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New Facile Synthesis of 2-Alkylthiopyrimidin-4(3*H*)-ones by Tandem Aza-Wittig Reaction Starting from the Baylis–Hillman Adducts

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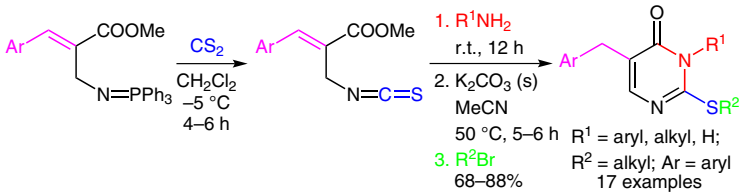

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Abstract Iminophosphoranes reacted with CS_2 at –5 °C to produce the isothiocyanates, which were treated with primary amine to give thioureas in 73–91% yields. The subsequent reaction of thioureas with alkyl bromides in the presence of solid K_2CO_3 produced 2-alkylthiopyrimidin-4(3*H*)-ones in 68–88% yield via tandem intramolecular cyclization–isomerization–S-alkylation.

Key words pyrimidin-4(3*H*)-one, Baylis–Hillman reaction, aza-Wittig reaction, isothiocyanate, isomerization

The 4(3*H*)-pyrimidinone scaffold represents a common motif in many biologically relevant compounds. A wide variety of derivatives of this ring system have shown good antiviral,[1] anticancer,[2] antimycobacterial,[3] herbicidal,[4] and dipeptidyl peptidase IV (DPP-4) inhibitive activities.[5] The human immunodeficiency virus type 1 (HIV-1) reverse transcriptase inhibitors have been one of the main ingredients of multidrug cocktails in AIDS patients therapy. Since the dihydroalkyloxybenzyloxopyrimidines (DABOs)[6] were disclosed as HIV-1 reverse transcriptase inhibitors, the related 2-alkylthiopyrimidin-4(3*H*)-ones (*S*-DABOs) have also been found to exhibit excellent anti-HIV-1 or anti-HBV (hepatitis B virus) activity.[7–12] For examples (Figure 1), *S*-DABO compounds **1** and **2** showed high inhibitory activities against wildtype and mutant HIV-1 in the low nanomolar or subnanomolar range with an additional merit of low cytotoxicity.[7,8] The *S*-DABO compound **3** possessed anti-HBV ability and could be used as potential agent against HBV infection.[9] Although there are some known approaches for the preparation of these 2-alkylthio-substituted 4(3*H*)-pyrimidinones,[7–9] new synthetic methods are still desirable to obtain diversely substituted *S*-DABOs for biological activity studies.

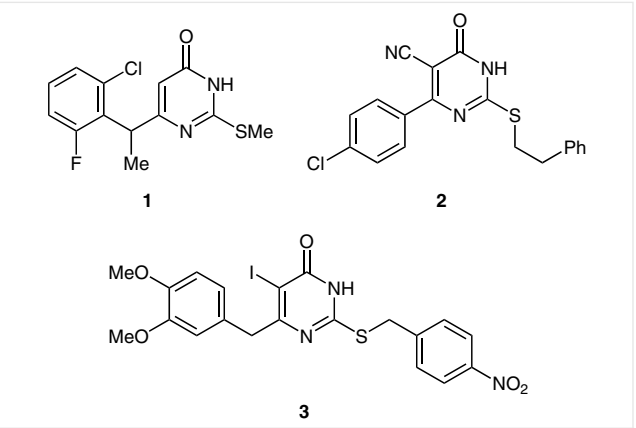

Figure 1 Representative bioactive 2-alkylthio-pyrimidin-4(3*H*)-ones (*S*-DABOs)

Baylis–Hillman reaction has become an effective method for the preparation of organic molecules with functional density through the construction of carbon–carbon bond in a one-pot procedure.[13] The Baylis–Hillman products have been utilized recently in further preparation of various heterocycles, such as 4-quinolones,[14] oxindoles,[15] 1,3-thiazinane-2-thiones,[16] and piperidines.[17] The aza-Wittig reaction has also provided a powerful method for the construction of C=N double bond and has recently applied widely in the synthesis of many heterocyclic compounds.[18] The aza-Wittig reactions between iminophosphoranes and CS_2 produce isothiocyanate intermediates, which may be utilized in preparing various heterocycles in further sequential reactions.[19] By using such isothiocyanates as intermediates, we have previously reported the efficient synthesis of 2-thioxo-4-imidazolidinones, imidazolidine-2-thiones, and thiazoles.[20] The reaction process involves tandem aza-Wittig–intermolecular nucleophilic addition–intramolecular cyclizations. Continuing our interests in synthesis of

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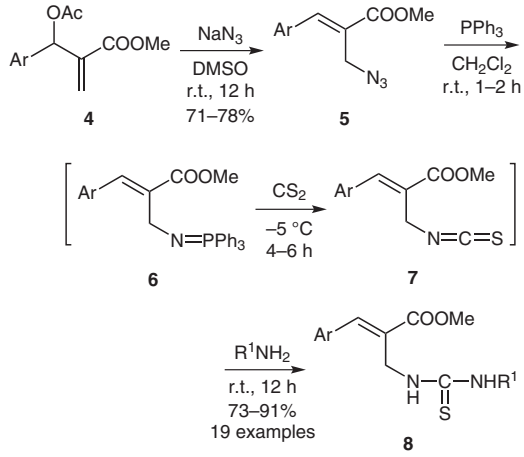
heterocycles via aza-Wittig reactions,[21] we reported herein a facile synthesis of 2-alkylthiopyrimidin-4(3*H*)-ones by a sequential aza-Wittig–intramolecular cyclization–isomerization–*S*-alkylation, starting from the Baylis–Hillman adducts.

Azides **5**, prepared from the reaction of Baylis–Hillman adducts **4** with sodium azide in DMSO,[22] reacted with triphenylphosphine to generate iminophosphoranes **6** via Staudinger reaction at room temperature. Initial attempts on reactions of iminophosphoranes **6** with CS_2 at room or refluxing temperature resulted in complex mixture probably due to side reactions. However, at low temperature (–5 °C), the reactions were found to take place smoothly to produce the isothiocyanate intermediates **7**, which were further treated with primary amine to give thioureas **8** in good overall yields (73–91%, Scheme 1 and Table 1).[23] As indicated in Table 1, various amines can be used in the above reaction to prepare thioureas **8**, including alkyl amines (Table 1, entries 1–12), aromatic amines (Table 1, entries 13–18), and ammonia (Table 1, entry 19). Even when the bulky *t*-$BuNH_2$ was utilized (Table 1, entry 6), 73% yield of the thiourea **8f** was also obtained.

The cyclization of thioureas **8** to 2-thioxopyrimidin-4(1*H*)-ones **9** or **10** did not occur in the presence of solid K_2CO_3 at room temperature (Scheme 2). But at 50 °C, the cyclization took place successfully to produce **10**, which were further treated with alkyl bromides to give 2-alkylthiopyrimidin-4(3*H*)-ones **11** (Table 1).[24] The intermediate **9** cannot be isolated but the intermediate **10** can be separated before the addition of alkyl bromides. The formation of compound **11** can be rationalized in terms of an initial cyclization of **8** to give **9**. Further isomerization of the inter-



Scheme 1 Preparation of thiourea intermediates **8**

Table 1 Preparation of Compounds **8a–s** and **11a–s**

Entry	Ar	R^1	Product	Yield (%)[a]	R^2	Product	Yield (%)[b]
1	Ph	*n*-Bu	**8a**	87	*n*-Pr	**11a**	84
2	Ph	*n*-Pr	**8b**	91	*n*-Pr	**11b**	78
3	Ph	Et	**8c**	75	Et	**11c**	74
4	Ph	$PhCH_2$	**8d**	88	Et	**11d**	86
5	Ph	4-$MeC_6H_4CH_2$	**8e**	90	*i*-Pr	**11e**	87
6	Ph	*t*-Bu	**8f**	73	Bn	**11f**	0
7	Ph	*i*-Pr	**8g**	78	Et	**11g**	0
8	4-ClC_6H_4	*n*-Bu	**8h**	79	Et	**11h**	88
9	4-ClC_6H_4	*n*-Pr	**8i**	81	Et	**11i**	81
10	4-ClC_6H_4	Et	**8j**	83	*i*-Pr	**11j**	80
11	4-ClC_6H_4	Bn	**8k**	84	*n*-Bu	**11k**	85
12	4-ClC_6H_4	4-$MeC_6H_4CH_2$	**8l**	75	*n*-Pr	**11l**	70
13	Ph	Ph	**8m**	90	*n*-Pr	**11m**	75
14	Ph	4-MeC_6H_4	**8n**	89	*n*-Pr	**11n**	72
15	Ph	4-ClC_6H_4	**8o**	77	Et	**11o**	69
16	4-ClC_6H_4	Ph	**8p**	87	*i*-Pr	**11p**	74
17	4-ClC_6H_4	4-MeC_6H_4	**8q**	84	*n*-Bu	**11q**	79
18	4-ClC_6H_4	4-ClC_6H_4	**8r**	75	*i*-Pr	**11r**	68
19	Ph	H	**8s**	82	Et	**11s**	75

[a] Yields based on azides **5**.
[b] Yields based on thioureas **8**.

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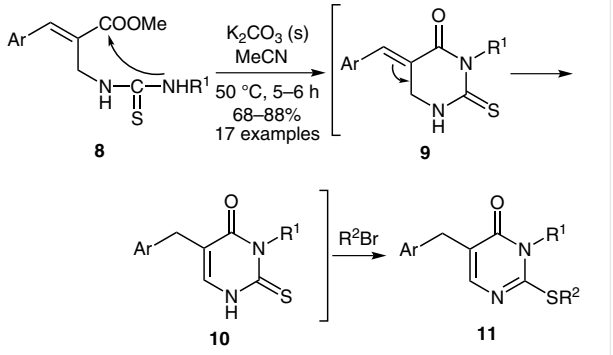
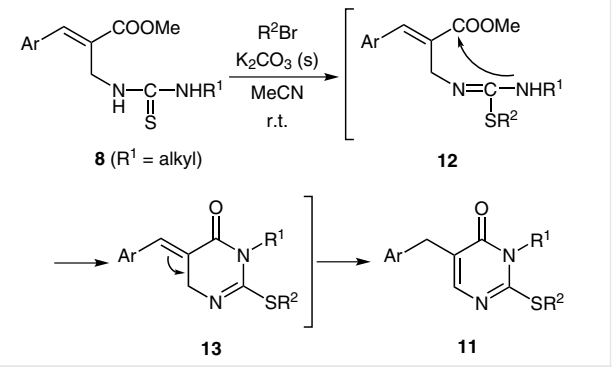
mediate **9** through 1,3-H shift takes place to give 2-thioxopyrimidin-4(1*H*)-one **10**, which was S-alkylated to produce 2-alkylthiopyrimidin-4(3*H*)-one **11** under the basic condition.



Scheme 2 Preparation of 2-alkylthiopyrimidin-4(3*H*)-one **11**

It is noteworthy that if solid K_2CO_3 was added to the mixture of thiourea **8** (R^1 = alkyl) and alkyl bromide, the cyclization could take place even at room temperature to give directly 2-alkylthiopyrimidin-4(3*H*)-one **11** (Scheme 3).[25] In this case, the formation of compound **11** presumably involves an initial S-alkylation of thiourea **8** to give the intermediate **12**, which undertakes further cyclization and isomerization to produce 2-alkylthiopyrimidin-4(3*H*)-one **11** under the basic conditions. MS detection of the reaction mixture of **8b** showed the $[M]^+$ at *m/z* = 334 of the intermediate **12b**, which verified its existence during the reaction process.



Scheme 3 Preparation of 2-alkylthiopyrimidin-4(3*H*)-one **11** at room temperature

The reaction yields of compounds **11** are found to relate with R^1 group (Table 1). When R^1 are alkyl or H groups, the reactions proceeded smoothly to give the corresponding 2-alkylthiopyrimidin-4(3*H*)-one **11a–e**, **11h–l**, and **11s** in 70–88% yields (Table 1, entries 1–5, 8–12, and 19). However, no product was got as R^1 are bulky *i*-Pr and *t*-Bu groups (**11f** and **11g**, Table 1, entries 6 and 7). In case that aromatic primary amines (R^1 = aryl, entries 13–18) were used, the products **11m–r** were obtained in moderate yields (68–79%).

The structure of 4(3*H*)-pyrimidinones **11** was confirmed by their spectral data. For example, the ^{1}H NMR (600 MHz, $CDCl_3$) spectrum of **11a** shows a singlet at δ = 3.73 ppm due to the Bn group. The signals of NCH_2 and SCH_2 appear at δ = 4.01 and 3.10 ppm as triplet absorptions. The signals of other CH_2 and CH_3 appear at δ = 1.73–0.95 ppm as multiplets. The signals attributable to the pyrimidinone-6-H and other Ar-Hs are found at δ = 7.50 ppm as singlet and δ = 7.29–7.19 ppm as multiplets. The ^{13}C NMR (150 MHz, $CDCl_3$) spectrum data in **11a** showed the signal of the pyrimidinone C-4 and C-2 carbon at δ = 162.1 and 160.0 ppm. The signals attributable to NCH_2, SCH_2, and CH_2 carbon are found at δ = 44.7, 33.8, and 33.7 ppm, respectively. The IR spectra of **11a** revealed C=O absorption bands at 1669 cm^{-1}. The HRMS spectrum of **11a** shows $[M + H]^+$ at *m/z* = 317.1683 (calcd 317.1682).

In conclusion, we have developed a facile synthesis of 2-alkylthio-pyrimidin-4(3*H*)-ones (*S*-DABOs) by a new sequential aza-Wittig–intramolecular cyclization–S-alkylation/–isomerization reaction, starting from the Baylis–Hillman adducts. Due to the easily accessible and versatile starting material, this method has the advantage in the synthesis of many biologically and pharmaceutically active *S*-DABOs derivatives.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0036-1588947.

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(23) **General Procedure for the Preparation of Thioureas 8**
To the azides **4** (2 mmol) in dry CH_2Cl_2 (10 mL) was added dropwise Ph_3P (0.52 g, 2 mmol) in CH_2Cl_2 (5 mL) under N_2. The mixture was stirred at r.t. for 1–2 h to form iminophosphorane (TLC monitoring). The CS_2 (1.52 g, 20 mmol) was then added at –5 °C, and the mixture was continuing stirred at –5 °C for 4–6 h. After the reaction was completed, the solvent and excess CS_2 were removed in reduced pressure. Primary amine (2 mmol) was added to the residue in CH_2Cl_2 (10 mL), and the mixture was stirred overnight at r.t. The solvent was removed, and the residue was purified by column chromatography (PE–EtOAc, 4:1) to give thioureas **8**.
Compound **8a**: light yellow solid (yield 0.53 g, 87%), mp 72–74 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.85 (s, 1 H, =CH), 7.42–7.38 (m, 5 H, Ar–H), 6.59 (br, 2 H, 2NH), 4.49 (br, 2 H, NCH_2), 3.82 (s, 3 H, OCH_3), 3.38 (br, 2 H, NCH_2), 1.49–1.29 (m, 4 H, $2CH_2$), 0.89 (t, *J* = 7.2 Hz, 3 H, CH_3). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 181.1, 168.4, 143.5, 133.8, 129.5, 129.4, 128.8, 127.2, 52.5, 44.6, 41.2, 30.8, 19.9, 13.7. HRMS: *m/z* calcd for $[C_{16}H_{22}N_2O_2S + H]^+$: 307.1475; found: 307.1479.
(24) **General Procedure for the Preparation of 2-Alkylthiopyrimidin-4(3*H*)-ones 11**
To the thioureas **8** (2 mmol) in MeCN (10 mL) was added solid K_2CO_3 (0.28 g, 2 mmol). The mixture was stirred at 50 °C for 5–6 h to form 2-thioxopyrimidin-4(1*H*)-ones **10** (TLC monitoring). The alkyl bromide (2 mmol) was then added with continuing stir. After the reaction was completed, the solid was filtered. The filtrate was removed, and the residue was purified by column chromatography (PE–EtOAc, 20:1) to give 2-alkylthiopyrimidin-4(3*H*)-ones **11**.
Compound **11m**: white solid (yield 0.502 g, 75%), mp 102–104 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.61 (s, 1 H, Ar–H), 7.51–7.21 (m, 10 H, Ar–H), 3.77 (s, 2 H, CH_2), 2.97 (t, *J* = 7.8 Hz, 2 H, SCH_2), 1.66–1.60 (m, 2 H, CH_2), 0.94 (t, *J* = 7.2 Hz, 3 H, CH_3). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 162.4, 161.4, 149.7, 138.8, 135.9, 129.8, 129.7, 129.1, 128.5, 128.4, 126.3, 123.4, 34.2, 33.6, 21.9, 13.4. HRMS: *m/z* calcd for $[C_{20}H_{20}N_2OS + H]^+$: 337.1369; found: 337.1373.
(25) **General Procedure for the Preparation of 2-Alkylthiopyrimidin-4(3*H*)-ones 11 (R^1 = alkyl) at Room Temperature**
To the thioureas **8** (2 mmol) and alkyl bromides (2 mmol) in MeCN (10 mL) was added solid K_2CO_3 (0.28 g, 2 mmol). The mixture was stirred at r.t. for 24–48 h. After the reaction was completed, the solid was filtered. The filtrate was removed, and the residue was purified by column chromatography (PE–EtOAc, 20:1) to give 2-alkylthiopyrimidin-4(3*H*)-ones **11**.
Compound **11a**: colorless oil (yield 0.53 g, 84%). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.50 (s, 1 H, Ar–H), 7.29–7.19 (m, 5 H, Ar–H), 4.01 (t, *J* = 7.8 Hz, 2 H, NCH_2), 3.73 (s, 2 H, CH_2), 3.10 (t, *J* =7.2 Hz, 2 H, SCH_2), 1.73–1.71 (m, 4 H, $2CH_2$), 1.43–1.39 (m, 2 H, CH_2), 1.03–0.95 (m, 6 H, 2 CH_3). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 162.1, 160.0, 149.2, 138.9, 129.0, 128.4, 126.2, 122.4, 44.7, 33.8, 33.7, 29.3, 22.1, 20.2, 13.7, 13.4. HRMS: *m/z* calcd for $[C_{18}H_{24}N_2OS + H]^+$: 317.1682; found: 317.1683.

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