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Synthesis of fused thiazolo[3,2-*a*]pyrimidinones: *N*-aryl-2-chloroacetamides as doubly electrophilic building blocks

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ABSTRACT

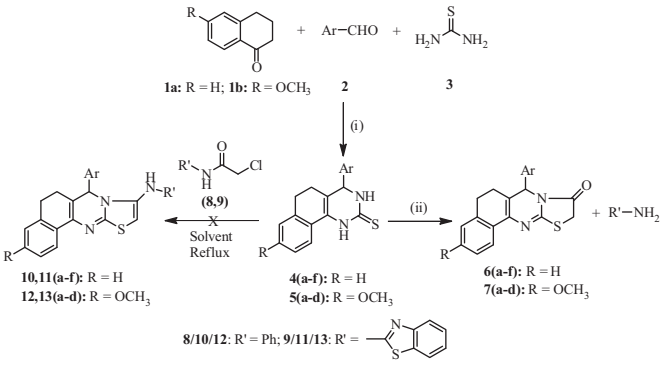
2-Chloro-*N*-phenylacetamide and *N*-(benzo[*d*]thiazol-2-yl)-2-chloroacetamide are doubly electrophilic building blocks for the formation of ring annulated thiazolo[3,2-*a*]pyrimidinone products. This synthetic route involves formation of the title compound in acceptable product yields by the elimination of the by-product, aniline/2-aminobenzothiazole. Analytical and spectral studies, as well as single crystal X-ray data on the representative compound **6c** confirmed the structure of all the reaction products.

Thiazolo[3,2-*a*]pyrimidinones have emerged as molecules with potentially useful therapeutic properties that have gained considerable attention from both synthetic and medicinal chemists due to their versatile biological activities, which include antimicrobial,[1] anticancer,[2] antioxidant,[3] antitumor,[4] anticonvulsant,[5] antiinflammatory,[6] antinociceptive,[7] analgesic, antiparkinsonian,[8] antiviral,[9] and antibiofilm properties.[10] Such compounds have also been reported as 5-HT_2 receptor antagonists,[11] and inhibitors of xanthine oxidase,[12] CDC25B phosphatase[13] enzymes, and the Bcl-2 family of proteins.[14]

Owing to these remarkably broad pharmacological properties, a variety of synthetic methods have been reported for the preparation of thiazolo[3,2-*a*]pyrimidinone derivatives involving the cyclization of 3,4-dihydropyrimidin-2(1*H*)-thiones with halogen-derived doubly electrophilic building blocks such as chloroacetic acid,[6,9,10,15] bromoacetic acid,[2,8] chloroacetyl chloride,[13] methyl chloroacetate,[16] ethyl bromoacetate,[4] and 2-haloacetamides.[17] Most of these methods utilize bases such as sodium acetate, triethylamine, and potassium hydroxide. Recently, Abbas et al.[18] have reported a regioselective isocyanide-based three-component reaction for the synthesis of thiazolo[3,2-*a*]pyrimidinone derivatives at ambient temperature.

In this Letter, we wish to report the utilization of 2-chloro-*N*-phenylacetamide and *N*-(benzo[*d*]thiazol-2-yl)-2-chloroacetamide as the source of building blocks for the ring annulation of 3,4-dihydropyrimidin-2(1*H*)-thiones to form fused thiazolo[3,2-*a*]pyrimidinone derivatives.

The general synthetic pathway to the title compounds, fused thiazolo[3,2-*a*]pyrimidinones (**6a–f** and **7a–d**), is illustrated in Scheme 1. The intermediate fused 3,4-dihydropyrimidin-2(1*H*)-thiones (**4a–f** and **5a–d**) were synthesized by the three-component condensation of a 6-substituted-1-tetralone (**1a**,**b**), an aromatic aldehyde (**2**), and thiourea (**3**) utilizing



Scheme 1. Synthesis of fused thiazolo[3,2-*a*]pyrimidinone derivatives. Reaction conditions: (i) P(4-VPH)HSO_4 (0.015 g), solvent-free, 120 °C, 10–20 min (yield: 88–94%); (ii) method A: 2-chloro-*N*-phenylacetamide (**8**), without or with Et_3N/AcONa/KOH (base), acetic acid, reflux, 4–6 h; method B: *N*-(benzo[*d*]thiazol-2-yl)-2-chloroacetamide (**9**), without or with Et_3N/AcONa/KOH (base), 1,4-dioxane, reflux, 4–6 h.

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poly(4-vinylpyridinium)hydrogen sulfate [P(4-VPH)HSO_4] as a catalyst under solvent-free conditions at 120 °C.[19] The desired products (**6a–f** and **7a–d**) were obtained in moderate yields by cyclization of **4a–f** and **5a–d** with 2-chloro-*N*-phenylacetamide (**8**)/*N*-(benzo[*d*]thiazol-2-yl)-2-chloroacetamide (**9**) and elimination of the aniline/2-aminobenzothiazole under conventional heating in acetic acid/1,4-dioxane. 2-Chloro-*N*-phenylacetamide (**8**) and *N*-(benzo[*d*]thiazol-2-yl)-2-chloroacetamide (**9**) were prepared according to literature procedures[20] by treatment of aniline and 2-aminobenzothiazole with chloroacetyl chloride doped with baked potassium carbonate in acetone/benzene under reflux.

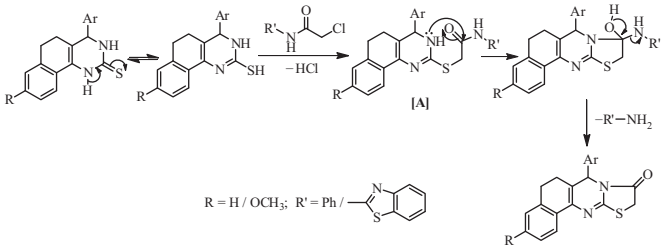
Ghorab et al.[21] have reported the synthesis of 5-aryl-8,9-dihydro-3-phenyl-5*H*-thiazolo[2,3-*b*]quinazolin-6(7*H*)-ones by the treatment of 4-aryl-1,2,3,4,7,8-hexahydro-2-thioxoquinazolin-5(6*H*)-ones with phenacyl bromide in refluxing ethanol. This prompted us to explore a similar strategy on fused 3,4-dihydropyrimidin-2(1*H*)-thiones utilizing 2-chloro-*N*-phenylacetamide instead of phenacyl bromide. Thus, we carried out a reaction utilizing equimolar quantities of 3,4,5,6-tetrahydro-4-phenylbenzo[*h*]quinazoline-2(1*H*)-thione (**4a**) and 2-chloro-*N*-phenylacetamide (**8**) in 10 mL of ethanol. As per the literature, we expected the product to be the fused thiazolo[3,2-*a*]pyrimidine (**10a**); however, the product obtained was identified as the fused thiazolo[3,2-*a*]pyrimidinone (**6a**) based on analytical and spectral data. The product **6a** was obtained in only low yield (58%) in ethanol even after 12 h at reflux. The same reaction was also carried out with *N*-(benzo[*d*]thiazol-2-yl)-2-chloroacetamide (**9**) in place of 2-chloro-*N*-phenylacetamide (**8**), and the same product (**6a**) was obtained in 53% yield. In an attempt to improve the yield of **6a**, the above reactions were carried out in a variety of solvents such as acetic acid, acetonitrile, 1,4-dioxane, and dimethylformamide at reflux temperature. The reaction conducted with 2-chloro-*N*-phenylacetamide (**8**) in acetic acid afforded a maximal yield of **6a** (69%), while the reaction with *N*-(benzo[*d*]thiazol-2-yl)-2-chloroacetamide (**9**) in 1,4-dioxane returned a yield of 66% of **6a**.

By adopting the above optimized reaction conditions, we have synthesized a series of fused thiazolo[3,2-*a*]pyrimidinone derivatives[22] (**6a–f** and **7a–d**) utilizing a variety of substituted 3,4,5,6-tetrahydro-4-arylbenzo[*h*]quinazoline-2(1*H*)-thiones (**4a–f** and **5a–d**). Several synthetic methodologies have been reported utilizing triethylamine/sodium acetate/potassium hydroxide as base.[4,10,16] Hence, we also carried out all the above reactions in the presence of triethylamine, sodium acetate, and potassium hydroxide,[23] and the results are summarized in Table 1. On comparing these results (Table 1), we deduce that AcONa and Et_3N have not shown much affect on product yield and reaction time, whereas in the presence of KOH the reactivity of **4e**, **5c**, and **5d** (possessing OH group) has decreased due to the formation of phenoxide ion which might hinder the cyclization step through the quinonoid form, and afforded the corresponding products **6e**, **7c**, and **7d** in only 5–15% yield. The structures of all the synthesized compounds were confirmed from analytical and spectral studies (IR, ^{1}H NMR, ^{13}C NMR, and mass spectral analysis) (see Supporting file), and the structure of compound **6c** was also determined from single crystal X-ray diffraction. No fused thiazolo[3,2-*a*]pyrimidines (**10–13**) were detected as products in the above reactions.

A plausible mechanism for the formation of the fused thiazolo[3,2-*a*]pyrimidinones is illustrated in Scheme 2. Reaction of 3,4,5,6-tetrahydro-4-arylbenzo[*h*]quinazoline-2-thiol with 2-chloro-*N*-phenylacetamide/*N*-(benzo[*d*]thiazol-2-yl)-2-chloroacetamide affords the intermediate thioether [**A**], which, on intramolecular cyclization followed by the elimination of aniline/2-aminobenzothiazole affords the title compounds.

Single crystal X-ray diffraction analysis of compound **6c** was carried out on crystals generated by slow evaporation in acetic acid. X-ray diffraction data were collected on a CCD detector-based diffractometer-SMART APEX from Bruker-Nonius AXS using Mo-Kα radiation (λ = 0.71073 Å) at 293 (2) K. The crystal structure was solved by direct method using SHELXS-97 program, and refinements of F^2 were performed using SHELXL-97 program. A summary of the crystallographic data, structure refinement details, supramolecular C–H···O dimer synthon, and packing diagram in the crystal structure are given in the supporting file. The ORTEP representation of the molecular structure of **6c** is shown in Figure 1.

We have developed a new synthetic route for the cyclocondensation of fused 3,4-dihydropyrimidin-2(1*H*)-thiones with 2-chloro-*N*-phenylacetamide/*N*-(benzo[*d*]thiazol-2-yl)-2-chloroacetamide to form fused thiazolo[3,2-*a*]pyrimidinone products. Here in this



Scheme 2. Plausible mechanism for the formation of fused thiazolo[3,2-*a*] pyrimidinones.

Table 1
Synthesis of fused thiazolo[3,2-*a*]pyrimidinone derivatives

Product[a]	Ar	R	Time (h)	Method A				Method B				
				Base-free	Et_3N	AcONa	KOH		Base-free	Et_3N	AcONa	KOH
				Yield[b] (%)								
6a	C_6H_5	H	5	69	68	67	62	5	66	68	62	62
6b	4-ClC_6H_4	H	4	70	72	66	67	4	68	69	65	63
6c	4-$OCH_3C_6H_4$	H	5	72	70	68	69	4	69	66	65	66
6d	3,4-$(OCH_3)_2C_6H_3$	H	4	64	61	60	63	4	65	66	63	66
6e	4-OHC_6H_4	H	6	67	63	68	10	6	62	60	60	5
6f	3-$NO_2C_6H_4$	H	6	65	65	65	60	5	62	63	60	59
7a	C_6H_5	OCH_3	6	65	64	63	62	5	63	63	65	60
7b	4-FC_6H_4	OCH_3	4	70	70	71	67	5	67	66	68	62
7c	4-OHC_6H_4	OCH_3	5	73	71	69	15	4	71	73	72	5
7d	4-OH-3-$OCH_3C_6H_3$	OCH_3	4	68	68	69	15	4	67	66	64	10

[a] Reaction conditions: method A: substituted 3,4,5,6-tetrahydro-4-arylbenzo[*h*]quinazoline-2(1*H*)-thione (1 mmol), 2-chloro-*N*-phenylacetamide (1 mmol), without or with Et_3N/AcONa/KOH (0.5 mmol), acetic acid, reflux. Method B: substituted 3,4,5,6-tetrahydro-4-arylbenzo[*h*]quinazoline-2(1*H*)-thione (1 mmol), *N*-(benzo[*d*]thiazol-2-yl)-2-chloroacetamide (1 mmol), without or with Et_3N/AcONa/KOH (0.5 mmol), 1,4-dioxane, reflux.
[b] Isolated yields.

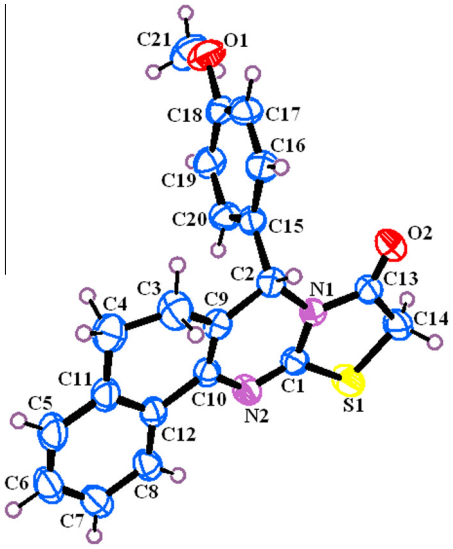


Figure 1. ORTEP representation of compound **6c**. Thermal ellipsoids are drawn at 50% probability level.

synthetic procedure, 2-chloro-*N*-phenylacetamide and *N*-(benzo[*d*]thiazol-2-yl)-2-chloroacetamide are both functioning as 1,2-dielectrophiles in a ring annulation reaction to afford thiazolo[3,2-*a*]pyrimidinones.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.11.001.

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22. *General experimental procedure (under base-free conditions):* Method A: A mixture of an appropriately substituted 3,4,5,6-tetrahydro-4-arylbenzo[*h*]quinazoline-2(1*H*)-thione (1 mmol) and 2-chloro-*N*-phenylacetamide (1 mmol) was mixed with 10 mL of acetic acid and the mixture stirred at reflux temperature for 4–6 h. After completion of the reaction (monitored by TLC), the reaction mixture was kept aside overnight. During this time, the crude thiazolo[3,2-*a*]pyrimidinone product separated out as a solid, and was filtered and quenched three times with 10 mL of cold acetic acid to remove the by-product aniline. All the compounds were purified by recrystallization from acetic acid. Method B: A mixture of an appropriately substituted 3,4,5,6-tetrahydro-4-arylbenzo[*h*]quinazoline-2(1*H*)-thione (1 mmol) and *N*-(benzo[*d*]thiazol-2-yl)-2-chloroacetamide (1 mmol) was mixed with 10 mL of 1,4-dioxane and the mixture stirred at reflux temperature for 4–6 h. The progress of the reaction was monitored by TLC, and after completion of the reaction the solid that separated out was filtered and identified as 2-aminobenzothiazole. The filtrate was poured into ice cold water, and the solid that formed was filtered, dried, and recystallised from acetic acid to afford the pure thiazolo[3,2-*a*]pyrimidinone product.
23. *General experimental procedure (in the presence of base):* Method A: To a mixture of an appropriately substituted 3,4,5,6-tetrahydro-4-arylbenzo[*h*]quinazoline-2(1*H*)-thione (1 mmol) and 2-chloro-*N*-phenylacetamide (1 mmol) in 10 mL of acetic acid, triethylamine/sodium acetate/potassium hydroxide (0.5 mmol) was added and stirred at reflux temperature for 4–6 h. After completion of the reaction (monitored by TLC), the reaction mixture was poured into ice cold water, thus the solid separated out was filtered, washed repeatedly with water, and purified by recrystallization from acetic acid. Method B: To a mixture of an appropriately substituted 3,4,5,6-tetrahydro-4-arylbenzo[*h*]quinazoline-2(1*H*)-thione (1 mmol) and *N*-(benzo[*d*]thiazol-2-yl)-2-chloroacetamide (1 mmol) in 10 mL of 1,4-dioxane, triethylamine/sodium acetate/potassium hydroxide (0.5 mmol) was added and stirred at reflux temperature for 4–6 h. The progress of the reaction was monitored by TLC. After completion of the reaction the solid that separated out was filtered and identified as 2-aminobenzothiazole. The filtrate was poured into ice cold water, and the solid that formed was filtered, dried, and recystallised from acetic acid to afford the pure thiazolo[3,2-*a*]pyrimidinone product.