Convenient Synthesis of 2,7-Disubstituted 5*H*-1,3,4-Thiadiazolo[3,2-*a*]-pyrimidin-5-ones and Related Compounds

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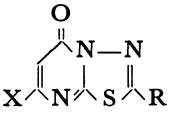
Synopsis. 2,7-Disubstituted 5*H*-1,3,4-thiadiazolo[3,-2-*a*]pyrimidin-5-ones were synthesized from the reaction of 3-amino-6-methyl-2-thiouracil with carboxylic acid or from that of thiosemicarbazide with carboxylic acid and β-keto ester in the presence of phosphorus pentaoxide and methanesulfonic acid. The synthesis of related compounds is also described.

Our work on the chemistry of 2,7-disubstituted 5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-ones (**1**)[1] has required a wide and convenient entry to this ring system, which is of their chemical[2,3] and biological[4] interests. Okabe *et al.*[4] have synthesized **1** by the condensation of 5-substituted 2-amino-1,3,4-thiadiazole (**2**) with β-keto ester in the presence of polyphosphoric acid (PPA). However, we failed to obtain the 2-(nitrophenyl or chlorophenyl) derivative of **1** by this method. This paper describes the general and facile methods for the synthesis of **1** and related compounds by the use of 1 : 5 molar ratio of phosphorus pentaoxide (P_2O_5)-methanesulfonic acid (MsOH).[5] The synthetic routes are illustrated in Scheme 1, and the results are summarized in Table 1. PPA was less effective in the present synthesis, since the product yields were generally poor in Method A and B; no desired product was obtained in Method C, D, or E.

The treatment of 3-acylamino-6-methyl-2-thiouracil (**4**) with P_2O_5–MsOH at 70 °C for 10 h, followed by aqueous basic work-up afforded **1** (Method A). Moreover, the reaction of 3-amino-6-methyl-2-thiouracil (**3**) with carboxylic acid (**5**) in the presence of P_2O_5–MsOH gave **1** including the 2-(nitrophenyl and chlorophenyl) derivatives in 37.8—97% yields (Method B).

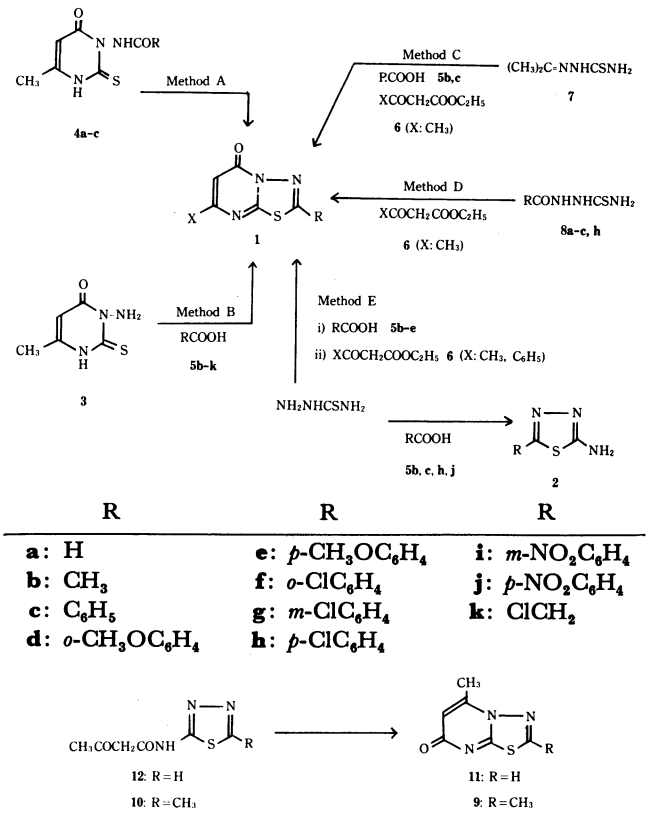
We then attempted the synthesis of **1** from thiosemicarbazide or its 1-substituted derivatives in the presence of P_2O_5–MsOH. Thus, **1** was obtained from the reaction of acetone thiosemicarbazone (**7**) with β-keto ester (**6**) and **5** (Method C), or from that of 1-acylthiosemicarbazide (**8**) with **6** (Method D), but the yields were unsatisfactory. In connection with these reactions, **2** was prepared by the treatment of thiosemicarbazide with **5** in 40.1—89.9% yields. Based on this result, one pot synthesis of **1** was carried out by

Table 1. Synthesis of 2,7-disubstituted 5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-ones (**1**)



Compound **1** R	X	Methods A[a]	B[b]	C[c]	D[d]	E[e]	Mp θ_m/°C	Formula	Found (Calcd) (%)			Ref.
H	CH_3	65.8			91.1		186—187[f]	$C_6H_5ON_3S$	43.08 (43.10	3.21 3.01	25.24 25.14)	1c, 4
CH_3	CH_3	70.6	57.2	24.8	77.1	72.4	153—154[f]	$C_7H_7ON_3S$	46.50 (46.39	4.01 3.89	23.22 23.19)	4
C_6H_5	CH_3	47.5	97	37.4	37.6	76.5	201—202[g,i]	$C_{12}H_9ON_3S$	59.23 (59.24	3.75 3.73	17.31 17.27)	4
o-$CH_3OC_6H_4$	CH_3		64.3			76.1	246—247[h]	$C_{13}H_{11}O_2N_3S$	57.01 (57.13	4.10 4.06	15.58 15.38)	
p-$CH_3OC_6H_4$	CH_3		78			75.1	245—246[h]	$C_{13}H_{11}O_2N_3S\cdot 1/4H_2O$	56.26 (56.20	3.96 4.17	15.18 15.13)	
o-ClC_6H_4	CH_3		53.5				198[g]	$C_{12}H_8ON_3SCl$	51.75 (51.89	2.70 2.90	14.99 15.13)	
m-ClC_6H_4	CH_3		74.8				192—193[g]	$C_{12}H_8ON_3SCl$	51.58 (51.89	2.70 2.90	15.32 15.13)	
p-ClC_6H_4	CH_3		83.9		29.8		220—221[g]	$C_{12}H_8ON_3SCl\cdot 1/2H_2O$	49.89 (50.26	2.74 3.16	14.94 14.66)	
m-$NO_2C_6H_4$	CH_3		68.4				233—234[g]	$C_{12}H_8O_3N_4S$	49.71 (49.99	2.71 2.80	19.15 19.44)	
p-$NO_2C_6H_4$	CH_3		49.8				303—304[h]	$C_{12}H_8O_3N_4S$	49.78 (49.99	2.76 2.80	19.23 19.44)	
$ClCH_2$	CH_3		37.8				181—183[g]	$C_7H_6ON_3SCl$	39.13 (38.98	2.79 2.80	19.72 19.49)	
CH_3	C_6H_5					72.4	193—194[g]	$C_{12}H_9ON_3S$	59.17 (59.24	3.64 3.73	17.27 17.27)	4

a) From **4**. b) From **3** with **5**. c) From **7** with **5** and ethyl acetoacetate. d) From **8** with ethyl acetoacetate. e) From thiosemicarbazide with **5** and **6** by one-pot reaction. f) Recrystallized from water. g) Recrystallized from methanol. h) Recrystallized from *N*,*N*-dimethylformamide. i) Lit,[4] mp 169—172 °C.



Scheme 1. Synthesis of 2,7-Disubstituted 5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-ones (**1**) and related compounds in the presence of P_2O_5–MsOH.

heating the mixture of thiosemicarbazide and **5** in the presence of P_2O_5–MsOH, followed by the treatment of the above mixture with **6**. The yields were 72.4—76.5% (Method E). This method is inapplicable to the synthesis of **1** which has a 2-(nitrophenyl or chlorophenyl) substituent.

Previously, 2,5-dimethyl-7*H*-1,3,4-thiadiazolo[3,2-*a*]-pyrimidin-7-one (**9**) was prepared by the treatment of 2-acetoacetylamino-5-methyl-1,3,4-thiadiazole (**10**) with PPA in 18% yield.[4] Upon heating **10** with P_2O_5-MsOH, the yield of **9** was raised to 87.4%. Similarly, compound (**11**) was obtained in 61.2% yield.

The P_2O_5–MsOH reagent was at first used for the intramolecular acylation of olefinic acids and the Beckmann rearrangement of ketoxime, since this reagent resembles PPA in reaction rate, product distribution and yield.[5] It is notable that the product yield increased markedly by converting the reagent from PPA to P_2O_5–MsOH in the synthesis of heterocycles.

Experimental

General Procedures for the Preparation of 2,7-Disubstituted 5H-*1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-ones (1).* *a) From 3 or Its Acyl Derivatives (4)*: Compound **4**[2] (0.01 mol) or a mixture of **3**[1a] (0.01 mol) and **5** (0.01 mol), MsOH (0.05 mol), and P_2O_5 (0.01 mol) was placed in a flask in this order, and heated at 70 °C for 10 h. When nitrobenzoic acids were used for **5**, the reaction was carried out at 100 °C. The reaction mixture was poured into water, and made basic with 10% NaOH to pH 8. The precipitate was extracted with chloroform, and the extract was washed with water. The dried extract was evaporated to dryness in vacuum to obtain **1**.

b) From Acetone Thiosemicarbazone (7): To the mixture of **7** (0.01 mol), ethyl acetoacetate (0.01 mol), and **5** (0.01 mol) was added MsOH (0.05 mol) and P_2O_5 (0.01 mol), and the whole was heated at 100 °C for 10 h. A work-up similar to that in Method A gave **1**.

c) From 1-Acylthiosemicarbazide (8): The mixture of **8** (8 mmol) and ethyl acetoacetate (8 mmol) was heated with P_2O_5 (8 mmol)–MsOH (40 mmol) at 70 °C for 5 h. In the case of **8c** or **8h**, the mixture was heated at 100 °C for 10 h.

d) From Thiosemicarbazide: The mixture of thiosemicarbazide (0.01 mol) and **5** (0.01 mol) was heated at 70 °C for 10 h with P_2O_5 (0.01 mol)–MsOH (0.05 mol). At the end of the reaction time, **6** (0.01 mol) and P_2O_5 (5 mmol) were added to the reaction mixture and the whole was further heated at 70 °C for 10 h. The resulting solution was similarly worked up to give **1**.

Preparation of 5-Substituted 2-Amino-1,3,4-thiadiazole (2). A mixture of thiosemicarbazide (0.01 mol), **5** (0.01 mol), MsOH (0.05 mol), and P_2O_5 (0.01 mol) was heated at 70 °C for 10 h. The reaction mixture was poured into water, and made basic (pH 8) with aqueous ammonia. **2** (R: CH_3,[6,7] C_2H_5,[8] C_6H_5,[6,8] p-$NO_2C_6H_4$,[8] and p-ClC_6H_4[9]) was obtained in 89.9, 64.5, 74.2, 40.4 and 40.1% yields, respectively.

Preparation of 2,5-Dimethyl-7H-1,3,4-thiadiazolo[3,2-a]pyrimidin-7-one (9). Upon heating **10** (5 mmol) with P_2O_5 (5 mmol)–MsOH (25 mmol) at 100 °C for 10 h, **9**[4] was obtained in 87.4% yield. In a similar manner, **11**[4] was prepared in 61.2% yield.

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