

Multicomponent Solvent-Free Cyclocondensation/Glycosylation Strategy for Thiazolo-*s*-triazine *N*-Nucleosides

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Abstract: A green protocol involving novel three-component one-pot cyclocondensation reactions of 2-amino-4-aryl-thiazoles, aromatic aldehydes and ammonium thiocyanate under solvent-free microwave irradiation (MWI) conditions expeditiously yields thiazolo-*s*-triazine nucleobases, which afford the corresponding pyrano *N*-nucleosides on I₂ promoted glycosylation with 1,2,3,4-tetra-*O*-acetyl-β-D-ribo-/xylopyranose under MWI followed by deacetylation.

Keywords: Multicomponent reactions, solvent-free, glycosylation, microwaves, thiazolo-*s*-triazines, pyrano *N*-nucleosides.

INTRODUCTION

Organic synthesis involving multicomponent reactions (MCRs) under solvent-free conditions is an ideal protocol because multistep synthesis produces considerable amounts of environmentally unfavourable wastes mainly due to a series of complex isolation procedures often involving expensive, toxic and hazardous solvents after each step. Thus, MCR strategies are perfectly suited for combinatorial library syntheses, and finding increasing use in the discovery process for new drugs and agrochemicals [1-4].

The application of microwave irradiation (MWI) as a non-conventional energy source for activation of reactions, in general and under solvent-free conditions in particular, has now gained popularity over the usual homogeneous and heterogeneous reactions [5-8], because it provides enhanced reaction rates and improved product yields along with several ecofriendly advantages in the context green chemistry which have been extended to modern drug discovery processes [9,10].

Thiazoles and *s*-triazine ring systems have a long history of applications in pharmaceutical and agrochemical industries. Glycosylation of such heterocycles that are rich in biological activity is a field of increasing interest because various glycosylated derivatives display improved biological property with respect to their nonglycosylated counterparts [11]. Thus, glycosylated thiazolo-*s*-triazines appear to be attractive scaffolds to be utilized for exploiting chemical diversity.

Considering the above valid points and our continued interest in devising new solvent-free cyclization procedures [12-14], we decided to investigate the potential of microwaves to accelerate the three-component coupling (3cc) reactions between 2-aminothiazoles, ammonium thiocyanate and aromatic aldehydes. In a recent letter, we have reported new diastereoselective synthetic protocol for thiazolo-*s*-triazine *C*-nucleosides [15]. As part of an ongoing research project on the search for new antiviral agents, we had to

develop a rapid and efficient synthesis of herein reported modified pyrano *N*-nucleosides incorporating thiazolo-*s*-triazine as the nucleobase and D-ribo-/xylopyranose as the sugar component for generating a drug-like library to screen for lead candidates.

In order to achieve our goal expeditiously, we relied upon significant advantages of multicomponent reactions under solvent-free MWI. The 3cc reactions reported herein involve 2-amino-4-arylthiazoles **1**, aromatic aldehydes **2**, and ammonium thiocyanate **3** to yield thiazolo-*s*-triazines **4** under MWI [16]. Compounds **4** on I₂ promoted glycosylation with 1,2,3,4-tetra-*O*-acetyl-β-D-ribo-/xylopyranose **5** followed by deacetylation afforded thiazolo-*s*-triazine pyrano *N*-nucleosides **7** (Scheme 1).

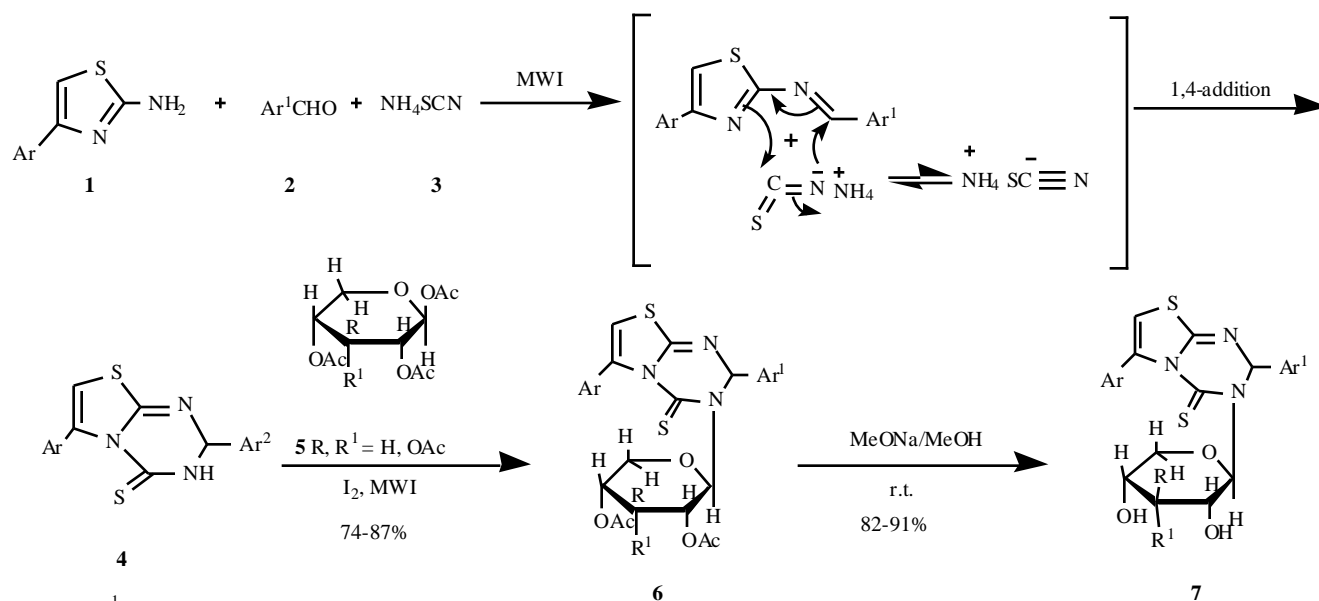
RESULTS AND DISCUSSION

The envisaged annulation method in its entirety involves intermittent MWI of an intimate mixture 2-amino-4-arylthiazoles **1**, aromatic aldehydes **2**, and ammonium thiocyanate **3** to yield (78-92 %) thiazolo-*s*-triazine nucleobases **4**. The formation of the nucleobases **4** may be tentatively rationalized by 1,4-addition of the ambident thiocyanate anion to Schiff bases resulting from **1** and **2** (Scheme 1). The nucleobases **4** expeditiously afforded β-D-ribo-/xylopyranosyl thiazolo-*s*-triazine pyrano *N*-nucleosides **7** on I₂ promoted glycosylation with 1,2,3,4-tetra-*O*-acetyl-β-D-ribo-/xylo pyranose **5** under solvent-free MWI conditions in 74-87 % yields (Table 1). Compounds **6** on deacetylation with MeONa/MeOH at room temperature furnished pyrano *N*-nucleosides **7** in 82-91 % yields.

The exclusive formation of the β-anomer **6** (Scheme 1) and not the α-anomer is mechanistically expected due to the neighbouring group participation of the 2'-*O*-acyl group and is supported by the literature precedent [17]. The β-linkage at the anomeric carbon (C-1') in all the products **6** and **7** was also confirmed by estimating the *J*_{1',2'} values, which were found to be 9.1–9.8 Hz.

For comparison purposes, the final temperature was recorded immediately after the MWI for 2 min and found to reach about 85 °C from 30 °C (room temperature). The reactions were also carried out using a thermostated oil-bath

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4a, Ar = Ar¹ = Ph

4b, Ar = Ph, Ar¹ = 4-ClC₆H₄

4c, Ar = 4-MeC₆H₄, Ar¹ = Ph

4d, Ar = 4-MeC₆H₄, Ar¹ = 4-ClC₆H₄

6	Ar	Ar ¹	R	R ¹	7	Ar	Ar ¹	R	R ¹
a	Ph	Ph	H	OAc	a	Ph	Ph	H	OH
b	Ph	Ph	OAc	H	b	Ph	Ph	OH	H
c	Ph	4-ClC ₆ H ₄	H	OAc	c	Ph	4-ClC ₆ H ₄	H	OH
d	Ph	4-ClC ₆ H ₄	OAc	H	d	Ph	4-ClC ₆ H ₄	OH	H
e	4-MeC ₆ H ₄	Ph	H	OAc	e	4-MeC ₆ H ₄	Ph	H	OH
f	4-MeC ₆ H ₄	Ph	OAc	H	f	4-MeC ₆ H ₄	Ph	OH	H
g	4-MeC ₆ H ₄	4-ClC ₆ H ₄	H	OAc	g	4-MeC ₆ H ₄	4-ClC ₆ H ₄	H	OH
h	4-MeC ₆ H ₄	4-ClC ₆ H ₄	OAc	H	h	4-MeC ₆ H ₄	4-ClC ₆ H ₄	OH	H

Scheme 1. Synthetic strategy for thiazolo-*s*-triazine pyrano *N*-nucleosides.

at the same temperature (85 °C) as for the MW-activated method but for a longer (optimized) period of time (Table 1) to ascertain whether the MW method improves the yield or simply increases conversion rates. It was found that significantly lower yields (29-42%) were obtained using oil-bath heating rather than the MW-activated method (Table 1).

In summary, we have developed a novel and simple synthetic strategy for various potentially pharmaceutically useful thiazolo-*s*-triazine pyrano *N*-nucleosides starting from readily and widely available simple substrates under solvent-free MWI conditions. The present high yielding, expeditious

and ecofriendly annulation and *N*-glycosylation may find application in library synthesis of such modified nucleobases and their pyrano *N*-nucleosides.

EXPERIMENTAL

General Procedure for the Synthesis of 2,6-Diarylthiazolo[3,2-*a*]-*s*-triazine-4-thiones 4a-d

An intimate mixture of 2-amino-4-arylthiazole **1** (5.0 mmol) and ammonium thiocyanate (6.0 mmol) was taken in a 20 mL vial and subjected to MW irradiation at 100 W for

Table 1. Solvent-Free Microwave-Activated Synthesis of Products 4-6

Product	Time		Yield (%) ^{c,d}	
	MW ^a (min)	Thermal ^b (h)	MW	Thermal
4a	10	5	86	38
4b	12	6	78	32
4c	10	6	92	36
4d	10	5	82	34
6a	8	4	80	40
6b	10	4	74	32
6c	10	3	78	35
6d	8	4	77	29
6e	8	3	81	32
6f	10	3	86	40
6g	8	4	83	37
6h	10	3	87	42

^aMicrowave irradiation time (power = 100 W).

^bTime for oil-bath heating at 85 °C.

^cYield of isolated and purified products.

^dAll compound gave C, H and N analyses within $\pm 0.35\%$ and satisfactory spectral (IR, ¹H NMR, ¹³C NMR and EIMS) data.

2 min. The reaction mixture was then thoroughly mixed outside the MW oven for 2 min and again irradiated for another 2 min. This intermittent irradiation-mixing cycle was repeated for the total irradiation time (Table 1). After completion of the reaction as indicated by TLC (hexane: AcOEt, 8:2, v/v), water 10 mL was added to the reaction mixture and stirred well. The yellow precipitate thus obtained was washed with water to give the crude product, which was recrystallized from ethanol to obtain an analytically pure sample of 4 as light yellow crystals [18].

General Procedure for the Synthesis of 2,6-Diaryl-3-(β -D-2,3,4-tri-O-acetylribo-/xylopyranosyl) thiazolo[3,2-a]-s-triazine-4-thiones 6a-h

Thoroughly mixed 2,6-diarylthiazolo[3,2-a]-s-triazine-4-thione **4** (2.0 mmol), 1,2,3,4-tetra-O-acetyl- β -D-ribo-/xylopyranose **5** (2.0 mmol) and I₂ (3.0 mmol) were taken in a 20 mL vial and subjected to intermittent MW irradiation at 100 W at the intervals of 2 min for the total irradiation time 8-10 min. To obtain analytically pure sample of compounds **6** [19], the same procedure was adopted as described for **4** [19].

General Procedure for the Synthesis of 2,6-Diaryl-3-(β -D-ribo-/xylopyranosyl)thiazolo[3,2-a]-s-triazine-4-thiones 7a-h

2,6-Diaryl-3-(β -D-2,3,4-tri-O-acetylribo-/xylopyranosyl)thiazolo[3,2-a]-s-triazine-4-thione **6** (2.8 mmol), 10 mL of dry methanol and 1.5 mL of a solution of NaOMe (prepared by dissolving 0.1 g of Na in 20 mL of dry methanol) were taken in a stoppered flask. The mixture was allowed to stand for 1 h with occasional shaking at room temperature. The

solution was neutralized by adding dil. HCl. The product thus precipitated was filtered and recrystallized from ethanol to afford analytically pure sample of compounds **7** [20].

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- [18] Data for **4a**: Pale yellow needles, mp 150-151 °C. ¹H NMR (400 MHz; DMSO-*d*₆/TMS): 9.31 (bs, 1H, NH exchanges with D₂O), 7.25-7.84 (m, 11H_{arom}), 6.70 (s, 1H, H-2). ¹³C NMR (100

- MHz; DMSO- d_6 /TMS): 185.6 (C=S), 161.5 (C=N), 153.8 (6-C), 133.6, 132.5, 131.2, 130.5, 129.8, 128.7, 128.0, 127.2, (2 \times Ph), 92.1 (7-C), 75.5 (2-C). Analysis: Found: C, 63.43; H, 4.26; N, 12.85. C₁₇H₁₃N₃S₂ requires C, 63.13; H, 4.05; N, 12.99.
- [19] *Data for 6a*: Yellowish crystals, Mp 178-179 °C. ¹H NMR (400 MHz; DMSO- d_6 /TMS): 7.26-7.84 (m, 11H_{arom}), 6.73 (s, 1H, H-2), 5.25 (d, 1H, $J_{1,2}$ =9.5 Hz, H-1'), 4.74 (dd, 1H, $J_{2,3}$ =0.8 Hz, $J_{1,2}$ =9.5 Hz, H-2'), 4.63 (dd, 1H, $J_{2,3}$ =0.8 Hz, $J_{3,4}$ =2.4 Hz, H-3'), 4.26-4.35 (m, 1H, H-4'), 4.12-4.19 (m, 2H, H-5'), 2.11, 2.22, 2.32 (s, 9H, 3 \times OAc). ¹³C NMR (100 MHz; DMSO- d_6 /TMS): 172.5 (C=O), 185.7 (C=S), 161.7 (C=N), 153.6 (6-C), 133.3, 132.4, 131.5, 130.3, 129.5, 128.0, 127.3, 126.5 (2 \times Ph), 92.3 (7-C), 79.6 (1'-C), 75.4 (2-C), 71.5 (2'-C), 69.3 (4'-C), 68.4 (3'-C), 65.5 (5'-C), 19.2 (OCOCH₃). Analysis: Found: C, 57.56; H, 4.85; N, 7.35. C₂₈H₂₇N₃O₇S₂ requires C, 57.82; H, 4.68; N, 7.22.
- [20] *Data for 7a*: Yellowish crystals, Mp 190-191 °C. ¹H NMR (400 MHz; DMSO- d_6 /TMS): 7.09-7.72 (m, 11H_{arom}), 6.18 (s, 1H, H-2), 5.30 (bs, 3H, 3 \times OH), 4.78 (d, 1H, $J_{1,2}$ =9.5 Hz, H-1'), 4.39 (dd, 1H, $J_{2,3}$ =0.6 Hz, $J_{1,2}$ =9.1 Hz, H-2'), 4.14 (dd, 1H, $J_{2,3}$ =0.6 Hz, $J_{3,4}$ =2.1 Hz, H-3'), 3.78-3.89 (m, 1H, H-4'), 3.65-3.82 (m, 2H, H-5'). ¹³C NMR (100 MHz; DMSO- d_6 /TMS): 185.9 (C=S), 161.5 (C=N), 153.5 (6-C), 133.2, 131.7, 130.4, 129.3, 128.5, 127.9, 127.1, 126.2, (2 \times Ph), 91.9 (7-C), 79.5 (1'-C), 75.2 (2-C), 71.7 (2'-C), 69.1 (4'-C), 68.5 (3'-C), 65.1 (5'-C). Analysis: Found: C, 58.31; H, 4.43; N, 9.31. C₂₂H₂₁N₃O₄S₂ requires C, 58.00; H, 4.65; N, 9.22.