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An efficient, one-pot three-component synthesis of $4H$-thiazolo[3,2-$a$][1,3,5]triazin-6-one derivatives

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Abstract: A simple and efficient protocol was established to synthesize thiazolo[3,2-$a$][1,3,5]triazin-6-ones via three-component one-pot condensation reaction of readily available thioglycolic acid or ethyl thioglycolate, aldehydes or ketones and dicyandiamide in the presence of ammonium acetate. All of the newly synthesized compounds were characterized by spectroscopic analyses.

Keywords: multicomponent reaction; one-pot reaction; thiazolo[3,2-$a$][1,3,5]triazin-6-ones.

Introduction

The design of highly efficient reaction sequences that provide the maximum structural complexity and diversity with a minimum number of synthetic steps is a great challenge for synthetic chemists [1, 2]. In this regard, the multi-component reaction (MCR) is one of the best tools available for the creation of several bonds in a single operation by virtue of efficiency and facility [3–6], because it allows more than two building blocks to be combined in a practical, time-saving, one-pot operation [7–13]. In recent years, the research on MCR has been rapidly evolved and hundreds of MCRs have been described [7–10, 14, 15]. In addition, such reactions also provide an efficient manner to discover biologically active compounds [9, 12, 16, 17]. Although impressive successes have been achieved, it is still of academic significance and application value to discover new multicomponent reactions [7, 18, 19].

The thiazolo-$s$-triazine moiety is found in wide range of biologically active compounds. Thiazolo-$s$-triazines have been found to possess antifolate activity [20, 21] and have been developed as anticancer, antibacterial, antifungal, and antiparasitic agents [22–24]. Thus, the synthesis of new compounds of this class of compounds may give a library of compounds as possible candidates for different biological activities. As a continuation to our program directed towards the synthesis of heterocyclic systems [25–31], we describe herein a powerful and highly effective synthetic route to thiazolo[3,2-$a$][1,3,5]triazin-6-ones via one-pot three-component reaction of thioglycolic acid/ethyl thioglycolate, aldehydes/ketones and dicyandiamide in the presence of ammonium acetate as a catalyst.

Results and discussion

The synthesis of the thiazolo[3,2-$a$][1,3,5]triazine skeleton has earlier been achieved by a multistep reaction. The most common synthetic methods reported for the preparation of this ring system involve annelation of the triazine ring onto a thiazole scaffold via Mannich reaction [32],

![Scheme 1](image-url)
multicomponent reactions of 2-aminothiazoles with heterocumulenes [33, 34], 2-aminothiazoles with C-N-C triatomic [35, 36], formal [4+2] cycloaddition [37], 1,3,5-triazine ring annelation on 2-substituted thiazoles using one-carbon inserting reagents [38] or annelation of thiazole ring into 1,3,5-triazine scaffold [39]. In the present work, it is noticed that the reaction is very much accommodative and more productive with thioglycolic ester in the place of thioglycolic acid.

The synthesis of thiazolo[3,2-a][1,3,5]triazines 5a-e (Scheme 1) was achieved by tandem cyclization of thioglycolic acid or ethyl thioglycolate (1) and dicyandiamide (2) with aromatic aldehydes 3, taken in a 1:1:1 molar ratio, in the presence of ammonium acetate. The hypothetical benzylidene derivatives 4a-e were not found in crude mixtures. When the reaction was carried out in the presence of ethyl thioglycolate instead of thioglycolic acid, the yield was improved and the reaction time was significantly reduced. Accordingly, the ester is the reagent of choice for this reaction.

The suggested mechanism is given in Scheme 2. The elementary step involves the formation of intermediate product A by nucleophilic addition of the sulfanyl group of thioglycolic acid or ethyl glycolate (1) to the cyano group of dicyandiamide (2). The intramolecular cyclization of A by loss of water or ethanol generates another non-isolable intermediate 4-thiazolinone product B. Then, the intermediate product B undergoes a reaction with an aldehyde 3 in the presence of ammonium acetate as a catalyst to furnish Schiff base C which is a direct precursor to thiazolo[3,2-a][1,3,5]triazines 5a-e.

The molecular structure of 5a–e was elucidated with the help of spectral and elemental analyses. In particular, all products 5 exist in a single tautomeric form, apparently 5-B, as suggested by the experimental data (Figure 1). We also studied the participation of ketones 6 as one-carbon inserting reagents. Thus, spiro- products 7a-c were readily obtained by one-pot three-component reaction of thioglycolic acid or ethyl thioglycolate, a ketone including barbituric acid and dicyandiamide in a 1:1:1 molar ratio in the presence of ammonium acetate as a catalyst. The spectral characteristics and analytical data of the products were in full agreement with the given structures 7a-c.
(Scheme 3). In a similar manner, dispiro compounds 8a-d were obtained as major products using thioglycolic acid or ethyl thioglycolate, ketone 6 and dicyandiamide in a 1:2:1 molar ratio.

Conclusions

An efficient procedure for the synthesis of thiazolo[3,2-a][1,3,5]triazin-6-ones 5a-e, 7a-c, 8a-d using one-pot three-component condensation reaction of ethyl thioglycolate, an aldehydes or a ketone, and dicyandiamide in the presence of ammonium acetate as an inexpensive catalyst is reported. The major advantages are simplicity, high yields of products and ease of the work-up including isolation of the products without chromatography.

Experimental

All chemicals were purchased from Aldrich or Merck and used without further purification. Melting points are uncorrected. IR spectra were taken in KBr pellets on Shimadzu 440 spectrometer, 1H NMR (400 MHz) spectra and 13C NMR (100 MHz) spectra were obtained in DMSO-d6 on a Varian Gemini 400 spectrometer using TMS as internal standard. The elemental analyses were carried out at the Regional Center for Mycology and Biotechnology, Al-Azhar University, Cairo.

General procedure for synthesis of 4H-thiazolo[3,2-a][1,3,5]triazin-6(7H)-ones 5a-e and spiro-4H-thiazolo[3,2-a][1,3,5]triazin-6(7H)-ones 7a-c

A mixture of the aldehyde 3 or ketone 6 (0.01 mol), ethyl thioglycolate (1, 0.01 mol), dicyandiamide (2, 0.01 mol) in acetic acid (30–50 mL) in the presence of ammonium acetate (3 g) was heated under reflux for a period of time indicated below. The reaction progress was monitored by TLC. The resultant solid product was filtered off, washed with ethanol, dried and crystallized to give 5a-e or 7a-c.

2-Amino-4-(2-hydroxyphenyl)-4H-thiazolo[3,2-a][1,3,5]triazin-6(7H)-one (5d)

This compound was obtained from furo-2-carbaldehyde in 87% yield as white crystals from dioxane; reaction time 3 h; mp 284–286°C; IR: 3305, 3115 (NH), 2930 (CH-arom.), 1688 (C=O), 1651, 1612 cm⁻¹ (C=N); 1H NMR: δ 6.69 (s, 1H, H-7), 6.89 (dd, 1H, H-3), 7.25 (dd, 1H, H-4'), 7.38 (d, 1H, H-5'), 7.51 (s, 1H, H-4), 8.34 (s, 2H, NH₂, exchangeable with D₂O), 11.98 (hump, 1H, OH, exchangeable with D₂O); 13C NMR: 69.5 (C-4), 74.6 (C-7), 106.8 (C-3'), 110.3 (C-3'), 142.7 (C-5'), 152.4 (C-2'), 158.6 (C-8a), 179.2 (C-6). Anal. Calcd for C₁₃H₁₁N₆O₄S: C, 51.26, H, 4.38, N, 20.28. Found: C, 51.09, H, 4.30, N, 20.21.

2-Amino-4-(furan-2-yl)-4H-thiazolo[3,2-a][1,3,5]triazin-6(7H)-one (5e)

This compound was obtained from furo-2-carbaldehyde in 87% yield as white crystals from dioxane; reaction time 3 h; mp 284–286°C; IR: 3305, 3115 (NH), 2930 (CH-arom.), 1688 (C=O), 1651, 1612 cm⁻¹ (C=N); 1H NMR: δ 6.69 (s, 1H, H-7), 6.89 (dd, 1H, H-3), 7.25 (dd, 1H, H-4'), 7.38 (d, 1H, H-5'), 7.51 (s, 1H, H-4), 8.34 (s, 2H, NH₂, exchangeable with D₂O), 11.98 (hump, 1H, OH, exchangeable with D₂O); 13C NMR: 69.5 (C-4), 74.6 (C-7), 106.8 (C-3'), 110.3 (C-3'), 142.7 (C-5'), 152.4 (C-2'), 158.6 (C-8a), 179.2 (C-6). Anal. Calcd for C₁₃H₁₁N₆O₄S: C, 51.26, H, 4.38, N, 20.28. Found: C, 51.09, H, 4.30, N, 20.21.

2-Amino-4-(4-methoxyphenyl)-4H-thiazolo[3,2-a][1,3,5]triazin-6(7H)-one (5f)

This compound was obtained from furo-2-carbaldehyde in 87% yield as white crystals from dioxane; reaction time 3 h; mp 284–286°C; IR: 3305, 3115 (NH), 2930 (CH-arom.), 1688 (C=O), 1651, 1612 cm⁻¹ (C=N); 1H NMR: δ 6.69 (s, 1H, H-7), 6.89 (dd, 1H, H-3), 7.25 (dd, 1H, H-4'), 7.38 (d, 1H, H-5'), 7.51 (s, 1H, H-4), 8.34 (s, 2H, NH₂, exchangeable with D₂O), 11.98 (hump, 1H, OH, exchangeable with D₂O); 13C NMR: 69.5 (C-4), 74.6 (C-7), 106.8 (C-3'), 110.3 (C-3'), 142.7 (C-5'), 152.4 (C-2'), 158.6 (C-8a), 179.2 (C-6). Anal. Calcd for C₁₃H₁₁N₆O₄S: C, 51.26, H, 4.38, N, 20.28. Found: C, 51.09, H, 4.30, N, 20.21.

2-Amino-4-(4-methoxyphenyl)-4H-thiazolo[3,2-a][1,3,5]triazin-6(7H)-one (5f)

This compound was obtained from furo-2-carbaldehyde in 87% yield as white crystals from dioxane; reaction time 3 h; mp 284–286°C; IR: 3305, 3115 (NH), 2930 (CH-arom.), 1688 (C=O), 1651, 1612 cm⁻¹ (C=N); 1H NMR: δ 6.69 (s, 1H, H-7), 6.89 (dd, 1H, H-3), 7.25 (dd, 1H, H-4'), 7.38 (d, 1H, H-5'), 7.51 (s, 1H, H-4), 8.34 (s, 2H, NH₂, exchangeable with D₂O), 11.98 (hump, 1H, OH, exchangeable with D₂O); 13C NMR: 69.5 (C-4), 74.6 (C-7), 106.8 (C-3'), 110.3 (C-3'), 142.7 (C-5'), 152.4 (C-2'), 158.6 (C-8a), 179.2 (C-6). Anal. Calcd for C₁₃H₁₁N₆O₄S: C, 51.26, H, 4.38, N, 20.28. Found: C, 51.09, H, 4.30, N, 20.21.
2'-Amino-1H-spiro[pyrimidine-2,4'-thiazolo[3,2-a][1,3,5]triazine]-4,6,6'-(3H,5H,7'H)-trione (7c) This compound was obtained from barbituric acid in 84% yield as brown crystals (from dioxane); mp 275–276 °C; IR: (potassium bromide, cm⁻¹): 3459, 3326, 3241 (NH₂), 1716, 1680 (C=O), 1618 cm⁻¹ (C=N); δ H NMR: δ: 7.33–8.05 (m, 8H, Ar-H), 8.17 (s, 2H, NH, exchangeable with D₂O); 9.92 (s, 2H, NH, exchangeable with D₂O), 10.74 (s, 2H, NH, exchangeable with D₂O). Anal. Calcd for C₈H₈N₆O₃S: C, 35.82, H, 3.01, N, 31.33. Found: C, 35.74, H, 2,88, N, 31.26.

2'-Amino-1H-spiro[pyrimidine-2,4'-thiazolo[3,2-a][1,3,5]triazine]-4,6,6'-(3H,5H,7'H)-trione (7c) This compound was obtained from ninhydrin in 92% yield as grey solid; reaction time 4 h; mp 309–311 °C; IR: 3389, 3210 (NH₂), 2920 (CH-aliph.), 1733, 1670, 1652 (C=O), 1547 cm⁻¹ (C=O). Anal. Calcd for C₈H₈N₆O₃S: C, 35.82, H, 3.01, N, 31.33. Found: C, 35.74, H, 2,88, N, 31.26.


