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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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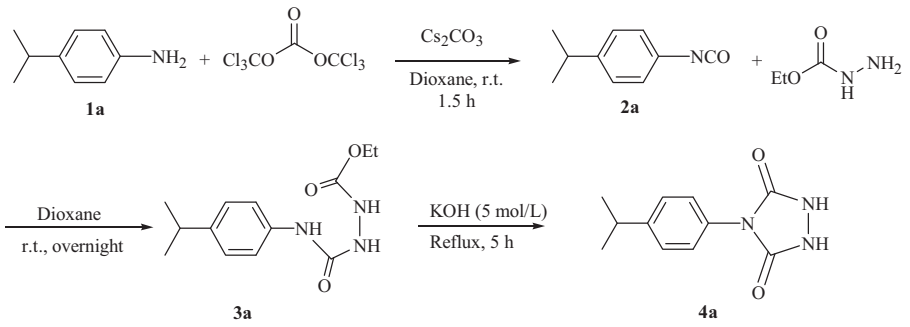


Scheme 1. Synthesis of 4-(4-*iso*propylphenyl)-1,2,4-triazolidine-3,5-dione.

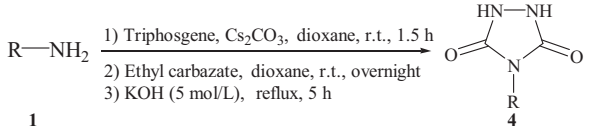
(400 MHz, DMSO-d_6): δ 10.46 (s, 2H), 7.33–7.36 (m, 4H), 2.65 (q, 2H, J = 7.2 Hz), 1.20 (t, 3H, J = 7.2 Hz); ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 154.0, 143.9, 129.9, 128.6, 126.6, 28.3, 16.1. Anal. Calcd. for $C_{10}H_{11}N_3O_2$: C, 58.53; H, 5.40; N, 20.48. Found: C, 58.34; H, 5.11; N, 20.21.

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.

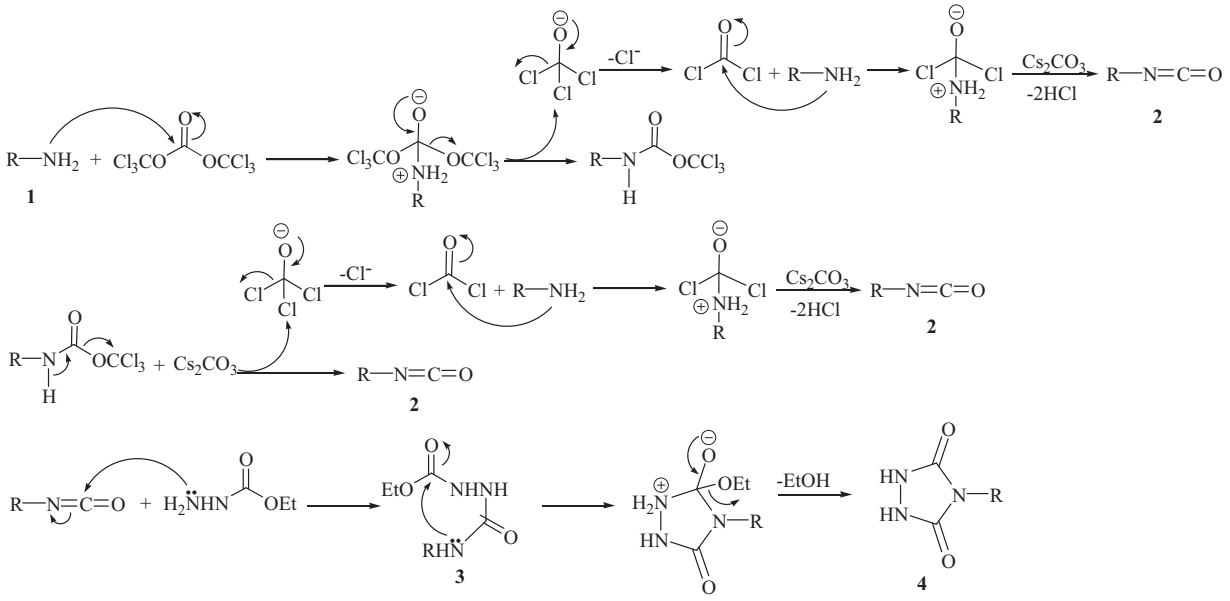


Scheme 2. Synthesis of 4-substituted-1,2,4-triazolidin-3,5-diones.

3. Results and discussion

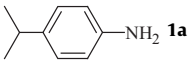
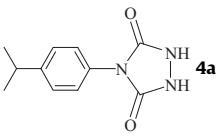
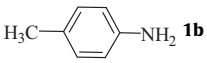
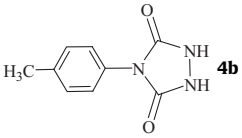
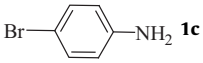
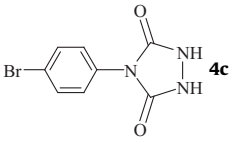
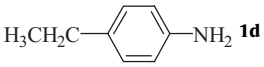
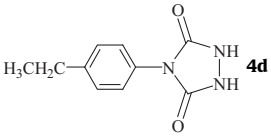
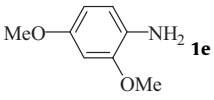
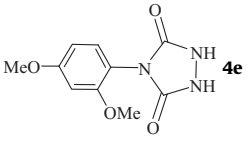
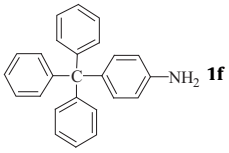
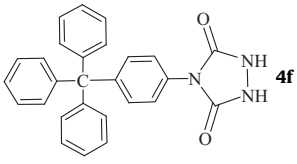
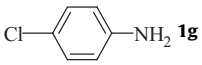
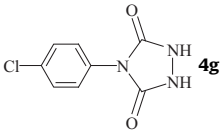
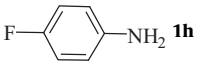
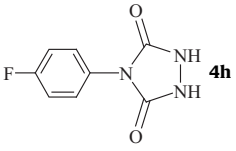
In light of the aforementioned biologic, laboratorial, and industrial activities and as part of our ongoing program towards the synthesis of heterocyclic compounds [10–15], we delineated an efficient route for the synthesis of urazole derivatives.

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.

Table 1
Synthesis of 4-substituted-1,2,4-triazolidin-3,5-diones *via* one-pot combination of different types of anilines with triphosgene and ethyl carbazate in the presence of cesium carbonate.

Entry	Amine	Urazole	Yield[a] (%)	Mp (°C)		Ref.
				Observed	Reported	
1	 **1a**	 **4a**	74	231–234	–	–
2	 **1b**	 **4b**	84	243–244	245–246	[2]
3	 **1c**	 **4c**	62	210–212	–	–
4	 **1d**	 **4d**	98	246–248	–	–
5	 **1e**	 **4e**	55	245–246	–	–
6	 **1f**	 **4f**	98	300 (dec)	–	–
7	 **1g**	 **4g**	65	224–227	231–232	[2]
8	 **1h**	 **4h**	77	269–270	–	–

[a] Isolated yield.

Based on these results, we investigate the scope and limitations of this synthesis strategy by varying the structure of amine. Therefore, a novel series of 4-substituted urazoles has been synthesized by a one-pot multicomponent reaction using different types of anilines, triphosgene, and ethyl carbazate (Scheme 2).

The results of these syntheses are summarized in Table 1. A plausible mechanism for the synthesis of 4-substituted urazoles, has been outlined in Scheme 3, based on previously reported papers [1,8,9,16]. The interesting point of this mechanism is the *in situ* generation of three equivalent isocyanates (**2**) from the reaction of one equivalent triphosgene and three equivalent aniline. Subsequently, reaction of isocyanate with ethyl carbazate was followed by cyclization of intermediate (**3**) to generate corresponding 4-substituted-1,2,4-triazolidin-3,5-dione (**4**).

4. Conclusion

In summary, we have delineated an efficient synthesis of structurally diverse 4-substituted urazoles *via* one-pot combination of a variety of anilines with triphosgene and ethyl carbazate in the presence of cesium carbonate. Simple reaction conditions, broad substrate scope, and no additional solvent extraction steps are the advantages of this procedure. The greenness and simplicity of this synthetic procedure makes it an interesting alternative to other approaches.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.cclet.2013.11.020.

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