NEW SYNTHESES OF BENZOTRIAZEPINES BY NON-CONVENIENT CYCLIZATION REACTION OF N^1,N^3-DIARYLAMIDRAZONES

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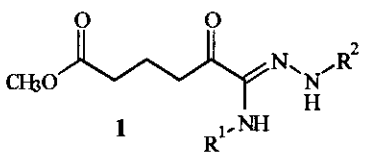
Abstract - Reactions of derivatives of amidrazones with formaldehyde give triazole, triazoline and unexpected benzotriazepine derivatives. We examined the effects of the substitution pattern of the N^3-aryl ring.

Recently we reported the unexpected formation of benzotriazepine derivatives by cyclization reaction of some amidrazone derivatives with formaldehyde.[1] These findings led us to re-examine the behaviour of amidrazones of the structure (**1**) with monocarbonyl compounds. Arylhydrazonoyl chlorides used as starting substances react with amines by nucleophilic substitution affording N^1-arylamidrazones (**1**).



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R^1: H, CH_3, aryl
R^2: aryl

Cyclization reactions of open-chain amidrazones with monocarbonyl compounds are known to give triazolines and triazoles.[2]

The triazole (**2**) was obtained by cyclization of the N^3-unsubstituted amidrazone (**1a**) with formaldehyde in refluxing ethanol under oxidative conditions (method a) analogue[3] in 55% yield (Scheme 1).

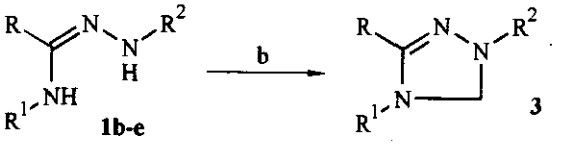
Scheme 1

1a **2**

R = $CH_3OCO(CH_2)_3CO$; R^2 = C_6H_5
a: 1) HCHO/TsOH, EtOH, reflux; 2) oxidation

Triazolines (**3**) were formed by reaction of N^3-monosubstituted amidrazones (**1b-1e**) with formaldehyde also in refluxing ethanol (method b, 40-50% yield) according to literature.[4] The reaction time was two hours. Only compound (**3d**) was obtained by refluxing in acetic acid for 10 min in 30% yield.

Scheme 2



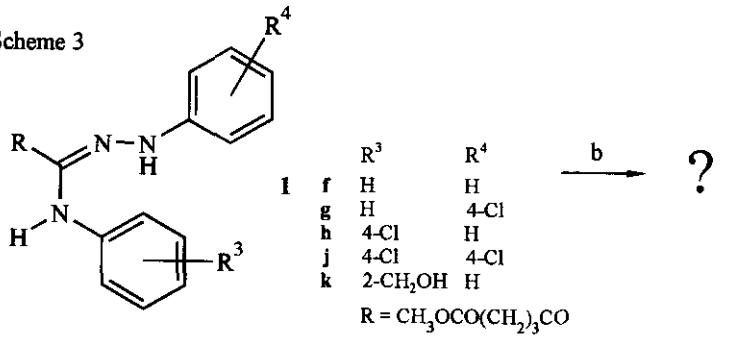
$R = CH_3OCO(CH_2)_3CO$

b: HCHO, TsOH, EtOH, reflux or AcOH, reflux

	R^1	R^2
b	CH_3	4-ClC_6H_4
c	2,6-$Cl_2C_6H_3$	4-ClC_6H_4
d	2,6-$Cl_2C_6H_3$	2,6-$Cl_2C_6H_3$
e	2,4,6-$Br_3C_6H_2$	4-ClC_6H_4

Surprisingly the reaction of 2-oxoadipic acid 6-methyl ester 1-N^1,N^3-diphenylamidrazones (**1f-1k**) with formaldehyde under the same conditions like for the preparation of triazoline (method b) did not result in the expected triazoline (**3**). What was happened?

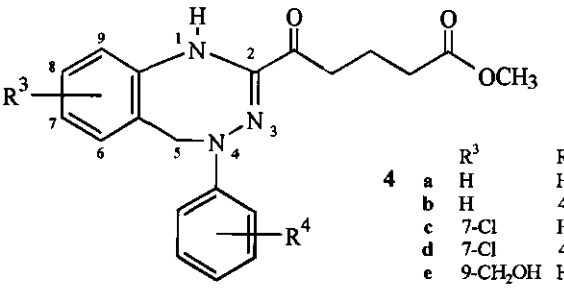
Scheme 3



		R^3	R^4
1	**f**	H	H
	g	H	4-Cl
	h	4-Cl	H
	j	4-Cl	4-Cl
	k	2-CH_2OH	H

$R = CH_3OCO(CH_2)_3CO$

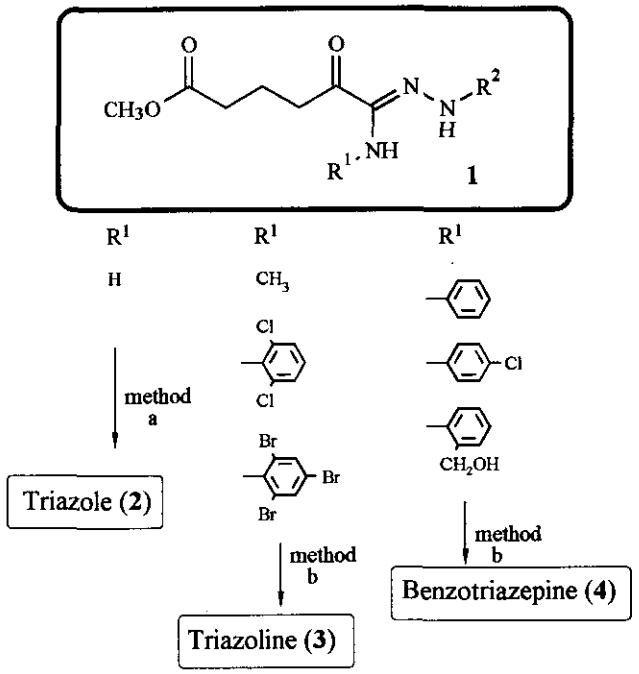
The analytical data of isolated compounds indicate structure (**4**).[1]



		R^3	R^4
4	**a**	H	H
	b	H	4-Cl
	c	7-Cl	H
	d	7-Cl	4-Cl
	e	9-CH_2OH	H

What was the difference between the reaction to triazolines and to benzotriazepines? The reaction conditions were all the same. Only the structure of the starting amidrazones differed. The comparison of the substitution pattern (Scheme 2 and Scheme 3) shows, that the triazolines (**3**) only formed from amidrazones, where the N^3 of the amidrazone is monoalkylated or substituted with ortho-blocked ring systems. If the phenyl substituent isn't occupied in 2- and 6-position there can be obtained the benzotriazepines (**4**) (Scheme 4), compound (**4a-c**) in 60-70% yield, derivatives (**4d**) and (**4e**) in 30% yield.

Scheme 4



The cyclization mechanism can follow two different ways. Either a hydroxymethylation of the N^3-aryl ring takes place or the formaldehyde reacts at first with the N^1-amidrazone nitrogen. In order to clarify the mechanism the amidrazone (**1k**) as the N^3-arylhydroxymethylated product of amidrazone (**1f**) should give by an intramolecular cyclization the benzotriazepine (**4a**). By refluxing **1k** and catalytic amounts of p-toluenesulfonic acid in ethanol but also by variation the reaction conditions the formation of benzotriazepine wasn't detectable. Furthermore by addition of formaldehyde to the solution of **1k** in ethanol and refluxing the mixture the benzotriazepine (**4e**) was obtained. This attempt excludes the hypothesis that the first cyclization step is the hydroxymethylation of the N^3-aryl substituent. In addition it is mentioned that the formation of an intermediate product wasn't detectable by tlc. It is to be proofed whether the formaldehyde reacts at first with the N^1-nitrogen of the amidrazone structure or the cyclization undergoes another way.

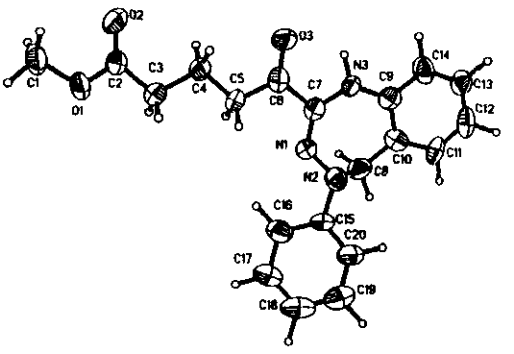


Figure 1

ORTEP-drawing[5] of the structure of one molecule in the crystal of compound (**4a**)

The structure of the compounds (**2**, **3** and **4**) was determined by appropriate analysing methods (ir, uv, ^{1}H-nmr and ms). Compound (**4a**) was also confirmed by X-ray diffraction study (Figure 1).

Another way to 4-phenyl-4,5-dihydro-1*H*-1,3,4-benzotriazepine derivatives was described the first time in 1982 by Fusco and Sannicolo.[6] They obtained these compounds by oxidation of N^1,N^3-diarylsubstituted amidrazones with methyl groups in ortho-position of the aromatic ring on the N^3 and following thermal cyclization under reflux in xylene.

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