

A NOVEL METHOD FOR THE PREPARATION OF SUBSTITUTED ENAMINOKETONES¹

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A novel method for the preparation of enaminoketones, which consists of the condensation of various hetero-aromatic 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.

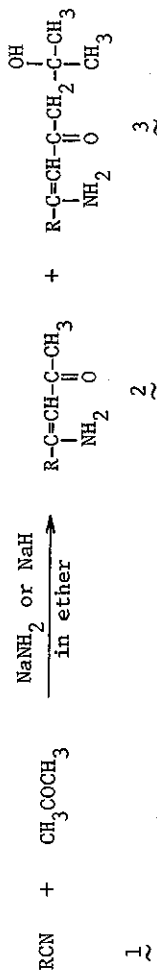
In a course of our study on synthesis of isothiazole derivatives it was required to prepare a large amount of 4-amino-4-(2-furyl)-3-buten-2-one **2** (R = 2-furyl). It was reported that the preparation of an enaminoketone was achieved by ammonolysis of a β -diketone^{2,3} or reductive cleavage of isoxazole 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-furyl-hydroxamic 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 4⁶ 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 enaminketones were carried out under similar conditions. The results are shown in TABLES I and II.

These enaminketones 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 Suzuki⁷ independently reported the preparation of enaminketones by the reactions of 2-cyanoquinoxaline with acetone, acetophenone, methylethylketone, and methylpropyl-

TABLE I. Reaction of Heteroaromatic Nitriles with Acetone^a



1

2

3


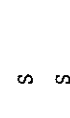
X	R						Yield (%) & Mp (°C) of 3			
	Position of substituent									
	2	3	4	5	6					
	0	CN					80.0	80-80.5	10	68-68.5
	0		CN				---	---	---	b
	S	CN					37.0	110-111	5.8	113-114.5
	S		CN				---	---	---	b, c
	NPh	CN					---	---	---	c
	NPh		CN				---	---	---	c
	0	CN				CH ₃	76.2	106.5-107	9.3	128.5-129.5
	0	CH ₃	CN			CH ₃	---	---	---	b, c
	0	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)









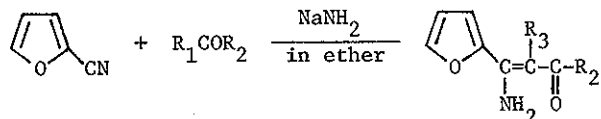
	X	R Position of substituent				Yield(%) & Mp(°C) of <u>2</u>		Yield(%) & Mp(°C) of <u>3</u>		
		2	3	4	5	6				
	O	CN			CH ₃		70.2	97-98	3.6	115.5-116
	O			CN			---		---	d
	O	CH ₃		CH ₃	CN		16.7	72-74	12.8	87-89 b
	S	CN					68.4	52-53		
	S	CH ₃		CN			---		---	b, c
	S	CH ₃			CN		---		---	d
	O		CN		Ph		57.2	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 ₂ Ph			CN	CH ₃		6.9	157-158		b, c
	NPh				CN		80.8	126-128		b

TABLE I (continued)

X	R						Yield(%) & Mp(°C) of 3		
	2	3	4	5	6	Yield(%) & Mp(°C) of 2			
	CN		CN			72.1	87-87.5	6.5	85.5-86.5
						---	---	---	c
	CN		CN			45.7	158-159	3.0	149-149.5
						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 ether.

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 ₂ H ₅	H	11.4	56.0-57.0
C ₂ H ₅	CH ₃	CH ₃	24.0	40.5-41.0
C ₂ H ₅	C ₂ H ₅	CH ₃	72.0	96.0-98.0
CH ₃	n-C ₃ H ₇	H	27.8	55.0-56.0
CH ₃	i-C ₃ H ₇	H	82.0	63.0-64.0
CH ₃	t-C ₄ H ₉	H	85.7	70.0-71.0
CH ₃	C ₆ H ₁₁	H	70.4	68.0-69.0
CH ₃	C ₆ H ₅	H	77.2	62.0-62.5
CH ₃	CH ₂ C ₆ H ₅	H	34.8	189.0-189.5
CH ₂ C ₆ H ₅	CH ₃	C ₆ H 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 solution.

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