Microwave-Assisted Synthesis of Substituted 2-(Benzylthio)imidazo[1,2*a*]pyrimidin-5-ones

Chai Hoon Soh and Yulin Lam*

Department of Chemistry, National University of Singapore, 3 Science Drive 3, Singapore 117543

Received November 15, 2009

A microwave-assisted solid-phase synthesis of 2-(benzylthio)imidazo[1,2*a*]pyrimidin-5-ones has been developed. Using microwave irradiation, the reaction time was significantly reduced from a few days to 80 min. A representative set of 10 2-(benzylthio)-6,7-substituted-imidazo[1,2a]pyrimidin-5-ones was prepared. These compounds were subsequently N-alkylated and formylated in good yields.

Introduction

Imidazo[1,2*a*]pyrimidin-5-ones constitute an interesting class of heterocycles that possess diverse biological activities,[1] and this structural motif is also present in phosphodiesterase inhibitors[2] and benzodiazepine receptor ligands,[1a] as well as gonadotrophin-releasing hormone antogonists.[3] The structural feature of the imidazo[1,2-*a*]pyrimidine nucleus is related to the purine and benzimidazole ring systems, and there have been reports on 2-benzylthiobenzimidazole, 8-benzylthiopurine, and other benzylthio heterocyclic analogs which have demonstrated stronger biological activity than the parent compounds.[4] The paucity of information on 2-benzylthio derivatives of imidazo[1,2*a*]pyrimidin-5-ones prompted us to initiate a study on the synthesis of this class of compounds. Since the synthesis would involve multistep reactions, which limits the synthesis of large number of compounds if performed using solution-phase methodology, a solid-phase approach would offer a good pathway to a large number of these analogues. However a major drawback of solid-phase reactions is their heterogeneous nature, which often results in a nonlinear kinetic behavior and slow reaction time.[5] Microwave applications in synthesis have allowed for reaction acceleration, while minimizing decomposition,[6] and the literature also cites an increasing number of examples of microwave-mediated heterocyclization.[7] We were thus interested to design a synthetic strategy which would provide an expedient preparation of 2-(benzylthio)imidazo[1,2*a*] pyrimidin-5(1*H*)-ones **1**. Herein, we describe a simple and efficient microwave-mediated procedure for the solid-phase synthesis (SPS) of **1**.

Results and Discussion

Solution-Phase Synthesis. Prior to the SPS, preliminary solution-phase studies were carried out to survey the requisite reaction conditions and establish the modifications for the solid-phase synthesis. For comparison purpose, we began our investigation by synthesizing 6-ethyl-2-mercaptopyrimidin-4-one **3a** (R^1= H, R^2= C_2H_5, Scheme 1) using a conventional heating procedure[4c] that involves condensing ethyl 3-oxopentanoate **2a** with thiourea in the presence of NaOEt/EtOH under reflux. The reaction was monitored by TLC and found to be completed after 24 h. The crude mixture was purified by flash chromatography (CH_2Cl_2/MeOH = 30:1) to provide **3a** in 75% yield. To facilitate the rapid synthesis of **3a**, we explored microwave irradiation (Table 1) and found that compound **3a** was obtained in the highest yield (83%) when the reaction was performed in EtOH/DMF mixture at 130 °C for 30 min. *S*-Benzylation of **3a** with benzyl bromide in EtOH under microwave irradiation[4c] for 10 min at 100, 110, and 120 °C gave 2-(benzylthio)-6-ethylpyrimidin-4-one **4** in 90%, 96%. and 90% yields, respectively. Attempts to alkylate the N3-position of **4** with chloroacetonitrile (10 equiv) did not provide the desired compound **5**. A more reactive bromoacetonitrile was used instead, and the reaction with **4** in the presence of TEA at 100 °C was monitored with TLC and found to be completed after 24 h. Alkylation occurred at two sites giving compound **5** and the O-alkylated product

Scheme 1. Solution-Phase Synthesis

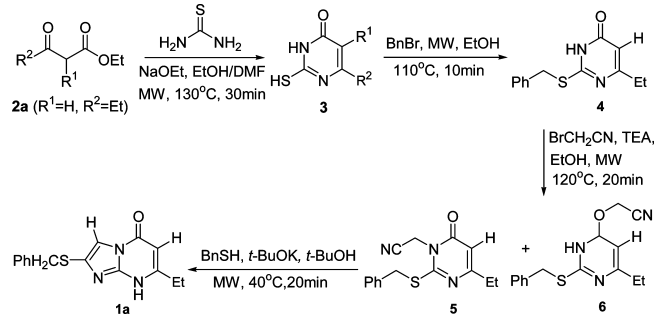


Table 1. Microwave-Assisted Synthesis of **3**

entry	solvent	temp (°C)	time (min)	yield (%)
1	EtOH	120	10	10
2	EtOH	120	20	32
3	EtOH/DMF[a]	130	10	46
4	EtOH/DMF[a]	130	20	69
5	EtOH/DMF[a]	130	30	83
6	EtOH/DMF[a]	140	10	75
8	EtOH/DMF[a]	140	20	70

[a] EtOH/DMF = 10:1.

* To whom correspondence should be addressed. E-mail: chmlamyl@nus.edu.sg. Fax: (65)-6779-1691.

10.1021/cc900176x
Published on Web 02/04/2010

Table 2. Microwave-Assisted Synthesis of **5**[a]

entry	solvent	temp (°C)	time (min)	yield[b] (%)	**5/6**
1	EtOH	100	10	16	1:5
2	EtOH	100	20	50	1:1
3	EtOH	120	10	43	1:1
4	EtOH	120	15	70	2:1
5	EtOH	120	20	74	3:1
6	EtOH	120	30	70	3:1
7	EtOH/DMF	130	20	69	2:1
8	EtOH	80	20	35	1:2
9	EtOH	70	20		

[a] TEA as base. [b] Yield of compound **5**.

Table 3. Conventional and Microwave-Assisted Synthesis of **1a**[a]

entry	base/thiol[b]	method	temp (°C)	time	yield[c] (%)
1	4.5:5	heat	40[b]	18 h	41
2	1:1	heat	40[b]	18 h	10
3	2:2	heat	40[b]	18 h	21
4	9:10	heat	40[b]	18 h	40
5	4.5:5	heat	60[b]	18 h	33
6	4.5:5	MW	60	10 min	
7	4.5:5	MW	50	10 min	12
8	4.5:5	MW	40	20 min	61
9	4.5:5	MW	40	30 min	59

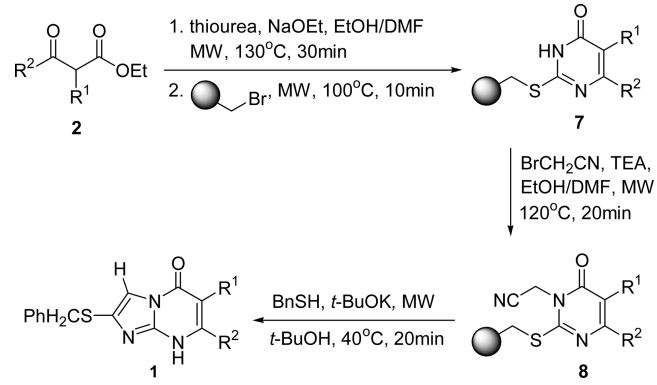
[a] *t*BuOH as solvent. [b] The equivalents of base and thiol used were calculated with respect to compound **5**. [c] Temperature of water bath.

6 in 60% and 39% yields, respectively. When the same reaction was heated in the microwave at 120 °C (Table 2, entry 5), complete conversion was observed within 20 min and compounds **5** and **6** was obtained in 74% and 25% yields, respectively. Attempts to further increase the proportion of **5** by varying the base (DBU, NaOEt, and TEA/KI (cat)) did not result in any improvement in the regioselectivity.

Synthesis of 2-(benzylthio)-7-ethylimidazo[1,2-*a*]pyrimidin-5(8*H*)-one **1a** was first carried out by adapting a reported conventional heating procedure.[8] The reaction between **5** and benzyl thiol at 40 °C for 18 h with *t*-butanol as solvent and potassium *tert*-butoxide as a base resulted in the formation of the **1a** in 41% yield (Table 3, entry 1). Varying the base: benzyl thiol ratio did not increase the yield of **1a** (Table 3, entries 1−4). However when the reaction was carried out under microwave irradiation at 40 °C, it was found to be completed after 20 min and **1a** obtained in 61% yield.

Solid-Phase Synthesis. With the solution-phase pathway evaluated, we proceeded to synthesize **1** via microwave-assisted SPS. To explore a one-pot synthesis of resin **7** (Scheme 2) from β-keto ester **2**, thiourea (3 equiv) was treated with an equal amount of **2** to provide 5,6-disubstituted-2-mercaptopyrimidin-4-one **3**, which was immediately reacted under microwave-irradiation with bromomethyl resin at 100 °C for 10 min to yield resin **7**, whose formation was amenable to KBr FTIR monitoring for the appearance of a strong C═N stretch at 1670 cm^{-1}. Resin **7** was then treated with bromoacetonitrile (10 equiv) in the presence of TEA (10 equiv) in a DMF/ethanol mixture to afford resin **8**, which according to FTIR analysis showed a CN stretch at 2220−2260 cm^{-1}. Subsequent reaction of resin **8** with benzyl thiol and *t*-butoxide as base under microwave irradiation at 40 °C resulted in self-cyclization with concomitant cleavage of the solid-support to give product **1**. To illustrate the generality of this microwave-assisted reaction, various β-keto

Scheme 2. SPS of Substituted 2-(Benzylthio)Imidazo[1,2-*a*]pyrimidin-5-ones



esters were used to generate a representative set of 10 members of compound **1** in 35−46% overall yield (purities of >95% by NMR), indicating an average yield of at least 70% for each step of the reaction (Figure 1).

To increase the diversity of compound **1**, we explored the *N*-alkylation of **1** using alkyl, benzyl, and allyl bromides and sodium hydride as a base. Generally, the reaction proceeded readily at 0 °C and provided both the N1- and N8-alkylated regioisomers, **9i** and **9ii**, respectively, whose assignments were confirmed by NOESY NMR experiments. For example in the NOESY spectrum of compound **9ai**, a clear interaction between the 1-benzylic protons (−NC**H**$_2$Ph) and 2-thiol benzylic protons (−SC**H**$_2$Ph) protons were observed, while **9aii** showed a clear interaction between the 7-methyl protons (-C**H**$_3$) and the 8-benzylic protons (-NC**H**$_2$Ph). Interestingly, the alkylation preferably occurred on the N8-position with the exception of cyclopentyl bromide where only the formation of the N1 isomer was observed (Figure 1) and confirmed using X-ray crystallography. This may be attributed to the bulkiness of the *sec*-bromide, which also provided no product when the reaction was carried out at 0 °C. Hence with cyclopentyl bromide, the reaction mixture was heated to 80 °C, and the reaction was found to be completed within 3 h.

Following N-alkylation, we examined the formylation of compounds **1** and **9** under Vilsmeier condition ($POCl_3$/DMF, 100 °C).[3a] When the reaction was carried out with compound **9ai** via conventional heating, the reaction was found to be completed after 5 h and formylation was observed to occur on the C6 position to give compound **10ai** in 67% yield. However under microwave irradiation, complete conversion was observed after 10 min and **10ai** was obtained in 82% yield (Figure 1). When the microwave-assisted formylation was applied to compound **1e** where the C6 proton is absent, formylation was observed to occur on the C3 position to afford **11ei** in 90% yield. This suggests that the C6 position is a more reactive site for electrophilic aromatic substitution.

In summary, we have described the first example of a SPS route to 2-(benzylthio)imidazo[1,2a] pyrimidin-5(1H)-ones. Using microwave irradiation, we have shown that the total

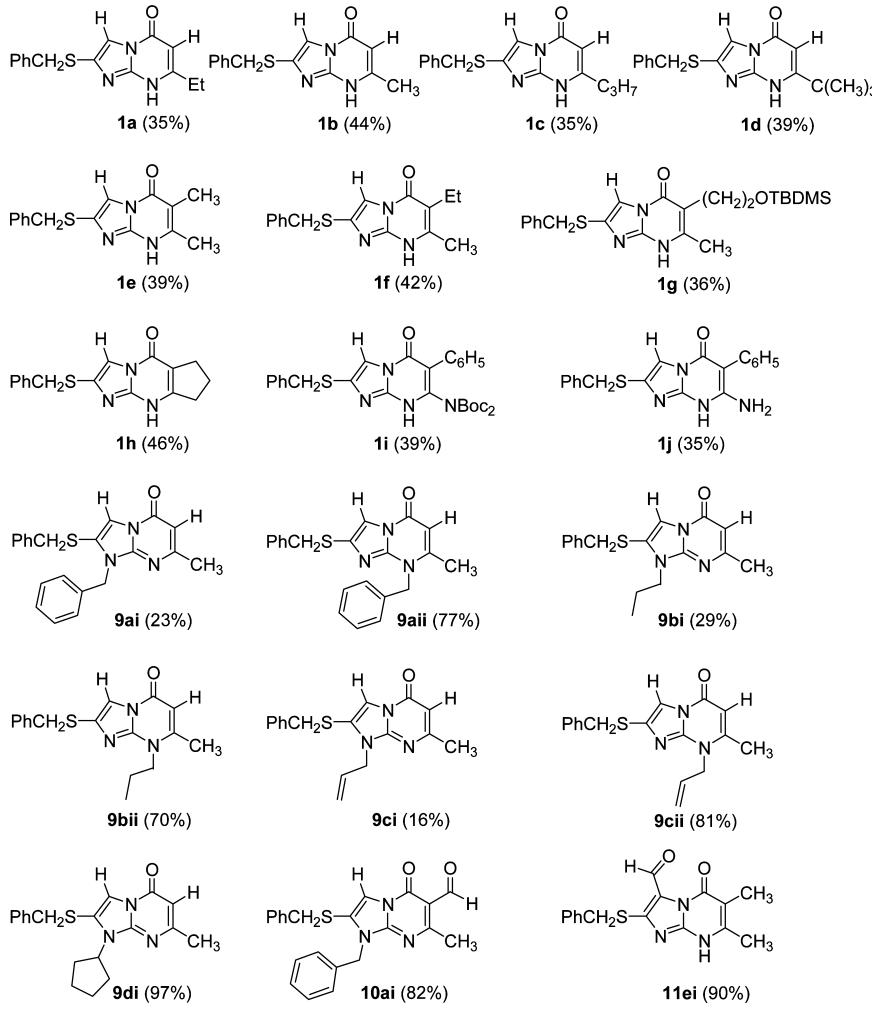


Figure 1. Library of substituted 2-(benzylthio)imidazo[1,2-*a*]pyrimidin-5-ones. For compound **1**, the yields reported refer to the overall yield, which is based on the bromomethyl resin loading. For compounds **9**−**11**, the yields reported refer to the yields of the alkylation or formylation reactions.

reaction time for the SPS could be shortened from a couple of days to 80 min.

Experimental Section

General Procedures. Bromomethyl resin was purchased from Tianjin Nankai Hecheng Science and Technology Co. (100−200 mesh, 1.5 mmol/g, 1% divinylbenzene cross-linking). All other chemical reagents were purchased from Aldrich, Merck, Lancaster, or Fluka and were used without further purification. The microwave-assisted reactions were performed using the Biotage Initiator microwave synthesizer at 300 W. Analytical TLC was carried out on precoated plates (Merck silica gel 60, F254) and visualized with UV light or stained with ninhydrin. Flash column chromatograph was performed with silica (Merck, 70−230 mesh).

^{1}H NMR and ^{13}C NMR spectra were measured at 298 K on a Bruker ACF 300 or AMX 500 Fourier Transform spectrometer. Chemical shifts were reported in δ (ppm), relative to the residual undeuterated solvent which was used an internal reference. The signals observed were described as s (singlet), d (doublet), t (triplet), and m (multiplet). The number of protons (n) for a given resonance was indicated as nH. All Infrared (IR) spectra were recorded on a Bio-Rad FTS 165 spectrometer. Mass spectra were performed on Finnigan MAT 95/XL-T spectrometer under electron impact (EI) or electrospray ionization (ESI) techniques.

Synthesis of 2-(Benzylthio)-6-ethylpyrimidin-4(3*H*)-one 4. Thiourea (2.2 mmol, 1.1 equiv) was added to a mixture of ethyl 3-oxopentanoate (2 mmol, 1 equiv.) and 21 wt % NaOEt in EtOH (8 mmol, 4 equiv.) in EtOH/DMF (10:1, 20 mL). The reaction mixture was heated under microwave irradiation to 130 °C for 30 min. Benzyl bromide (2.4 mmol, 1.2 equiv) was then added, and the reaction mixture was heated under microwave irradiation to 110 °C for another 10 min. The crude mixture was purified by flash chromatography (eluent MeOH/CH_2Cl_2 = 1:30) to provide **4** in 79% overall yield. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.41−7.39 (m, 2H, ArH), 7.28−7.25(m, 3H, Ar*H*), 5.96(s, 1H, −C*H*), 4.44(s, 2H,-CH_2Ph), 2.53(q, 2H, −CH_2CH$_3$, J = 7.7 Hz), 1.22 (t, 3H, −CH$_2$CH_3, J = 7.7 Hz). HRMS (ESI, M + H) Calcd for $C_{13}H_{14}N_2OS$: 246.0827; found 246.0827.

Synthesis of 2-(2-(Benzylthio)-4-ethyl-6-oxopyrimidin-1(6*H*)-yl) acetonitrile 5. Bromoacetonitrile (20 mmol, 10 equiv) was added to a reaction mixture of TEA (20 mmol, 10 equiv) and 2-(benzylthio)-6-ethylpyrimidin-4(3*H*)-one, **4** (2 mmol, 1equiv), using EtOH as solvent. The reaction mixture was heated at 120 °C using microwave irradiation, monitored with TLC, and was found to be completed after

20 min. The crude mixture was purified by flash chromatography (eluent EA/Hex = 1:10) to obtain **5** in 74% yield. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.47−7.44 (m, 2H, ArH), 7.35−7.25 (m, 3H, Ar*H*), 6.67 (s, 1H, −C*H*), 5.27 (s, 2H, −CH_2CN), 4.46(s, 2H, −CH_2Ph), 2.66 (q, 2H, −CH_2CH$_3$, J = 7.7 Hz), 1.19 (t, 3H, −CH$_2$CH_3, J = 7.7 Hz). HRMS (ESI, M + H) Calcd for $C_{15}H_{15}N_3NaOS$: 308.0834; found 308.0834.

Synthesis of 2-(Benzylthio)-7-ethylimidazo[1,2*a*]pyrimidin-5(1*H*)-one 1a. Benzyl thiol (5 mmol, 5 equiv) was added into a stirring solution of potassium *tert*-butoxide (4.5 mmol, 4.5 equiv) in *t*-butanol (10 mL). After it was stirred for 30 min, compound **5** (1 mmol, 1 equiv) was added; the reaction mixture was heated under microwave irradiation to 40 °C, and the reaction was found to be completed after 20 min (monitored by TLC). The crude mixture was purified by flash chromatography (eluent MeOH/CH_2Cl_2 = 1:30) to provide **1a** in 61% yield. ^{1}H NMR (300 MHz, CD_2Cl_2): δ 7.37(s, 1H, −C*H*), 7.25−7.20 (m, 5H, Ar*H*), 5.65(s, 1H, −C*H*), 4.07 (s, 2H, −CH_2), 2.81(q, 2H, −CH_2CH$_3$, J = 7.6 Hz), 1.28 (t, 3H, −CH$_2$CH_3, J = 7.7 Hz). ^{13}C NMR (75 MHz, CD_2Cl_2): δ 142.7, 137.5, 134.9 (×2), 134.5 (×2), 133.7,131.5, 123.2, 123.1, 118.2, 104.4, 50.5, 46.8, 28.3. HRMS (ESI, M + H) Calcd for $C_{15}H_{15}N_3NaOS$: 308.0834; found 308.0834.

General Procedure for Preparation of Resin 7. Thiourea (3 equiv) was added to the respective β-keto-ester (3 equiv) and 21% v/v NaOEt in EtOH (12 equiv) in EtOH/DMF (10/1, 20 mL). The reaction mixture was heated microwave irradiation to 130 °C for 30 min. Bromomethyl resin (loading 1.5 mmol/g) was swollen in DMF for 30 min and then added to the reaction mixture. The reaction was heated under microwave irradiation at 110 °C for another 10 min. After which, the mixture was filtered, and the resin was washed sequentially with DMF (20 mL × 2), H_2O (20 mL × 2), EtOH (20 mL × 2), CH_2Cl_2 (20 mL × 2), and ether (20 mL × 2) and dried overnight in a vacuum oven at 40 °C to afford resin **7**.

General Procedure for Preparation of Resin 8. Resin **7** was swollen in DMF for 30 min. Thereafter, a solution of bromoacetonitrile (10 equiv) and TEA (10 equiv) in ethanol (30 mL) was added. The reaction mixture was heated under microwave irradiation at 120 °C for 20 min. The resin was then filtered, washed with DMF (20 mL × 2), EtOH (20 mL × 2), and CH_2Cl_2 (20 mL × 2), and dried overnight in a vacuum oven at 40 °C to afford resin **8**.

General Procedure for Preparation of 2-(Benzylthio)-imidazo[1,2*a*]pyrimidin-5(8*H*)-one 1. Benzyl thiol (5 equiv) was first added into a stirring solution of potassium tert-butoxide (4.5 equiv) in t-butanol (10 mL) and stirred for 30 min. Resin **8** was swollen in THF for 30 min and added to the reaction mixture. The reaction mixture was heated under microwave irradiation to 40 °C for 20 min. The resin was filtered and washed with methanol (20 mL × 2) and CH_2Cl_2 (20 mL × 2). The washings were combined with the filtrate, concentrated to dryness and purified by column chromatography.

2-(Benzylthio)-7-methylimidazo[1,2-*a*]pyrimidin-5(1*H*)-one 1b. ^{1}H NMR (300 MHz, DMSO-d_6): δ 13.10 (bs, 1H, N*H*), 7.79 (s, 1H, −C*H*), 7.33−7.21 (m, 5H, Ar*H*), 5.74 (s, 1H, −C*H*), 4.65 (s, 2H, −CH_2−), 2.34 (s, 3H, −CH_3). ^{13}C NMR (75 MHz, DMSO-d_6): δ 156.7, 153.4, 143.5, 138.5, 130.9 (×2), 128.4 (×2), 128.3 (×2), 112.4, 95.2, 59.6, 19.0. HRMS (ESI, M + H) Calcd for $C_{14}H_{13}N_3OS$: 272.0858; found 272.0857.

2-(Benzylthio)-7-propylimidazo[1,2*a*]pyrimidin-5(1*H*)-one 1c. ^{1}H NMR (300 MHz, CD_3OD): δ 7.31 (s, 1H,-C*H*), 7.26−7.25 (m, 5H, Ar*H*), 5.71 (s, 1H, −CH−), 4.13 (s, 2H, −CH_2−), 2.58 (t, 2H, −CH_2CH$_2$CH$_3$, J = 8.0 Hz), 1.73 (q, 2H, −CH$_2$CH_2CH$_3$, J = 7.7 Hz), 1.00 (t, 3H, −CH$_2$CH$_2$CH_3, J = 7.7 Hz). ^{13}C NMR (75 MHz, DMSO-d_6): δ 156.4, 143.7, 137.8, 129.0 (×2), 128.6 (×2) 128.4, 127.0, 106.8, 98.2, 94.4, 36.6, 34.8, 21.3, 13.3. HRMS(ESI, M + H) Calcd for $C_{16}H_{17}N_3NaOS$: 322.099; found 322.0985.

2-(Benzylthio)-7-*tert*-butylimidazo[1,2-*a*]pyrimidin-5(1*H*)-one 1d. ^{1}H NMR (300 MHz, CD_3OD): δ 7.30 (s, 1H, −C*H*), 7.26−7.22 (m, 5H, Ar*H*), 5.91 (s, 1H, −CH−), 4.14 (s, 2H, −CH_2−), 1.33 (s, 9H, −C(CH_3)$_3$) ^{13}C NMR (75 MHz, DMSO-d_6): δ 171.8, 166.8, 161.4, 160.5, 136.5, 128.8, 128.4 (×2), 127.3 (×2), 103.3, 45.1, 36.8, 35.4, 28.3 (×3). HRMS (ESI, M + H) Calcd for $C_{17}H_{19}N_3NaOS$: 336.1147; found 336.1141.

2-(Benzylthio)-6,7-dimethylimidazo[1,2-*a*]pyrimidin-5(1*H*)-one 1e. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.33−7.28 (m, 6H, Ar*H* + −C*H*), 4.20 (s, 2H, −CH_2−), 2.29 (s, 3H, −CH_3), 1.93 (s, 3H, −CH_3). ^{13}C NMR (75 MHz, DMSO-d_6): δ 156.8, 147.7, 142.8, 138.0, 134.5, 128.6 (×2), 128.3 (×2), 127.0, 106.3, 100.6, 38.9, 38.7, 36.6. HRMS (ESI, M + H) Calcd for $C_{15}H_{17}N_3OS$: 286.1014; found 286.1015.

2-(Benzylthio)-6-ethyl-7-methylimidazo[1,2-*a*]pyrimidin-5(1*H*)-one 1f. ^{1}H NMR (300 MHz, CD_3OD): δ 7.26−7.20 (m, 6H, Ar*H* + −C*H*), 4.12 (s, 2H, PhCH_2−), 2.55 (q, 2H, −CH_2CH$_3$, J = 7.3 Hz), 2.40 (s, 3H, −CH_3), 1.08 (t, 3H, −CH$_2$CH_3, J = 7.3 Hz). ^{13}C NMR (75 MHz, CD_3OD): δ 156.5, 146.9, 142.6, 138.0, 128.6 (×2), 128.3 (×2), 128.1, 127.0, 107.1, 106.3, 36.5, 18.0, 17.0, 13.4. HRMS (ESI, M + H) Calcd $C_{16}H_{18}N_3OS$: 300.1171; found 300.1171.

2-(Benzylthio)-6-(2-(*tert*-butyldimethylsilyloxy)ethyl)-7-methylimidazo[1,2-*a*]pyrimidin-5(1*H*)-one 1g. ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.62 (bs, 1H, −NH), 7.35 (s, 1H, −CH−), 7.30−7.28 (m, 5H, ArH), 4.20 (s, 2H, −CH$_2$−), 3.65 (t, 2H, −CH$_2$CH$_2$−, J = 6.3 Hz), 2.62 (t, 2H, −CH$_2$CH$_2$−, J = 6.6 Hz), 2.34 (s, 3H, −CH$_3$), 0.81 (s, 9H, −SiC(CH$_3$)$_3$), −0.06 (s, 6H, −Si(CH$_3$)$_2$). ^{13}C NMR (75 MHz, DMSO-d_6): δ 156.6, 142.7, 142.6, 137.9, 128.6 (×2), 128.3 (×2), 127.0, 106.5, 102.2, 61.2, 36.5, 38.7, 28.3, 25.7, 17.9, 17.6 (×2), −5.5 (×3). HRMS (ESI, M + H) Calcd for $C_{22}H_{32}N_3O_2SSi$: 430.1984; found 430.1984.

2-(Benzylthio)-6,7-cyclopenyllimidazo[1,2-*a*]pyrimidin-5(1*H*)-one 1h. ^{1}H NMR (500 MHz, DMSO-d_6): δ 12.8−12.9, (bs, 1H, −N*H*), 7.29−7.22 (m, 5H, −Ar*H*−), 4.19 (s, 2H, −CH_2−), 2.87−2.84 (m, 2H, −CH_2CH$_2$CH$_2$−), 2.66−2.63 (m, 2H, −CH$_2$CH_2−), 2.07−2.01 (m, 2H, −CH$_2$CH_2CH$_2$−). ^{13}C NMR (75 MHz, DMSO-d_6): δ 154.4, 144.4, 137.7, 133.6, 128.6 (×2), 128.3 (×2), 127.0, 107.5, 106.7, 37.0, 32.1, 26.5, 21.6 (×2). HRMS (ESI, M − H) Calcd for $C_{16}H_{14}N_3OS$: 296.0858; found 296.0844.

7-(*N*,*N*-Di-*tert*-butoxycarbonyl)-2-(benzylthio)-6-phenylimidazo[1,2-*a*]pyrimidin-5(1*H*)-one 1i. ^{1}H NMR (300 MHz, CD_3OD): δ 7.46 (s, 1H, −C*H*), 7.36−7.24 (m, 10H, Ar*H*), 4.18 (s, 2H, −CH_2−), 1.33 (s, 18H, −2Boc). ^{13}C NMR (75 MHz, DMSO-d_6): δ 154.0, 151.9, 149.7, 144.2, 139.7, 136.5, 131.6, 130.8, 130.4, 129.7 (×2), 129.6, 129.5, 129.2,

128.8, 112.9, 112.6, 97.9, 87.4, 85.9, 78.1, 77.7 (×2), 77.3, 40.6, 40.1, 35.1, 28.7, 28.4. HRMS (ESI, M + H) Calcd for $C_{29}H_{32}N_4OS$: 54.2093; found 548.091.

7-Amino-2-(benzylthio)-6-phenylimidazo[1,2-*a*]pyrimidin-5(1*H*)-one 1j. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.38−7.24(m, 11H, −Ar*H*), 4.17(s, 2H, −CH_2−), 1.60(s, 2H, −NH_2). ^{13}C NMR (75 MHz, DMSO-d_6): δ 157.9, 144.9, 137.2, 134.1, 131.2, 131.0, 130.7 (×2), 129.4, 128.8 (×2), 128.5 (×2), 128.4, 127.3 (×2), 126.4, 110.4, 90.4. HRMS (ESI, M + H) Calcd for $C_{19}H_{16}N_4OS$: 348.1045; found 348.1044.

General Procedure for Alkylation of N1- and N8-Substituted 2-(Benzylthio)Imidazo[1,2*a*]pyrimidin-5(8*H*)-one 9i and 9ii. Sodium hydride (10 mmol, 2 equiv) was dissolved in DMF (5 mL) and added dropwise at 0 °C to a mixture of the respective bromide (7.5 mmol, 1.5 equiv) and compound **1** (5 mmol, 1equiv) in DMF. The reaction was monitored by TLC and found to be completed after 3hrs. The crude mixture was purified by flash chromatography (eluent EA/Hex = 1:8) to yield 2 products, N1-substituted-2-(benzylthio)imidazo[1,2*a*]pyrimidin-5(8*H*)-one **9i** and N8-substituted-2-(benzylthio)imidazo[1,2*a*]pyrimidin-5(8*H*)-one **9ii**.

1-Benzyl-2-(benzylthio)-7-methylimidazo[1,2-*a*]pyrimidin-5(1*H*)-one 9ai. ^{1}H NMR (300 MHz, acetone-d_6): δ 7.41 (s, 1H, −C*H*), 7.34−7.15 (m, 10H, −Ar*H*−), 5.72 (s, 1H, −C*H*), 5.24 (s, 2H, −CH_2N−), 3.88 (s, 2H, −CH_2S−), 2.03 (t, 3H, −CH_3). ^{13}C NMR (75 MHz, CD_3OD): δ 153.7, 139.1, 137.6, 136.8, 130.0, 129.8, 129.6, 129.3, 128.6, 128.0, 127.4, 113.0, 110.6, 99.3, 98.6, 50.7, 46.7, 41.7, 38.7, 24.6, 19.3. HRMS (ESI, M + H) Calcd for $C_{21}H_{19}N_3NaOS$: 384.1147; found 384.1141.

8-Benzyl-2-(benzylthio)-7-methylimidazo[1,2-*a*]pyrimidin-5(8*H*)-one 9aii. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41 (s, 1H, −C*H*), 7.36−7.15 (m, 10H, −Ar*H*), 5.74 (s, 1H, −C*H*), 5.62 (s, 2H, −CH_2N−), 4.18 (s, 2H, −CH_2S−), 2.34 (s, 3H, −CH_3). ^{13}C NMR (75 MHz, acetone-d_6): δ 130.6, 130.4, 130.3 (×2), 130.1, 129.8, 129.4, 129.2, 129.1, 128.4, 128.1, 128.0, 113.6, 110.0, 99.6, 99.0, 50.8, 45.9, 42.2, 38.5, 19.9. HRMS (ESI, M + H) Calcd for $C_{21}H_{19}N_3NaOS$: 384.1147; found 384.1141.

2-(Benzylthio)-7-methyl-1-propylimidazo[1,2-*a*]pyrimidin-5(1*H*)-one 9bi. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.31 (s, 1H, −C*H*), 7.30−7.17 (m, 5H, −Ar*H*−), 5.89 (s, 1H, −C*H*), 3.98 (s, 2H, −CH_2S−), 3.95 (t, 2H, $CH_3CH_2CH_2$N−, J = 7.6 Hz), 2.38 (s, 3H, −CH_3), 1.76 (q, 2H, $CH_3CH_2CH_2$N−, J = 7.6 Hz), 0.92 (t, $CH_3CH_2CH_2$N−, J = 7.6 Hz). ^{13}C NMR (75 MHz, DMSO-d_6): δ 163.8, 155.6, 145.4, 136.8, 128.9 (×2), 128.5 (×2), 127.5, 124.0, 110.5, 109.2, 97.5, 43.6, 24.2, 21.7, 10.8. HRMS (ESI, M + H) Calcd for $C_{17}H_{20}N_3OS$: 314.1327; found 314.1326.

2-(Benzylthio)-7-methyl-8-propylimidazo[1,2-*a*]pyrimidin-5(8*H*)-one 9bii. ^{1}H NMR (500 MHz, acetone-d_6): δ 7.39−7.21 (m, 6H, Ar*H* + −C*H*), 5.65 (s, 1H, −C*H*−), 4.28−4.25 (m, 4H, PhCH_2− + −C$H_2$$CH_2CH_3$), 2.52 (s, 3H, −C$H_3$), 1.93−1.85 (m, 2H, −$CH_2CH_2CH_3$), 1.03 (t, 3H, −$CH_2CH_2CH_3$, J = 4.3 Hz) ^{13}C NMR (75 MHz, DMSO-d_6): δ 165.4, 157.5, 148.5, 138.6, 130.6, 130.1 (×2), 129.2, 125.6, 112.8, 99.3, 45.5, 42.4, 25.1, 25.0, 23.7, 11.9. HRMS (ESI, M + H) Calcd for $C_{17}H_{20}N_3OS$: 314.1327; found 314.1327.

1-Allyl-2-(benzylthio)-7-methylimidazo[1,2-*a*]pyrimidin-5(1*H*)-one 9ci. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.46 (s, 1H, −C*H*), 7.29−7.26 (m, 3H, −Ar*H*), 7.15−7.13 (m, 2H, −Ar*H*), 5.95−5.88 (m, 2H, −C*H* + −C*H*=CH_2−), 5.25 (d, 1H, −CH=CH_2), 5.12 (d, 1H, −CH=CH_2), 4.77−4.76 (m, 2H, −CH_2CH=CH_2), 3.95 (s, 2H, −CH_2−), 2.41 (s, 3H, −CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.0, 155.8, 144.9, 135.7, 131.1, 128.9, 128.7, 128.4, 128.2, 124.8, 118.8, 112.5, 99.6, 45.3, 41.5, 29.6, 23.2. HRMS (ESI, M + H) Calcd for $C_{17}H_{17}N_3OS$: 312.1171; found 312.1170.

8-Allyl-2-(benzylthio)-7-methylimidazo[1,2-*a*]pyrimidin-5(8*H*)-one 9cii. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.25−7.18 (m, 7H, −Ar*H*), 6.02−5.95 (m, 1H, −C*H*=CH_2), 5.72 (s, 1H, −C*H*), 5.30 (d, 1H, −CH=CH_2), 5.12 (d, 1H, −CH=CH_2), 5.00−4.99 (m, 2H, −CH_2CH=CH_2), 4.20 (s, 2H, −CH_2), 2.41 (s, 3H, −CH_3). ^{13}C NMR (75 MHz, acetone-d_6): δ 130.6 (×2), 130.4 (×2), 130.1, 129.8, 129.2, 128.5, 112.8, 99.3, 49.5, 45.5, 42.4, 38.7, 23.1, 19.7, 11.9. HRMS (ESI, M + H) Calcd for $C_{17}H_{17}N_3OS$: 312.1171; found 312.1169.

2-(Benzylthio)-1-cyclopentyl-7-methylimidazo[1,2-*a*]pyrimidin-5(1*H*)-one 9di. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.40−7.26 (m, 6H, −Ar*H*), 5.93 (s, 1H, −C*H*−), 4.11 (s, 2H, −CH_2−), 2.62 (s, 3H, −CH_3), 2.22 (s, 4H, −C_5H_9), 2.04 (s, 3H, −C_5H_9), 1.80 (s, 2H, −C_5H_9). ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.4, 153.6, 141.4, 134.4, 129.2, 129.0, 128.8, 128.7, 127.3, 111.8, 100.2, 59.4, 41.4, 30.9, 30.0, 29.7, 25.2, 25.0, 20.8. HRMS (ESI, M + H) Calcd for $C_{19}H_{21}N_3NaOS$: 362.1303; found 362.1301.

Synthesis of 2-(Benzylthio)-7-methyl-5-oxo-1,5-dihydroimidazo[1,2-*a*]pyrimidine-6-carbaldehyde 10ai. Phosphoryl trichloride (20 mmol, 10 equiv) was added to a solution of compound **9ai** (2 mmol, 1 equiv) in DMF (10 mL). The reaction mixture was heated under microwave irradiation at 100 °C, monitored, and found to be completed in 10 min. The product was isolated with flash chromatography using EA/Hex 1:5 as eluent and **10ai** was obtained in 82% yield. ^{1}H NMR (300 MHz, CD_3OD): δ 10.29 (bs, 1H, −C*H*O), 7.59 (s, 1H, −C*H*−), 7.36−7.06 (m, 10H, Ar*H*), 5.30 (s, 2H, −CH_2SPh), 3.77 (s, 2H, −CH_2NPh), 2.70 (s, 3H, −CH_3). ^{13}C NMR (75 MHz, DMSO-d_6): δ 188.1, 168.5, 157.7, 146.2, 136.3 (×2), 135.5, 129.0, 128.7 (×2), 128.5 (×2), 127.9 (×2), 127.7, 127.2 (×2), 125.4, 112.6, 107.1, 45.4, 24.7. HRMS (ESI, M + H) Calcd $C_{22}H_{20}N_3O_2S$: 390.1276; found 390.1276.

Synthesis of 2-(Benzylthio)-6,7-dimethyl-5-oxo-5,8-dihydroimidazo[1,2*a*]pyrimidine-3-carbaldehyde 11ei. Phosphoryl trichloride (20 mmol, 10 equiv) was added to a solution of compound **1e** (2 mmol, 1equiv) in DMF (10 mL). The reaction mixture was heated under microwave at 100 °C, monitored, and found to be completed in 10 min. The product was isolated with flash chromatography using EA/Hex 1:5 as eluent, and **11ei** was obtained in 90% yield. ^{1}H NMR (500 MHz, DMSO-d_6): δ 13.30 (bs, 1H, −CHO), 10.50 (bs, 1H, −N*H*−), 7.45−7.24 (m, 5H, Ar*H*), 4.44(s, 2H, −CH_2SPh), 2.34(s, 3H, −CH_3), 1.99(s, 3H, −CH_3). ^{13}C NMR (125 MHz, DMSO-d_6): δ 178.1, 158.5, 152.0, 145.9, 144.8, 137.7, 128.9 (×2), 128.4 (×2), 127.1, 121.1, 121.4, 104.7, 33.6, 16.9, 10.1. HRMS (ESI, M + H) Calcd $C_{16}H_{15}N_3O_2S$: 314.0958; found 314.0955.

Acknowledgment. We thank the A*Star Biomedical Research Council for financial support of this work (Grant R-143-000-348-305).

Supporting Information Available. ^{1}H and ^{13}C NMR spectra of compound **1a**−**1j**, **9ai**, **9aii**, **9bi**, **9bii**, **9ci**, **9cii**,

9di, **10ai**, and **11ei**, 2D-NOESY NMR spectra of compound **9ai**, **9aii**, **9bi**, **9bii**, **9ci**, **9cii**, and **9di**, IR spectra of resin **7a** and **8a**, and the crystallographic file in CIF format of **6j**, **1b**, **9di**, and **10ai**. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) (a) Trapani, G.; Franco, M.; Latrofa, A.; Genchi, G.; Iacobazzi, V.; Ghiani, C. A.; Maciocco, E.; Liso, G. *Eur. J. Med. Chem.* **1997**, *32*, 83–89. (b) Gueiffieri, A.; Blache, Y.; Chapat, J. P.; Elhakmaoui, E. M. E.; Andrei, G.; Snoeck, R.; De Chlercq, E.; Chavignon, O.; Teulade, J. C.; Fauvelle, F. *Nucleosides, Nucleotides Nucleic Acids* **1995**, *14*, 551–554. (c) Dalla Via, L.; Gia, O.; Magno, S. M.; Da Settimo, A.; Marini, A. M.; Primofiore, G.; Da Settimo, F.; Salaerno, S. I. *Farmaco* **2001**, *56*, 159–167. (d) Rival, Y.; Grassy, G.; Michel, G. *Chem. Pharm. Bull.* **1992**, *40*, 1170–1176. (e) Rival, Y.; Grassy, G.; Taudon, A.; Ecalle, R. *Eur. J. Med. Chem.* **1991**, *26*, 13–18. (f) Mai, A.; Artico, M.; Sbardella, G.; Quartarone, S.; Massa, S.; Loi, A. G.; Montis, A. D.; Scintu, F.; Putzolu, M.; Colla, P. L. *J. Med. Chem.* **1997**, *40*, 1447–1454. (g) Mai, A.; Artico, M.; Sbardella, G.; Massa, S.; Novellino, E.; Greco, G.; Loi, A. G.; Tramontano, E.; Marongiu, M. E.; Colla, P. L. *J. Med. Chem.* **1999**, *42*, 619–627. (h) Kappe, T. *J. Heterocycl. Chem.* **1995**, 1003–1006. (i) Ahn, H. S.; Bercovic, A.; Boykow, G.; Bronnenkant, A.; Chackalamannil, S.; Chow, J.; Cleven, R.; Cook, J.; Czarniecki, M.; Domalski, C.; Fawzi, A.; Green, M.; Gundes, A.; Ho, G.; Laudicina, M.; Lindo, N.; Ma, K.; Manna, M.; McKittrick, B.; Mirzai, B.; Nechuta, T.; Neustadt, B.; Puchalski, C.; Pula, K.; Silverman, L.; Smith, E.; Stamford, A.; Tedesco, R. P.; Tsai, H.; Tulshian, D.; Vaccaro, H.; Watkins, R. W.; Weng, X.; Witkoski, J. T.; Xia, Y.; Zhang, H. *J. Med. Chem.* **1997**, *40*, 2196–2210.

(2) (a) Boryski, J.; Golankiewicz, B.; DeClercq, E. *J. Med. Chem.* **1988**, *31*, 1351–1355. (b) Golankiewicz, B.; Ostrowski, T.; Januszczyk, P.; Zeidler, J.; Baranowski, D.; De Clercq, E. *J. Med. Chem.* **2001**, *44*, 4284–4287.

(3) (a) Zhu, Y. F.; Guo, A. Q.; Gross, T. D.; Gao, Y. H.; Cornnors, P. J., Jr.; Struthers, R. S.; Xie, Q.; Tucci, F. C.; Reinhart, G. J.; Wu, D. P.; Saunders, J.; Chen, C. *J. Med. Chem.* **2003**, *46*, 1769–1772. (b) Zhu, Y. F.; Struthers, R. S.; Conners, P.J.Jr.; Gao, Y. H.; Gross, T. D.; Saunders, J.; Wilcoxen, K.; Reinhart, G. J.; Ling, N.; Chen, C. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 399–402.

(4) (a) Devivar, R. W.; Kawashima, E.; Revankar, G. R.; Breitenbach, J. M.; Kreske, E. D.; Drach, J. C.; Townsend, L. B. *J. Med. Chem.* **1994**, *37*, 2942–2949. (b) Miller, J. P.; Boswell, K. H.; Meyer, R. B., Jr.; Christensen, L. F.; Robins, R. K. *J. Med. Chem.* **1980**, *23*, 242–251. (c) Manetti, F.; Esté, J. A.; Codina, I. C.; Armand-Ugón, M.; Maga, G.; Crespan, E.; Cancio, R.; Mugnaini, C.; Bernardini, C.; Togninelli, A.; Carmi, C.; Alongi, M.; Petricci, E.; Massa, S.; Corelli, F.; Botta, M. *J. Med. Chem.* **2005**, *48*, 8000–8008.

(5) Dorwald, F. Z. *Organic Synthesis on Solid-Phase*; Wiley-VCH: Weinheim, Germany, 2002.

(6) (a) Lew, A.; Krutzik, P. O.; Hart, M. E.; Chamberlin, A. R. *J. Comb. Chem.* **2002**, *4*, 95–105. (b) Kappe, C. O. *Angew. Chem., Int. Ed.* **2004**, *43*, 6250–6284.

(7) (a) Majetich, G.; Wheless, K. In *Microwave-Enhanced Chemistry*; Kinsington, H. M., Haswell. S. J., Eds.; American Chemical Society: Washington, DC, 1997; pp455−505. (b) Soh, C. H.; Chui, W. K.; Lam, Y. *J. Comb. Chem.* **2008**, *10*, 118–122. (c) Soh, C. H.; Chui, W. K.; Lam, Y. *J. Comb. Chem.* **2006**, *8*, 464–468.

(8) Gütschow, M.; Powers, J. C. *J. Org. Chem.* **2001**, *66*, 4723–4727.

CC900176X