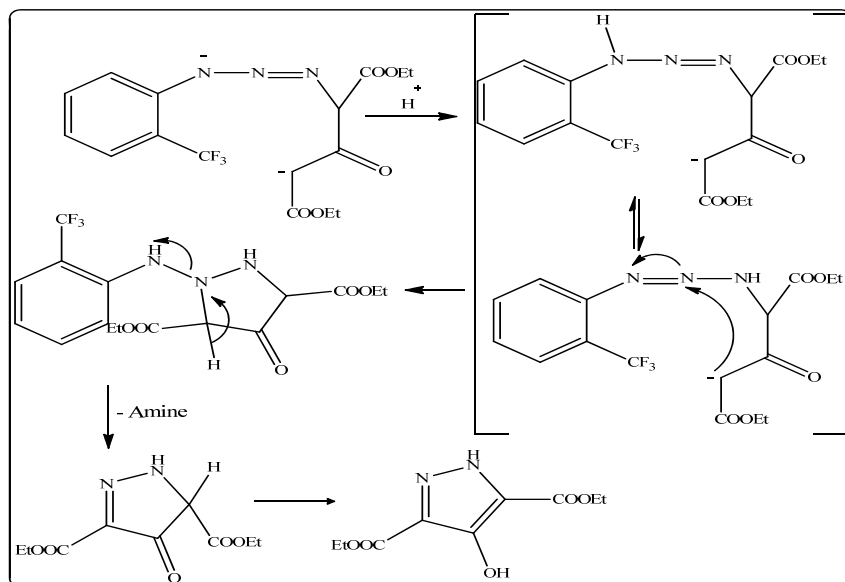
In contrast, when sodium ethoxide, in ethanol was added to the solution in one portion, the expected triazole was isolated in high yield 86%. A solid was isolated from the condensation of 2-trifluoromethyl phenyl azide 6 and DEAD 9 in the presence of EtONa. The salt was dissolved in water and gave an organic compound when acidified with a dilute solution of HCl. The product has a melting point of 104–106 °C, and it was identified as Pyrazole-3,5-dicarboxylate from its spectral analysis.



Scheme 1 – Phenyl azides synthesis.



Scheme 2 – Reaction of some aryl azides with diethyl-1,3-acetonedicarboxylate.



Scheme 3 – The proposed mechanism of pyrazole formation.

## CONCLUSIONS

In conclusion, we have applied a very simple, convenient, mild condition and high yielding protocol to synthesize a series of 1,4,5-

trisubstituted 1,2,3-triazoles, from aryl azides and DEAD in the presence of sodium ethoxide. The base (sodium ethoxide) must be added in one portion to the reaction mixture in order to prevent the decomposition of the 1,2,3-triazole ring.

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