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THE REACTION OF ENAMINOKETONES WITH BENZOYL ISOTHIOCYANATE[1]

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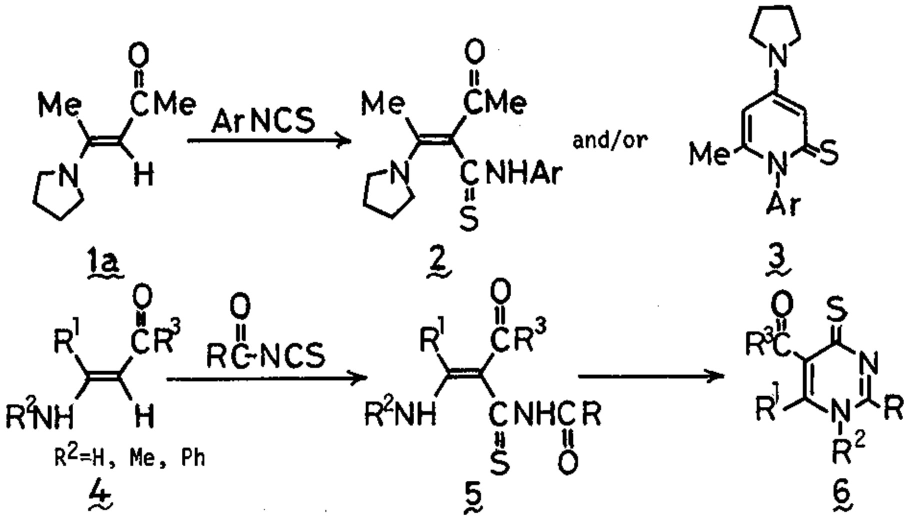
The reaction of enaminoketone **1a** *with benzoyl isothio*cyanate (**7**) in benzene afforded 2-thiopyridone derivatives, **8** [1:1 adduct - H_2O] and **9a** [1:2 adduct - H_2S], and 3-benzamidothiocarbamoyl compound **11** [1:1 adduct]: the relative yields depended upon the reaction conditions. On 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



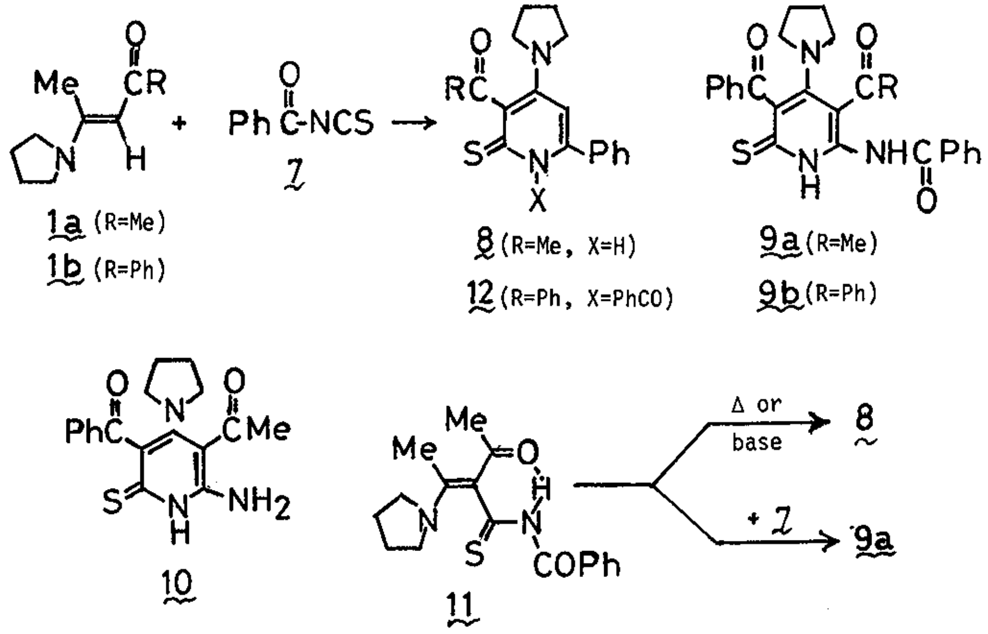
isothiocyanate.

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, $COC\underline{H}_3$), 6.28 (1H, s, $=C\underline{H}$), 7.53 (5H, m, aromatic protons), 9.65 (1H, br, $N\underline{H}$)].

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, $COC\underline{H}_3$), 7.4-8.2 (10H, m, aromatic protons), 12.3, 13.1 (each 1H, br, $N\underline{H}$); 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 (3H, s, $COC\underline{H}_3$), 6.90 (2H, br, $N\underline{H}_2$), 7.3-8.1 (5H, m, aromatic protons), 12.2 (1H, br, $N\underline{H}$), 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	--

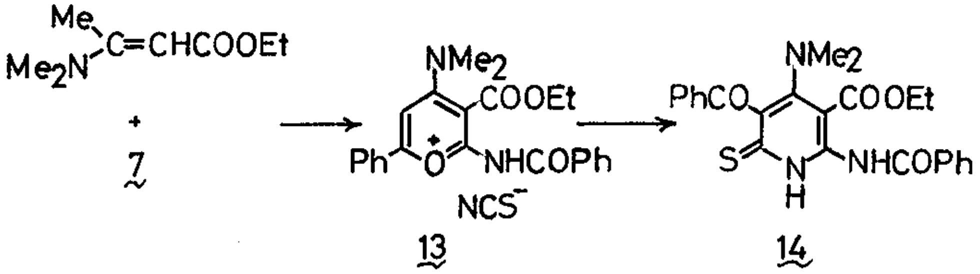
Upon heating at 150° for 30 min or treatment with 6.5N potassium hydroxide aqueous solution at room temperature for 5 hr, 11 was transformed into 8 in 38 or 42% yield respectively. In addition, 11 reacted with 1 equiv of 7 in boiling 1,2-dichloroethane to form 9a in 39% yield. Thus, the formation of 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, =C<u>H</u>), 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, N<u>H</u>); 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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