THE REACTION OF ENAMINOKETONES WITH BENZOYL ISOTHIOCYANATE[1]

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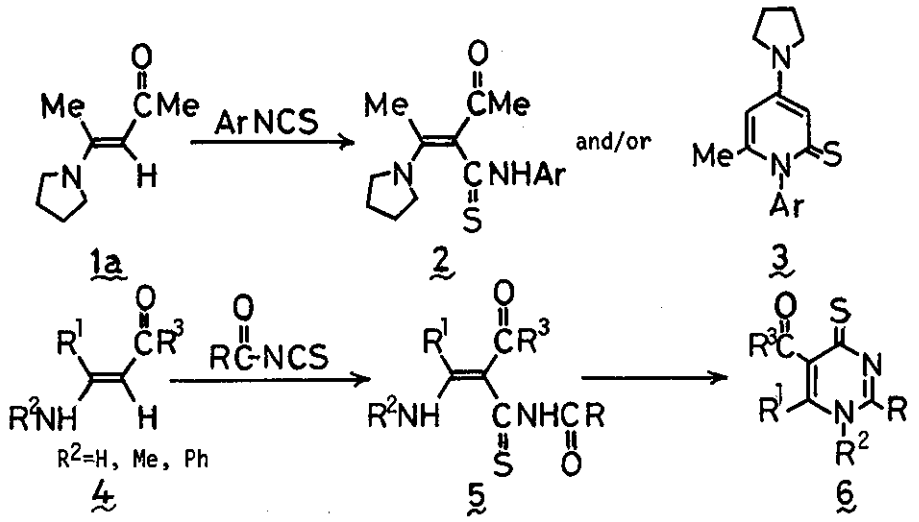
The reaction of enaminoketone 1a *with benzoyl isothiocyanate* (7) in benzene afforded 2-thiopyridone derivatives, 8 [1:1 adduct - H_2O] and 9a [1:2 adduct - H_2S], and 3-benzamidothiocarbamoyl compound 11 [1:1 adduct]: the relative yields depended upon the reaction conditions. On the other hand, enaminoketone 1b reacted with 7 in benzene to yield the 1-benzoyl-2-thiopyridone 12 [1:2 adduct - (HNCS + H_2O)], while the same reaction in dichloroethane gave the 2-thiopyridone 9b [1:2 adduct - H_2S].

We earlier reported that an enaminoketone, 4-(1-pyrrolidinyl)-3-penten-2-one (1a), reacted with aryl isothiocyanates to yield 3-arylthiocarbamoyl derivatives 2 and/or 2-thiopyridones 3, depending upon the nature of aryl isothiocyanates and the reaction conditions.[2] On the other hand, the reactions of enaminoketones of type 4 with acyl isothiocyanates afford 1:1 adducts 5, which are readily converted into thiopyrimidines 6 by dehydration.[3-5] However, little attention has been paid to the reaction of enaminoketone of type 1a with acyl



isothiocyanate.

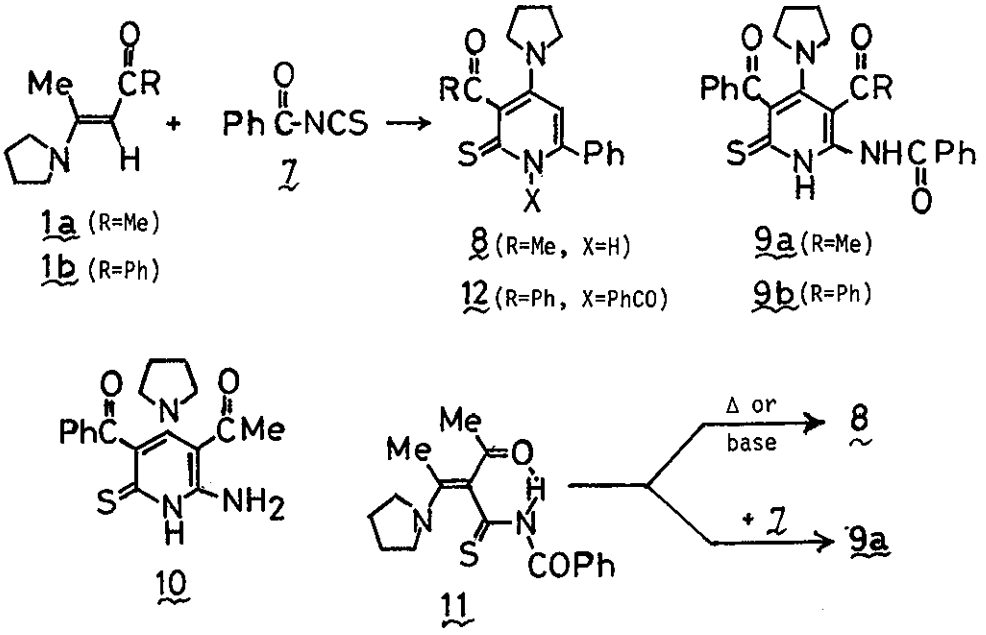
For comparison with the reaction of enaminoketone 1a with aryl isothiocyanates, and that of enaminoketones 4 with acyl isothiocyanates, it seemed of interest to investigate the reaction of enaminoketone of type 1a with acyl isothiocyanate. This paper deals with the reaction of enaminoketones, 1a and 1-phenyl-3-(1-pyrrolidinyl)-2-buten-1-one (1b), with benzoyl isothiocyanate (7).

When enaminoketone 1a was allowed to react with 1 equiv of isothiocyanate 7 in benzene at room temperature, two products, 8 [colorless prisms, mp 243-245° dec] and 9a [yellow needles, mp 225-226° dec], were formed, together with tarry material. The molecular formula of 8 [$C_{17}H_{18}N_2OS$, m/e 298 (M^+)] agreed with that of the compound derived from an 1:1 adduct with dehydration, and 8 was deduced to be 3-acetyl-6-phenyl-4-(1-pyrrolidinyl)-2-thiopyridone on the basis of its spectral data [ir ν_{max}^{KBr} cm^{-1} 3160 (NH), 1700 (CO); nmr δ ($CDCl_3$) 1.99, 3.36 (each 4H, m, pyrrolidinyl protons), 2.88 (3H, s, $COCH_3$), 6.28 (1H, s, =CH), 7.53 (5H, m, aromatic protons), 9.65 (1H, br, NH)].

The elemental analysis and molecular ion peak of 9a indicated that 2 equiv

of 7 and 1 equiv of 1a had combined with the loss of hydrogen sulfide. On the basis of the spectral data and chemical conversion, 9a was assigned as 5-acetyl-3-benzoyl-6-benzamido-4-(1-pyrrolidinyl)-2-thiopyridone [ir ν_{max}^{KBr} cm^{-1} 3200 (NH), 1670, 1640 (CO); nmr δ ($CDCl_3$) 1.81, 3.31 (each 4H, m, pyrrolidinyl protons), 2.46 (3H, s, $COCH_3$), 7.4-8.2 (10H, m, aromatic protons), 12.3, 13.1 (each 1H, br, NH); mass m/e 445 (M^+)].

Hydrolysis of 9a with 1N potassium hydroxide aqueous solution under reflux for 1 hr afforded 6-amino-5-acetyl-3-benzoyl-4-(1-pyrrolidinyl)-2-thiopyridone (10) quantitatively. 10: mp 198-200° dec; ir ν_{max}^{KBr} cm^{-1} 3360, 3260, 3160 (NH), 1640 (CO); nmr δ ($CDCl_3$) 1.76, 3.30 (each 4H, m, pyrrolidinyl protons), 2.31 ($COCH_3$), 6.90 (2H, br, NH_2), 7.3-8.1 (5H, m, aromatic protons), 12.2 (1H, br, NH), mass m/e 341 (M^+)].



Scheme 1

On the other hand, the reaction of 1a with 0.5 equiv of 7 at room temperature afforded 3-benzoylthiocarbamoyl-4-(1-pyrrolidinyl)-3-penten-2-one (11), mp 128-129° dec, as orange prisms. The ir spectrum of 11 exhibited no well-defined bands ascribable to νNH absorptions, but the following spectral data supported the assigned structure [ir ν_{max}^{KBr} 1700 cm^{-1} (CO); nmr δ ($CDCl_3$) 1.83 (3H, s, CH_3), 2.17, 3.92 (each 4H, m, pyrrolidinyl protons), 2.75 (3H, s, CO-CH_3), 7.8-8.3 (5H, m, aromatic protons), 14.82 (1H, br, NH); mass m/e 298 (M^+ - H_2O)]. The spectral data also indicate that 11 exists as the chelating form[6] as shown in Scheme 1. The results under various reaction conditions are given in Table 1.

Table 1 Reaction of 1a with 7 in benzene

Reaction conditions			Product, yield %		
1a/7 (mol/mol)	Temp. °C	Time hr	8	9a	11
1	room temp.	10	13.2	4.7	--
1	〃	3 days	1.0	12.4	--
0.5	〃	20	--	25.8	--
2	〃	3	--	--	69.6
2	80	2	--	27.0	--

Upon heating at 150° for 30 min or treatment with 6.5N potassium hydroxide aqueous solution at room temperature for 5 hr, 11 was transformed into 8 in 38 or 42% yield respectively. In addition, 11 reacted with 1 equiv of 7 in boiling 1,2-dichloroethane to form 9a in 39% yield. Thus, the formation of 8 and 9a can be interpreted as arising from 11.

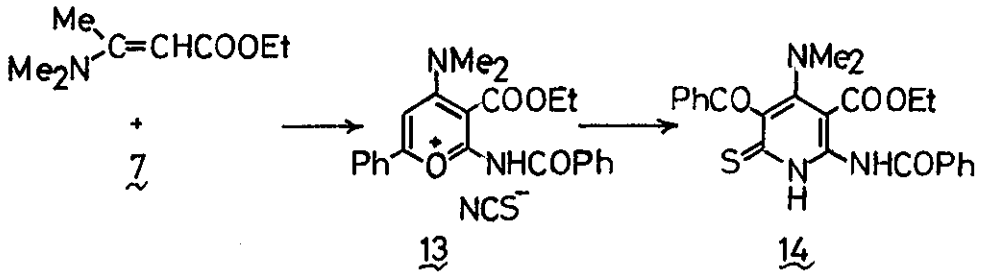
The reaction of enaminoketone 1b with 1 equiv of 7 in benzene at room

temperature for 5 hr did not form the expected products of types 8 and 9a, but 1,3-dibenzoyl-6-phenyl-4-(1-pyrrolidinyl)-2-thiopyridone (12) whose structure corresponded to the compound derived from an 1:2 adduct of 1b and 7 with the loss of water and of hydrogen isothiocyanate, was obtained in 42.2% yield. However, the same reaction in 1,2-dichloroethane at room temperature gave 3,5-dibenzoyl-6-benzamido-4-(1-pyrrolidinyl)-2-thiopyridone (9b) in 15.4% yield. The structures of 12 and 9b were deduced on the basis of their spectral data.

12: yellow prisms; mp 254-255° dec; ir ν_{max}^{KBr} 1685 cm^{-1}(CO); nmr δ ($CDCl_3$) 1.89, 3.45 (each 4H, m, pyrrolidinyl protons), 7.2 (1H, s, =CH), 7.1-8.3 (15H, m, aromatic protons); mass m/e 464 (M^+), 359 (M^+ - PhCO, base peak).

9b: yellow needles; mp 242° dec; ir ν_{max}^{KBr} cm^{-1} 3180 (NH), 1652 (CO); nmr δ (DMSO-d_6) 1.40, 3.0 (each 4H, m, pyrrolidinyl protons), 7.3-8.2 (15H, m, aromatic protons), 11.0, 13.0 (each 1H, br, NH); mass m/e 507 (M^+), 402 (M^+ - PhCO, base peak).

Recently, Carney, et al.[7] found that ethyl 2-benzamido-5-benzoyl-4-dimethylamino-6-thioxonicotinate (14), whose structure is the same as that of 9, was formed in the reaction of ethyl β-dimethylaminocrotonate with 7 in chloroform. They also proposed a complicated reaction pathway via the pyrylium intermediate 13.



The pathway of formation of 9 from 1 and 7 may be similar to that proposed

by Carney et al.; this is now under investigation.

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6 3-Arylthiocarbamoyl-4-(1-pyrrolidinyl)-3-penten-2-ones 2 exist as the same chelating forms that 11 does.[2]

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