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Solid-phase synthesis of 2-alkylidene-6-alkyl-imidazo[2,1-*b*]thiazole-3,5[2*H*,6*H*]-dione derivatives

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ABSTRACT

A solid-phase synthesis of 2-alkylidene-6-alkyl-imidazo[2,1-*b*]thiazole-3,5[2*H*,6*H*]-dione derivatives is reported. The desired products were obtained in good purities and yields.

The thiazolidinone core plays an important role as a widely exploited pharmacophore in medicinal chemistry.[1] Diverse biological activities such as antimicrobial,[2] protein tyrosine phosphatase inhibitory,[3] anticancer,[4] follicle-stimulating hormone (FSH) agonists,[5] anticonvulsant,[6] antipsychotic,[7] and class I phosphoinositide 3-kinases inhibitory[8] have been found to be associated with thiazolidinone derivatives. Thiazolidinone has three isomers: with a carbonyl group at positions 2, 4, and 5. 4-Thiazolidinone represents one of the most privileged thiazolidinone scaffolds in drug discovery among the thiazolidinone derivatives. Thus far the majority of the thiazolidinone derivatives reported as being biologically active are 4-thiazolidinones.[9] The exploitation of diversity around this privileged core is of high demand.

Combinatorial chemistry, together with solid-phase synthetic approaches, provides an efficient methodology for the high-speed synthesis of large compound collections. Although the synthesis of 4-thiazolidinone derivatives in solution-phase has been largely explored, conversely there is a paucity of solid-phase synthetic approaches for these structures.[10] Herein, we report an efficient solid-phase synthetic approach for the synthesis of 2-alkylidene-6-alkyl-imidazo[2,1-*b*]thiazole-3,5[2*H*,6*H*]-dione derivatives, bicyclic products of 5-alkylidene-4-thiazolidinones fused with 5′-alkyl-4-imidazolidinones.

The resin-bound 4-thiazolidinone core was synthesized by reacting resin-bound bromoacetamide with potassium thiocyanate. HF cleavage of the 4-thiazolidinone derivatives from the resin resulted in the second ring closure and thus formed the final product, 2-alkylidene-6-alkyl-imidazo[2,1-*b*]thiazole-3,5[2*H*,6*H*]-dione derivatives (Scheme 1).[11] Starting from MBHA resin **1**, a Boc-amino acid was coupled on the resin using a standard DIC/HOBt protocol to generate the resin-bound peptide **2**. After removal of the Boc group, a bromoacetic acid was coupled in order to generate the resin-bound bromoacetamide **3**. The resin-bound bromoacetamide **3** was treated with potassium thiocyanate forming the resin-bound 4-thiazolidinone **4**. A Knovenagel condensation using various aryl aldehydes catalyzed with piperidine was applied to functionalize position 5 of the resin-bound 4-thiazolidinone ring to generate the resin-bound 5-alkylidene-4-thiazolidinone **5**. Cleavage of the product was performed by 100% anhydrous HF at 0 °C for 1.5 h. Simultaneous ring closure was carried out during the cleavage step to form the second ring of 4-imidazolidinone,thus obtaining the final products of 2-alkylidene-6-alkyl-imidazo[2,1-*b*]thiazole-3,5[2*H*,6*H*]-dione derivatives **6** (Table 1).

The Knovenagel condensation between 4-thiazolidinone and aryl aldehydes in solution has been reported to be catalyzed either by acid or by base.[11] Sodium acetate/acetic acid buffer solution and piperidine were generally used as the catalyst, respectively. In our efforts to apply Knovenagel condensation on solid phase, both conditions were found satisfactory. However the two different catalytic conditions did have an effect on the generation of the final product. Under catalysis with piperidine the desired biheterocyclo 2-alkylidene-6-alkyl-imidazo[2,1-*b*]thiazole-3,5[2*H*,6*H*]-dione was found to be the major end product. However it is interesting to point out that under catalysis by sodium acetate/acetic acid, the monoheterocycle was the only product after cleavage. The second imidazolidinone ring could not form during the HF cleavage. The effect of the R^1 group on the ring fusing was also investigated. It was found that the second imidazolidinone ring did not form when R^1 was H. The monoheterocycle **7** was the only product obtained (Fig. 1). The ring fusing was also affected by the nature of aldehyde. The presence of electron-donating substituents at the *ortho* and *para* positions of benzyl ring of the aryl aldehyde significantly decreased the purities and yields of the desired products. These substituents decreased the positive charge on the carbonyl carbon atoms in aldehydes. This, in turn, reduced the activity of carbonyl group.

Side chain-protected amino acids were also applied to increase the diversity of R^1. Serine (hydroxyl), histidine (imidazole), lysine (amino), and glutamic acid (carboxyl) were selected to determine their application in generating 2-alkylidene-6-alkyl-imidazo

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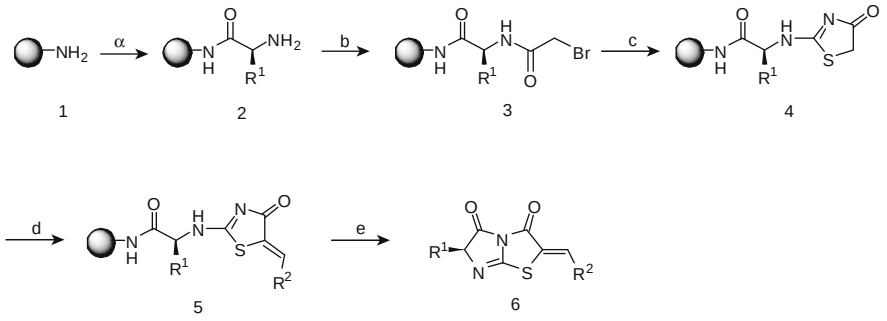
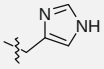


Scheme 1. Synthesis of 2-alkylidene-6-alkyl-imidazo[2,1-*b*]thiazole-3,5[2*H*,6*H*]-dione derivatives. Reagents and conditions: (a) Boc-AA-OH, DIC, HOBt; 55% TFA/DCM; (b) bromoacetic acid/DIC; (c) KSCN/DMF, 65 °C, overnight; (d) RCHO/piperidine/DMF, 65 °C, 48 h; and (e) anhydrous HF, 0 °C, 1.5 h.

Table 1
Individual products of imidazo[2,1-*b*]thiazole-3,5-dione derivatives

Entry	R^1	R^2	Purity[a] (%)	Yield[b] (%)	MW[c] (fd)
6a	$-CH_3$	$-C_6H_5$	85	73	259.0 (M+H)
6b	$-CH_3$	$-C_6H_4$(*p*-OCH_3)	50	75	289.1 (M+H)
6c	$-CH_3$	$-C_6H_4$(*m*-Cl)	75	72	293.0 (M+H)
6d	$-CH_2CH(CH_3)_2$	$-C_6H_4$(*o*-Br)	84	85	381.0 (M+H)
6e	$-CH_2C_6H_5$	$-C_6H_4$(*m*-Cl)	72	74	369.0 (M+H)
6f	$-CH_2C_6H_5$	$-C_6H_4$(*p*-CF_3)	80	87	403.1 (M+H)
6g	$-CH_2C_6H_5$	$-C_6H_4$(*o*-Br)	54	82	414.9 (M+H)
6h	$-CH_2OH$	$-C_6H_4$(*m*-CH_3)	70	74	289.1 (M+H)
6i	$-CH(CH_3)_2$	$-C_6H_5$	60	80	287.1 (M+H)
6j	$-CH(CH_3)_2$	$-C_6H_4$(*p*-CF_3)	62	80	355.1 (M+H)
6k		$-C_6H_4$(*p*-OH)	52	83	341.1 (M+H)

[a] Purity (in%) is determined by the peak area of HPLC at 214 nm.
[b] Yields (in%) are based on the weight of the crude product and are relative to the substitution of the resin (1.1 mmol/g).
[c] Determined by ESI-MS.

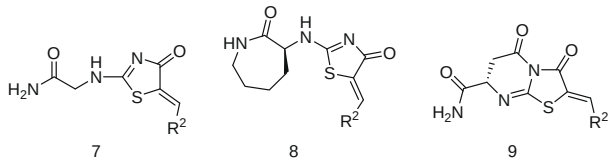


Figure 1.

[2,1-*b*]thiazole-3,5[2*H*,6*H*]-dione under these synthetic conditions. It was found that the use of lysine generated a biheterocyclo byproduct **8** that formed by attacking the carbonyl by the ε-amino of lysine (Fig. 1). The use of glutamic acid had a similar problem. The side chain carboxyl group of glutamic acid reacted preferentially during the HF cleavage, resulting in the biheterocyclo product **9**.

In summary, we present here an efficient solid-phase synthetic approach for the synthesis of biheterocyclo 2-alkylidene-6-alkyl-imidazo[2,1-*b*]thiazole-3,5[2*H*,6*H*]-dione derivatives. Various amino acids and aryl aldehydes have been used, resulting in high product yields and purities under optimized conditions. The methodology is of value for high throughput synthesis of these potentially bioactive molecules.

Acknowledgments

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11. *General procedure for the synthesis of 2-alkylidene-6-alkyl-imidazo[2,1-b] thiazole-3,5[2H,6H]-dione derivatives*: 100 mg of MBHA resin (loading: 1.1 mmol/g) was sealed within a polypropylene mesh packet.[12] Reactions were carried out in polypropylene bottles. A solution of *N*-Boc-amino acid (5 equiv, 0.1 M in DMF), HOBt (5 equiv, 0.1 M in DMF), and DIC (5 equiv, 0.1 M in DMF) was added to the reaction vessel. The reaction mixture was shaken at room temperature for 2 h, followed by washing with DMF (3 times). Upon removal of the Boc group with 55% TFA in DCM for 30 min, the resin was

washed and neutralized with 5% DIEA in DCM. The resin-bound amine was reacted with bromoacetic acid (5 equiv, 0.1 M in DCM), and DIC (5 equiv, 0.1 M in DCM) overnight. After washing with DCM (2 times), DMF (1 time), DCM (2 times), and air dried, potassium thiocyanate (10 equiv, 0.1 M in DMF) was added into the reaction vessel. The Knovenagel condensation was performed at 65 °C for 24 h, followed by DMF wash (3 times). Piperidine (10 equiv, 0.1 M in DMF) and aryl aldehyde (25 equiv, 0.25 M in DMF) were added and allowed to react at 65 °C for 24 h. This condensation was performed twice. The resin packet was then washed with DMF (3 times), DCM (3 times), and MeOH (3 times). The cleavage of the product was carried out by the treatment with 100% anhydrous HF at 0 °C for 1.5 h, followed by nitrogen gas flow to remove the HF. The product was extracted by 95% acetic acid. After lyophilization, the product of 2-alkylidene-6-alkyl-imidazo[2,1-*b*] thiazole-3, 5[2*H*,6*H*]-dione was obtained. The product was characterized by electrospray LC-MS under ESI conditions and ^{1}H and ^{13}C NMR. ESI-MS (*m*/*z*) of **6a**: 259.0 [M+H]; ^{1}H NMR of compound **6a**: (500 MHz, DMSO-d_6): δ 1.53 (3H, d, J = 7.1 Hz), 4.58 (1H, q, J = 7.1 Hz), 7.55–7.61 (3H, m), 7.72–7.74 (2H, m), 8.02 (1H, s). ^{13}C NMR (125 MHz, DMSO-d_6): δ 13.6, 56.7, 122.3, 129.5, 129.6, 130.0, 130.2, 131.2, 132.4, 135.5, 159.9, 181.7, 188.6.

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