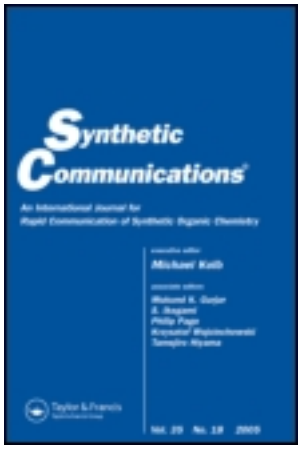

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SIMPLE, THREE-COMPONENT, HIGHLY EFFICIENT GREEN SYNTHESIS OF THIAZOLO[3,2-a]PYRIDINE DERIVATIVES UNDER NEAT CONDITIONS

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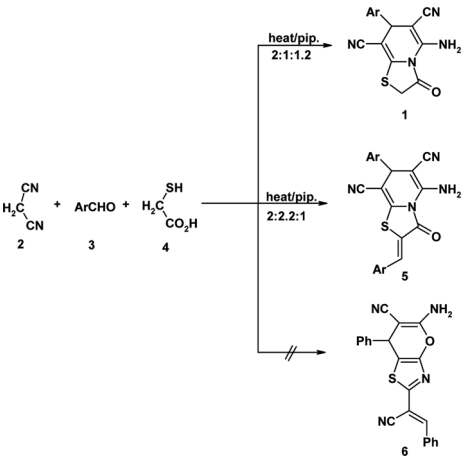
GRAPHICAL ABSTRACT



Abstract *Green, highly efficient, three-component syntheses of thiazolo-[3,2-a]pyridine derivatives via reaction of malononitrile, aromatic aldehydes, and 2-mercaptoacetic acid with a catalytic amount of piperidine without solvent with molar ratios of 2:2:1.2 and 2:2.2:1, respectively, has been reported.*

Keywords Neat conditions; thiazolo[3,2-a]pyridines; three component

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INTRODUCTION

Thiazolo[3,2-a]pyridines have received considerable interest because of their biological activity.[1] They possess many significant bioactivities such as α-glucoside inhibitors,[2] antibacterial and antifungal activities,[3] β-amyloid production inhibitors,[4] and many other biological activities.[5,6] In spite of their biological activity, synthesis of 5-amino-7-aryl-6,8-dicyano-3-oxo-2,3-dihydro-7*H*-thiazolo[3,2-*a*]pyridine derivatives have received little attention. The conventional methods for their synthesis are a multistep reaction or use complicated starting materials.[7–9] A three-component synthesis was achieved from the reaction of benzylidenemalononitrile, *N*-substituted thiocarbamoylacetamides, and methyl-2-chloroacetate in methanol catalyzed by piperidine.[10] Previously, Elnagdi et al. have also reported an efficient synthesis of these molecules from the reaction of 2-(α-functionally substituted alkyl)-4-hydroxythiazoloes with α-functionally substituted cinnamonitrile derivatives or alternatively from the reaction of the later with 2-mercaptoacetic acid, both in ethanol in the presence of piperidine or triethylamine as catalyst and reflux.[11,12] Very recently,[13] a microwave-assisted three-component synthesis of thiazolo[3,2-a]pyridines in water with moderate to good yields has been reported. It is worth mentioning that multicomponent reactions (MCRs) have attracted the attention of synthetic organic chemists for building highly functionalized organic molecules for their atom economy, selectivity, simplicity, energy savings, as well as environmental friendliness. Also, application of environmentally benign solvent-free organic reactions represents a powerful green procedure.[14,15]

RESULTS AND DISCUSSION

In continuation our interest in applying environmentally friendly techniques,[16–18] we found that there is no need for prolonged conventional heating, microwave irradiation, or solvent (even it is a benign one) for the synthesis of thiazolo [3,2-a]pyridines. In the current study, we reported a facile, highly efficient, solventless, three-component protocol for the synthesis of 5-amino-3-oxo-7-aryl-2, 3-dihydro-7H-pyrido[2,1-b][1,3]thiazole-6,8-dicarbonitrile **1** and 5-amino-7-aryl-3-oxo-2-(1-arylmethylidene)-2,3-dihydro-7H-pyrido[2,1-b][1,3]thiazole-6,8-dicarbonitrile **5** employing malononitrile (**2**), aromatic aldehydes (**3**), and 2-mercaptoacetic acid (**4**) with different molar ratios. Thus, in a typical procedure, when a mixture of neat malononitrite (**2**), benzaldehyde (**3a**), mercaptoacetic acid (**4**), and piperidine (two drops) in a molar ratio 2:1:1 was fused for 30 s, the reaction mixture was solidified instantaneously, and a mixture of compounds **1a** and **5a** were obtained in which their structures were established via ^{1}H NMR spectra, which reflects the effect of the reactants' molar ratio on the nature of the end product. After conducting numerous experiments we have concluded that a molar ratio of 2:2:1.2 of **2**, **3**, and **4** yields mainly product **1.** However, changing the molar ratio of the same reactants to 2:2.2:1 yields **5** as the sole isolable product (cf. Scheme 1).

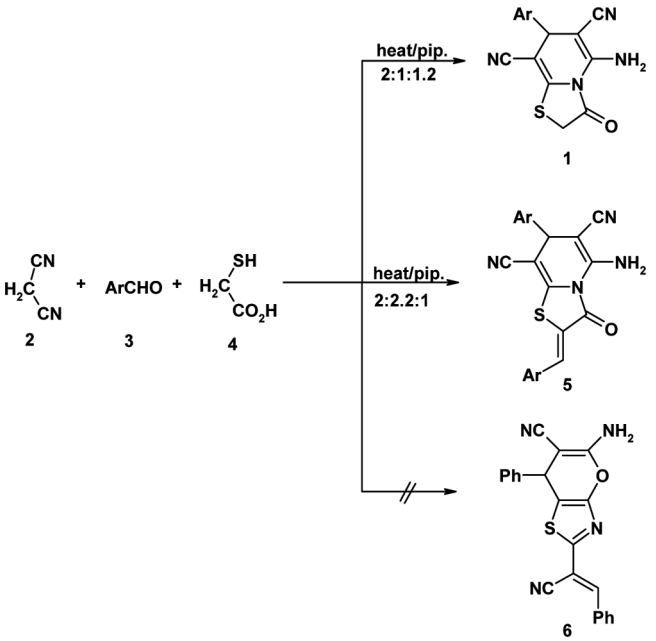
The structure of thiazolo[3,2-a]pyridines **1** and **5** were characterized by infrared (IR), ^{1}H NMR, ^{13}C NMR, heteronuclear multiple-bond correlation (HMBC), and heteronuclear multiple-quantum correlation (HMQC). It was noticed in HMBC of **5a** that the carbonyl carbon atom at 161.5 ppm is coupled to an arylmethylene

Table 1. List of thiazolo[3,2-*a*]pyridines **1a–d** and **5a–e**

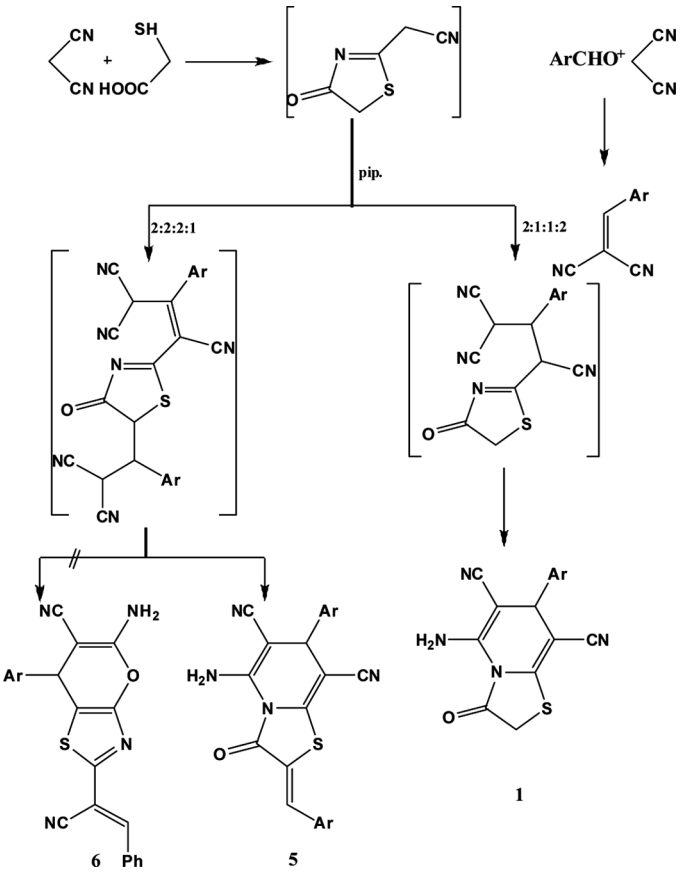
Product	Ar	Time (s)	Yield	Mp (1it.) (°C)
1a	C_6H_5	30	85	239–241 (268–240)[13]
1b	4-Br-C_6H_4	40	82	293–294 (292–294)[13]
1c	2-Cl-C_6H_4	40	80	234–238 (234–236)[13]
1d	4-OCH_3-C_6H_4	60	88	236–238 (236–238)[13]
1e	3-NO_2-C_6H_4	35	82	232–233
5a	C_6H_5	30	90	264–266 (265)[11]
5b	4-OCH_3-C_6H_4	60	92	
5c	4-NO_2-C_6H_4	45	87	259–261 (>230)[12]
5d	3-NO_2-C_6H_5	45	87	288–290 (278–279)[13]
5e	4-Cl-C_6H_4	40	88	197–199 (198)[12]
5f	4-Br-C_6H_4	45	80	273–274 (272–273)[13]

proton at 8.41 ppm. The coupling constant value of $\delta = 6.6$ Hz suggested that the molecule is thiazolo[3,2-a]pyridines with an arylmethylene moiety that adopts the Z configuration. These results were in agreement with our previous results and in contrast to the reported formation of pyranothiazoles in a similar reaction.[19]

Thiazolo[3,2-a]pyridine derivatives **1** and **5** were chemoselectively synthesized under their particular optimal reaction conditions, and the results are summarized in Table 1. To examine the effect of substituted aryl aldehyde (**3**) on the reaction rate and the overall yield, various functionalized aryl aldehydes were used. It has been found that the reaction proceeds smoothly to give thiazolo[3,2-a]pyridines



Scheme 1. Structures of compounds **1** and **5**.



Scheme 2. Mechanism to account for formation of **1** and **5**.

derivatives in good yields. However, when the aryl substituent was an electron-donating group, the yields are better. This reflects the effect of the nature of substituent on the reactivity of the arylidene derivative supposed to be formed as an intermediate.

On the other hand, conducting the reaction under these conditions without catalyst resulted in the formation of the corresponding arylidenemalononitrite derivative as the sole isolable product. Accordingly, the presence of a basic catalyst is essential. A mechanism to account for the formation of **1** and **5** was demonstrated in Scheme 2.

CONCLUSION

In conclusion, in green chemistry, it is generally recognized that the best reaction requires no solvent. This study does provide a simple, three-component, green chemoselective synthesis of thiazolo[3,2-a]pyridines with good yields and almost no reaction time.

EXPERIMENTAL

Melting points are uncorrected and were determined on a Shimadzu Gallenkamp apparatus. Infrared (IR) spectra were recorded on a Perkin-Elmer 2000 Fourier transform (FT)–IR system in KBr disk. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker DPX spectrometer operating at 400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR in dimethylsulfoxide (DMSO-d_6) as a solvent and tetramethylsilane (TMS) as internal standard; chemical shifts are reported in δ (ppm). Mass spectra were measured on VG Autospec QMS, MS, and MS 9 (AEI) spectrometers with electron impact (EI) of 70 ev.

General Procedure

A mixture of malononitrite, aryl aldehydes, and mercaptoacetic acid with piperidine (two drops) in molar ratios of 2:1:1.2 or 2:2.2:1 was fused for 30–60 s, in which a precipitate was instantly formed, which was directly crystallized from the proper solvent to afford either compounds **1a–d** or **5a–e**. Compounds **1a–d** and **5a, c–e** have been described previously, and our spectral data (IR, ^{1}H and ^{13}C-NMR) are substantially identical to those reported in literature.

Compound 5b

Mp: 242–243 °C ^{1}H NMR (400 MHz, DMSO-d6): δ = 3.33 (s, 3H), 3.57 (S, br, 2H), 3.77 (S, 3H), 4.43 (s, 1H), 6.87 (d, J = 8.8 Hz, 1H), 6.94 (d, J = 8.8 Hz, 1H), 7.12 (d, J = 8.8 Hz, 1H), 7.62 (d, J = 8.8 Hz, 1H), 8.41 (s, 1H). ^{13}C NMR (100 MHz, 1) (DMSO-d_6): δ = 38.6, 55.8, 60.2, 70.4, 114.2, 117.3, 118.5, 127.0, 127.3, 130.2, 130.4, 133.1, 134.5, 152.3, 157.6, 158.2, 159.8, 161.5. Found: C, 65.32; H, 3.86; N, 12.66; S, 7.33; Calcd. for $C_{24}H_{17}O_3N_4S$: C, 65.29; H, 3.88; N, 12.69; S, 7.26.

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