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A NOVEL METHOD FOR THE PREPARATION OF SUBSTITUTED ENAMINOKETONES[1]

Tsunetoshi Honma* and Yukio Tada
Shionogi Research Laboratory, Shionogi & Co., Ltd.,
Fukushima-ku, Osaka, 553 Japan

A novel method for the preparation of enaminoketones, which consists of the condensation of various heteroaromatic cyano compounds with ketones in the presence of base, such as sodium amide or sodium hydride is described. The enaminoketones can easily be converted to the corresponding β-diketones and heterocyclic compounds, such as isothiazole, isoxazole, pyrazole, pyrimidine, and thiazole.

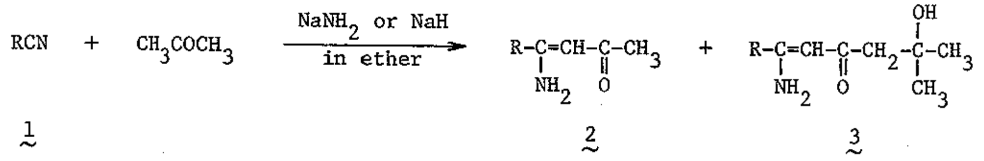
In a course of our study on synthesis of isothiazole derivatives it was required to prepare a large amount of 4-amino-4-(2-furyl)-3-buten-2-one **2** (R = 2-furyl). It was reported that the preparation of an enaminoketone was achieved by ammonolysis of a β-diketone[2,3] or reductive cleavage of isoxazole using Raney nickel as catalyst.[4,5] To prepare **2** (R = 2-furyl), however, these methods appeared to be unsatisfactory. Reaction of 4-(2-furyl)butane-2,4-dione with hydroxylamine in the presence of an acid or a base resulted in the formation of 3-methyl-5-(2-furyl)isoxazole in a high yield but not 3-(2-

furyl)-5-methylisoxazole **4**.[6] **4** was obtained in only 5% yield from 2-furylhydroximic acid chloride with methylacetylene. **4** was also obtained by treatment of 4-acetyl-3-(2-furyl)isoxazole-5-one with an alkali though in only 4% yield.[6] Reduction of **4** with Raney nickel gave **2** (R = 2-furyl) in 65.5% yield.

It became necessary to search for a new method for the preparation of **2** (R = 2-furyl). When a mixture of acetone (1.2 moles) and 2-cyanofuran (1.0 mole) was added dropwise to a suspension of sodium amide (1.2 moles) or sodium hydride (1.2 moles) in anhydrous ether at 10°C with stirring, the reaction occurred very quickly (within 5 min) and a crystalline compound was obtained in 80% yield. This was identical with **2** (R = 2-furyl) obtained from **4**[6] by comparison of their IR, UV and NMR spectra and by the mixed melting point determination. In this reaction 6-amino-6-(2-furyl)-2-hydroxy-2-methylhex-5-en-4-one (**3**, R = 2-furyl) was obtained in 10% yield as a byproduct from the mother liquor. In order to establish that this procedure is generally applicable, the syntheses of a number of enaminoketones were carried out under similar conditions. The results are shown in TABLES I and II.

These enaminoketones **2** appeared to be very useful intermediates for the synthesis of a number of heterocyclic compounds and β-diketones. Treatment of **2** with phosphorus pentasulfide in the presence of chloranil,[5] hydroxylamine, hydrazine, formamide, and rhodanamine gave the corresponding derivatives of isothiazole, isoxazole, pyrazole, pyrimidine, and thiazole, respectively, in high yields. Hydrolysis of **2** with hydrochloric acid gave the corresponding β-diketones. After completion of this work, Hayashi and Suzuki[7] independently reported the preparation of enaminoketones by the reactions of 2-cyanoquinoxaline with acetone, acetophenone, methylethylketone, and methylpropyl-

TABLE I. Reaction of Heteroaromatic Nitriles with Acetone[a]



$$\underset{\mathbf{1}}{RCN} + CH_3COCH_3 \xrightarrow[\text{in ether}]{NaNH_2 \text{ or } NaH} \underset{\mathbf{2}}{R\text{-}\underset{NH_2}{C}{=}CH\text{-}\underset{O}{\overset{\|}{C}}\text{-}CH_3} + \underset{\mathbf{3}}{R\text{-}\underset{NH_2}{C}{=}CH\text{-}\underset{O}{\overset{\|}{C}}\text{-}CH_2\text{-}\overset{OH}{\underset{CH_3}{C}}\text{-}CH_3}$$

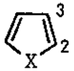
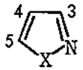
	X	R Position of substituent 2	3	4	5	6	Yield(%) & Mp(°C) of 2		Yield(%) & Mp(°C) of 3	
	O	CN					80.0	80-80.5	10	68-68.5
	O		CN				---		---	b
	S	CN					37.0	110-111	5.8	113-114.5
	S		CN				---		---	b,c
	NPh	CN					---		---	c
	NPh		CN				---		---	c
	O		CN		CH_3		76.2	106.5-107	9.3	128.5-129.5
	O		CH_3	CN	CH_3		---		---	b,c
	O		CH_3		CN		77.4	108-108.5	8.2	100.5-102.5
	S		CN		CH_3		71.5	125.5-127	16.7	110-115
	S		CH_3	CN			---		---	b
	S		CH_3		CN		74.6	114-115	6.3	127.5-129
	NPh		CN		CH_3		33.1	122.5-123	10.0	137.5-138
	NPh			CN			---		---	b,c
	NPh		CH_3		CN		19.0	105-105.5		c

TABLE I (continued)

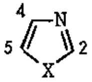
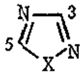
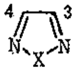
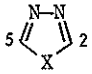
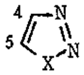
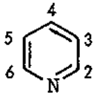
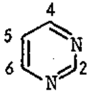
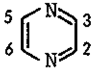
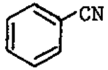
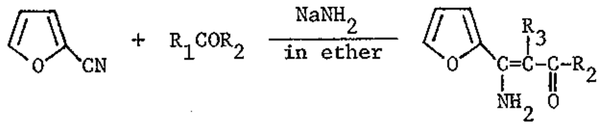
	X	R Position of substituent					Yield(%) & Mp(°C) of 2		Yield(%) & Mp(°C) of 3	
		2	3	4	5	6				
	O	CN			CH_3		70.2	97-98	3.6	115.5-116
	O			CN			---		---	d
	O	CH_3		CH_3	CN		16.7	72-74	12.8	87-89 b
	S	CN					68.4	52-53		
	S	CH_3		CN			---		---	b,c
	S	CH_3			CN		---		---	d
	O		CN		Ph		57.2	131.5-132	29.7	137-137.5
	O		Ph		CN		13.8	122.5-124.5	10.0	148-149
	NPh		CN				61.4	182-183	9.0	139-141 b
	NPh				CN		78.0	92-93	6.4	79-81
	O		CN	CH_3			78.3	99.5-100.5	9.9	74.5-75.5
	S		CN				43.3	84-85.5	---	
	NPh		CN				67.9	122-122.5	7.0	147-148.5
	O	CN			Ph		35.8	164.5-165.5	44.9	154-155
	NCH_2Ph			CN	CH_3		6.9	157-158		b,c
	NPh				CN		80.8	126-128		b

TABLE I (continued)

X	R Position of substituent 2	 3	 4	 5	 6	Yield(%) & Mp(°C) of 2		Yield(%) & Mp(°C) of 3	
	CN					72.1	87-87.5	6.5	85.5-86.5
		CN				---		--- c	
			CN			45.7	158-159	3.0	149-149.5
	CN					36.8	114.5-116	3.7	80-82
	CH_3		CN		CH_3	65.8	92-93	9.2	129-131
	CH_3		CH_3	CN		---		--- b,c	
	CN					---		--- c	
	CN	CH_3				---		--- b,c	
						---		--- c,e	

a) All the compounds obtained showed a satisfactory elemental analysis. b) Other side reaction occurred. c) Starting material was recovered. d) Ring cleavage occurred. e) p-Methoxy-, p-dimethylamino-, p-cyano-, p-nitro-, and m-nitro-benzonitriles did not react with acetone either.

TABLE II. Base-catalyzed Condensation of 2-Cyanofuran with Various Ketones in Anhydrous Ether[a]



R_1	R_2	R_3	Yield(%) & Mp(°C) of 5	
CH_3	C_2H_5	H	11.4	56.0-57.0
C_2H_5	CH_3	CH_3	24.0	40.5-41.0
C_2H_5	C_2H_5	CH_3	72.0	96.0-98.0
CH_3	n-C_3H_7	H	27.8	55.0-56.0
CH_3	i-C_3H_7	H	82.0	63.0-64.0
CH_3	t-C_4H_9	H	85.7	70.0-71.0
CH_3	C_6H_{11}	H	70.4	68.0-69.0
CH_3	C_6H_5	H	77.2	62.0-62.5
CH_3	$CH_2C_6H_5$	H	34.8	189.0-189.5
$CH_2C_6H_5$	CH_3	C_6H_5	28.6	128.0-129.0
R_1—R_2	R_2—R_3			
$-(CH_2)_5-$	$-(CH_2)_4-$		8.0	60.0-62.0
$-(CH_2)_4-$	$-(CH_2)_3-$		1.6	98.0-99.0

a) All the compounds obtained showed a satisfactory elemental analysis.

ketone in the presence of sodium amide in benzene soultion.

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