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One-pot and novel route for the synthesis of 4-substituted-1,2,4-triazolidine-3,5-diones

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ABSTRACT

The efficient and one-pot synthesis of 4-substituted-1,2,4-triazolidin-3,5-dione derivatives (4-substituted urazoles) *via* combination of triphosgene, substituted anilines, and ethyl carbazate in the presence of cesium carbonate is presented.

1. Introduction

Heterocyclic compounds are important and valuable parts of biologically active molecules and natural products; therefore, the design of new strategies to synthesize them is currently an important area of research. An interesting class of these compounds is 1,2,4-triazolidine-3,5-diones, which are five-membered heterocyclic compounds including three azo atoms with a wide variety of aliphatic as well as aromatic constituents at position 4 [1]. 1,2,4-Triazolidine-3,5-diones are of interest because of their role as reagents in laboratory and industry; for instance, application in preparing of automobile air bags, as a blowing agent in plastic compounds, in the production of herbicides, as an anticonvulsant, in antifungal compounds, and in polymeric materials [2–6]. These compounds are also used for the preparation of organometallic compounds [7]. There are few reports for the synthesis of these heterocyclic compounds [1,8,9]. Many of these reported methods suffer from one or more drawbacks, such as low yields, hazardous reaction conditions, and multistep processes. Therefore, the search for a more suitable preparation of 1,2,4-triazolidine-3,5-diones continues today.

2. Experimental

Typical procedure for the synthesis of 4-substituted-urazoles: *p*-toluidine (3 mmol) and cesium carbonate (3.5 mmol) were dissolved in anhydrous 1,4-dioxane (10 mL). Triphosgene (1 mmol) was added in portions over 2, 3 min, and this mixture was stirred at room temperature. After 1.5 h, ethyl carbazate (3.2 mmol) was added, and the reaction mixture was stirred overnight. Following evaporation to dryness, the reaction mixture was refluxed in aqueous 5 mol/L KOH for 5 h then cooled down in an ice bath. The solution was neutralized with concentrated HCl to reach pH 1, 2. The white crystalline product was collected and dried to give 4-(4-methylphenyl)-1,2,4-triazolidine-3,5-dione with 84% yield.

4-(4-Isopropylphenyl)-1,2,4-triazolidine-3,5-dione (**4a**): White crystalline solid, 0.162 g (74%); mp: 231–234 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.45 (s, 2H), 7.36 (br, 4H), 2.94 (septet, 1H, J = 6.8 Hz), 1.21 (d, 6H, J = 6.8 Hz); ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 154.1, 148.5, 130.0, 127.1, 126.6, 33.7, 24.3. Anal. Calcd. for $C_{11}H_{13}N_3O_2$: C, 60.26; H, 5.98; N, 19.17. Found: C, 61.13; H, 5.68; N, 18.89.

4-(4-Bromophenyl)-1,2,4-triazolidine-3,5-dione (**4c**): White crystalline solid, 0.159 g (62%); mp: 210–212 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.60 (s, 2H), 7.70 (d, 2H, J = 8.8 Hz), 7.47 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 153.4, 132.2, 131.8, 128.2, 120.7. Anal. Calcd. for $C_8H_6BrN_3O_2$: C, 37.53; H, 2.36; N, 16.41. Found: C, 37.88; H, 2.68; N, 15.87.

4-(4-Ethylphenyl)-1,2,4-triazolidine-3,5-dione (**4d**): White crystalline solid, 0.201 g (98%); mp: 246–248 °C; ^{1}H NMR

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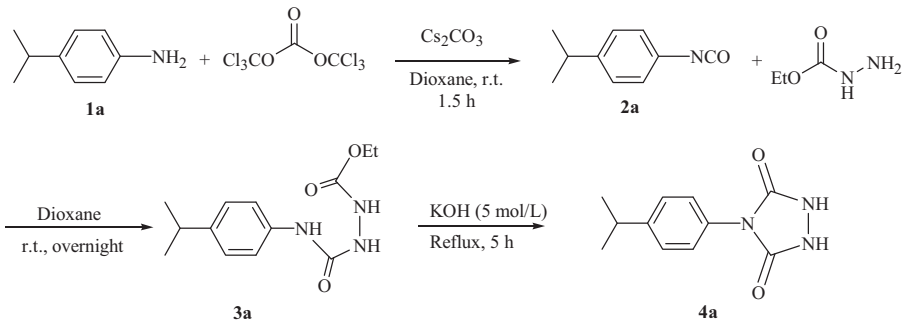


Scheme 1. Synthesis of 4-(4-*iso*propylphenyl)-1,2,4-triazolidine-3,5-dione.

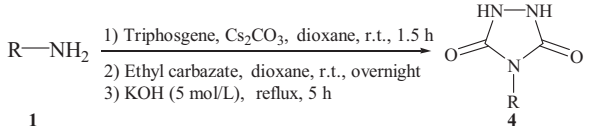
(400 MHz, DMSO-d_6): δ 10.46 (s, 2H), 7.33–7.36 (m, 4H), 2.65 (q, 2H, J = 7.2 Hz), 1.20 (t, 3H, J = 7.2 Hz); ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 154.0, 143.9, 129.9, 128.6, 126.6, 28.3, 16.1. Anal. Calcd. for $C_{10}H_{11}N_3O_2$: C, 58.53; H, 5.40; N, 20.48. Found: C, 58.34; H, 5.11; N, 20.21.

4-(2,4-Dimethoxyphenyl)-1,2,4-triazolidine-3,5-dione (**4e**): White crystalline solid, 0.130 g (55%); mp: 245–246 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.20 (s, 2H), 7.16 (d, 1H, J = 8.4 Hz), 6.71 (s, 1H), 6.60 (d, 1H, J = 8.4 Hz), 3.82 (s, 3H), 3.76 (s, 3H); ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 161.6, 156.9, 154.8, 131.4, 113,2, 105.4, 99.7, 56.3, 56.0. Anal. Calcd. for $C_{10}H_{11}N_3O_4$: C, 50.63; H, 4.67; N, 17.71. Found: C, 49.28; H, 3.13; N, 17.78.

4-(4-Tritylphenyl)-1,2,4-triazolidine-3,5-dione (**4f**): White crystalline solid, 0.411 g (98%); mp: 300 °C (dec.); ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.58 (s, 2H), 7.02–7.41 (m, 19H); ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 153.7, 146.7, 146.2, 131.2, 130.9, 130.1, 128.4, 126.6, 125.6, 64.8. Anal. Calcd. for $C_{27}H_{21}N_3O_4$: C, 77.31; H, 5.05; N, 10.02. Found: C, 76.89; H, 2.90; N, 9.52.

4-(4-Fluorophenyl)-1,2,4-triazolidine-3,5-dione (**4h**): White crystalline solid, 0.150 g (77%); mp: 269–270 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.53 (s, 2H), 7.45-7.53 (m, 2H), 7.31–7.36 (m, 2H); ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 161.4 (d, J_{c-F} = 243 Hz), 153.8, 128.7 (d, J_{c-F} = 9 Hz), 120.5 (d, J_{c-F} = 8 Hz), 116.1 (d, J_{c-F} = 23 Hz). Anal. Calcd. for $C_8H_6FN_3O_4$: C, 49.24; H, 3.10; N, 21.53. Found: C, 49.97; H, 2.56; N, 21.53.

The NMR spectra can be found in the Supporting information file.

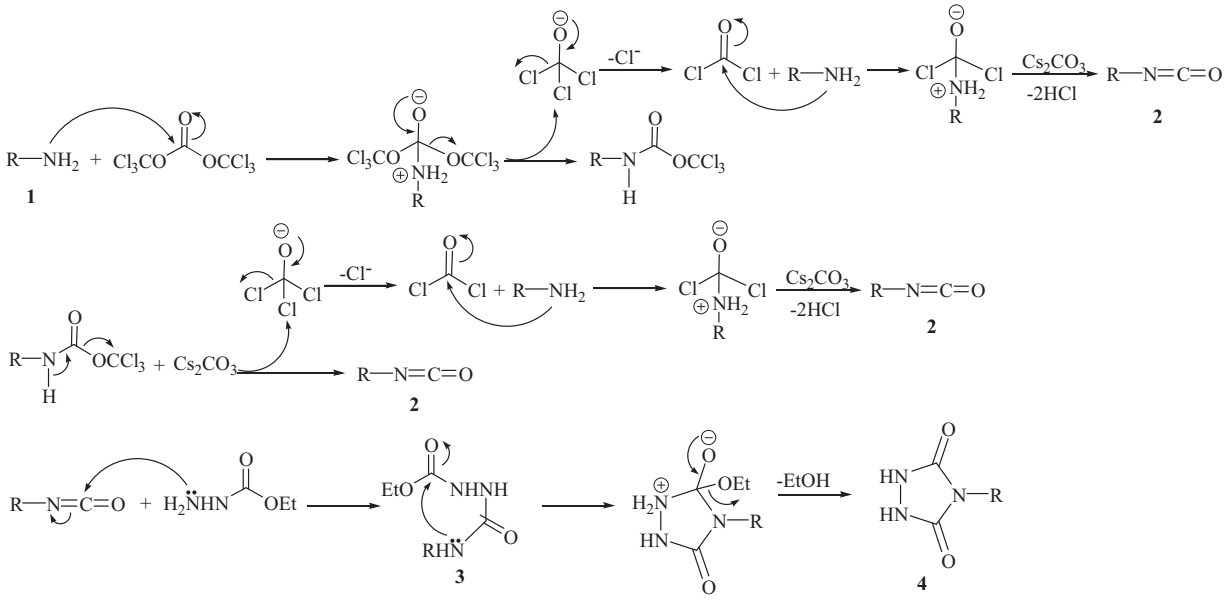


Scheme 2. Synthesis of 4-substituted-1,2,4-triazolidin-3,5-diones.

3. Results and discussion

In light of the aforementioned biologic, laboratorial, and industrial activities and as part of our ongoing program towards the synthesis of heterocyclic compounds [10–15], we delineated an efficient route for the synthesis of urazole derivatives.

Initially, we performed the reaction between 4-*iso*propylaniline **1a** and triphosgene in the presence of different bases (such as triethylamine, potassium hydroxide, sodium carbonate, and cesium carbonate) and solvents (such as dichloromethane, acetone, 1,4-dioxane, ethyl acetate, and tetrahydro furane) to achieve 4-*iso*propylisocyanate **2a**. After consumption of 4-*iso*-propylaniline, ethyl carbazate was added to the solution to afford intermediate **3a**. The best solvent and base for these two steps were 1,4-dioxane and cesium carbonate, respectively. After consumption of 4-*iso*propylisocyanate, the solvent was evaporated and 5 mol/L KOH was added to the mixture and refluxed; this step was found to be completed within 5 h, affording 4-(4-*iso*propyl-phenyl)-1,2,4-triazolidine-3,5-dione **4a** (Scheme 1).



Scheme 3. Mechanism of the urazole synthesis.