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A CONVENIENT SYNTHESIS OF 3,5-DISUBSTITUTED-1,2,4-TRIAZOLES

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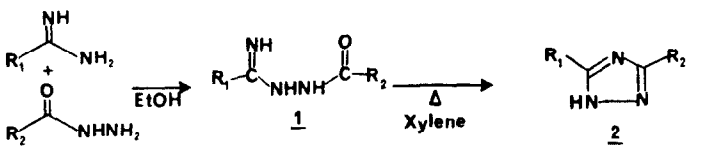
Abstract: The condensation of an acyl hydrazide and an amidine to afford an acylamidrazone, followed by thermal cyclization, provides a convenient method for preparing 3,5-disubstituted-1,2,4-triazoles in high yields.

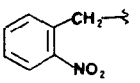
The condensation of an imidic ester with an acyl hydrazide to afford an acylamidrazone, followed by thermal cyclization, is a standard way of preparing 3,5-disubstituted-1,2,4-triazoles[2]. A recent report[3] of the condensation of formamidine acetate with a variety of oxamic acid hydrazides to produce the corresponding 1,2,4-triazole-3-carboxamides prompts us to report an interesting and general method of preparation of acyl amidrazones by condensing amidines with acyl hydrazides. Controlled thermal cyclization of the resulting acyl amidrazones then affords the desired 3,5-disubstituted-1,2,4-triazoles.

Compared to imidic esters and imidoyl halides, amidines are much less readily attacked by nitrogen nucleophiles. This displacement reaction usually requires elevated temperatures (100° to 250°C)[4] or the presence of an acid.[5,6,7] The reaction of 2-furoic acid hydrazide with formamidine acetate in refluxing aqueous solution as suggested by the patented method[3] led to the recovery of the hydrazide and the hydrolysis of the amidine, as evidenced by the evolution of ammonia. However, the free bases obtained from commercially available amidine salts (i.e. acetamidine and benzamidine) were found to react readily with the terminal nitrogen of an acyl hydrazide under either neutral conditions (Table 1) or basic conditions (Table 2). In the case of the alkyl amidine, this was evidenced by the consistent evolution of ammonia at room temperature and the precipitation of the desired acyl amidrazone. The same reaction with an aryl amidine did not proceed at room temperature. Heating the solution produced the desired acyl amidrazone but it also initiated the thermal cyclization to the triazole. The addition of a catalytic amount of sodium methoxide accelerated the overall reaction and increased the overall yield (see Table 2). While the intermediate acyl amidrazones from the aryl

amidines were observed by TLC, they were not isolated and the reaction was allowed to proceed to cyclized product.

TABLE 1



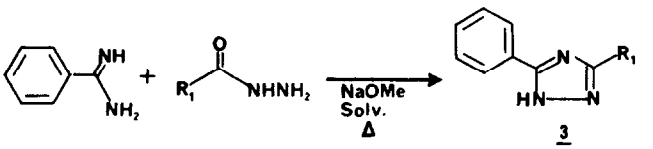
Entry	R_1	R_2	% Yield of 1[a] (based on hydrazide)	mp	% Yield of 2[a]	mp
a	CH_3		85	174-175°	93	165-166°
b	CH_3	C_6H_5-	80	170-172° (168-169°[2a])	81	163-165° (163-164°[2a])
c	CH_3		80	176-177°	98	176-178°
d	CH_3	$CH_3(CH_2)_8$-	71	125-127°	78	64-66° (66°[9])
e	CH_3		89	177-178°	79	211-213°
f	CH_3		88	152-153°	99	120-123° (119-123°[8])

[a] satisfactory C H and N analyses were obtained for all products. NMR and IR spectra were consistent with the proposed structures.

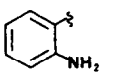
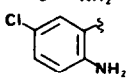
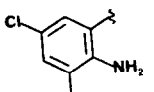
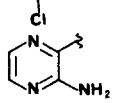
In a typical reaction, a solution of sodium methoxide (6.43 g, 0.12 mol) in anhydrous ethanol (50 mL) was added to a solution of acetamidine hydrochloride (11.25 g, 0.12 mol) in anhydrous ethanol (100 mL) at room temperature. The milky slurry was stirred at room temperature for 30 min and filtered. To the ethanol filtrate was added 2-furoic acid hydrazide (10.0 g, 0.08 mol) and the reaction mixture was stirred at room temperature overnight. The resulting slurry was cooled to 0°C, stirred for 2 hours and the precipitated acyl amidrazone collected by filtration, rinsed with cold anhydrous ethanol (2 x 25 mL) and dried in vacuo at 50°C to afford 11.22 g (85% yield) of 1a. A slurry of 1a (8.0 g, 0.05 mol) in a mixture of xylenes (80 mL) and 1-octanol (4 mL) was refluxed in an apparatus fitted with a Dean-Stark trap. After 45 min, a rapid evolution of water ensued and the starting material dissolved. The solution was allowed to cool to room temperature and was then cooled to -5°C (ice/methanol bath) and stirred for 30 minutes. The precipitated product was collected by filtration, washed with cold xylenes (4 x 25

mL) and dried in vacuo at 50°C to afford 6.95 g of 3-(2-furanyl)-5-methyl-[1H]-1,2,4-triazole, 2a (93.2% yield from 1a).

TABLE 2



3

ENTRY	R_1	Solvent	% Yield of 3[a] (based on hydrazide)	mp
a	C_6H_5-	Ethanol	97	188-190° (189-190°[2a])
b		Ethanol	71	190-193°
c		Ethanol	91	212-214°
d	$CH_3(CH_2)_8$-	Ethanol	79	125-127°[b]
e		Ethanol/ Diphenyl ether	74	257-258°
f		Ethanol/ chlorobenzene	73	257-258°
g		Ethanol/ chlorobenzene	66	235-238°
h		Ethanol/ chlorobenzene	66	265-268°

[a] Satisfactory C, H and N analyses were obtained for all products. NMR and IR spectra were consistant with the proposed structures.
[b] isolated as the oxalic acid salt.

In a typical reaction from Table 2, a solution of sodium methoxide (3.24 g, 0.06 mol) in anhydrous ethanol (60 mL) was added to a room temperature solution of benzamidine hydrochloride hydrate (7.05 g, 0.045 mol) in anhydrous ethanol (70 mL). The milky slurry was stirred at room temperature for 45 min and filtered. To the ethanol filtrate was added 2-thiophenecarboxylic acid hydrazide (4.27 g, 0.03 mol) and the resulting yellow solution was heated to reflux[10] and the reaction monitored by TLC (silica gel: 10:90 methanol:chloroform). After 48 hours, the reaction mixture was cooled to room temperature and the solvent evaporated in vacuo. The solids were washed with water (2 x 25 mL) and dried at 50°C in a vacuum oven to afford 6.21 g of 3c (91% yield from 2-thiophenecarboxylic acid hydrazide).

This modification of the procedure of Postovskii and Vereshchagina[2a] allows for the use of stable and readily available amidine salts in the preparation of acyl amidrazones. The subsequent cyclization to the corresponding 3,5-disubstituted-1,2,4-triazoles under significantly less vigorous conditions affords an attractive method of preparing this class of heterocycles.

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1 a. Drug Discovery Division, Research Department.
b. Chemical Operations Unit, Technical Operations Department.

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10. A higher boiling solvent, when required, was added at this point. The alcohol was distilled from the reaction before raising the internal temperature to the desired reaction temperature.

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