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Synthesis of isoxazolo[4,5-*e*][1,4]diazepin-5-ones from 5-acyl-4-(haloacetylamino)isoxazoles

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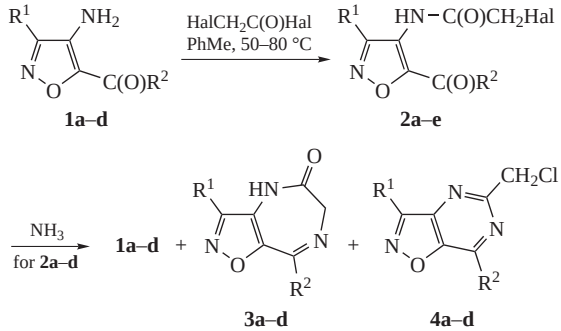
Treatment of 5-benzoyl-4-(iodoacetylamino)isoxazoles with alcoholic ammonia leads to isoxazolo[4,5-*e*][1,4]diazepin-5-ones, whereas the analogous chloroacetylamino derivatives are converted into a mixture of the deacylated 4-aminoisoxazoles and isoxazolo-[4,5-*d*]pyrimidines.

Although various heterocyclic analogues of 1,4-benzodiazepines possessing biological activity[1,2] have been extensively studied, information on isoxazolo[1,4]diazepines is limited.[3–6] 4-Amino-isoxazole-3-carboxamides **1a**,**b** (Scheme 1), which are available by cyclization of O-alkylated hydroxyiminonitriles,[7,8] we reasoned herein, could serve as precursors to isoxazolo[4,5-*e*][1,4]diazepin-5-ones **3** and/or isoxazolo[4,3-*e*][1,4]diazepine-5,8-diones. To our knowledge, no synthesis of isoxazolo[4,5-*e*][1,4]diazepin-5-ones **3** has been published so far.

Intermediate haloacetylated compounds **2** were obtained by heating of aminoisoxazoles **1** with $HalCH_2C(O)Hal$ (Hal = Cl, Br) in toluene in the absence of a base. Although acetylation with $ClCOCH_2Cl$ in the presence of triethylamine proceeds at room temperature, the chloroacetylated products in this case are contaminated with diacetylated ones.

When chloroacetylated derivatives **2** were allowed to react with ammonia in methanol, a mixtures of parent aminoisoxazole **1**, isoxazolodiazepine **3** and isoxazolopyrimidine **4** were obtained. In the case of aminoisoxazoles **2a**,**b** bearing two electron-withdrawing groups, deacetylation is the only process (Table 1).

Both N-deacetylation and closure into pyrimidine ring are not usual reactions for the similar systems. Acyclic aminoacetylamino benzophenones,[2] 3,4-epoxy-2-quinolones, 3-amino-2(1*H*)-quinolones and 3-hydroxyquinolones were previously reported[9] as side products which commonly accompany the preparation of benzodiazepines. 3,4-Epoxyquinolones could be prepared with yields up to 64% by processing in mixture of liquid NH_3 and THF.[10]



a $R^1 = C(O)NH_2$, R^2 = Ph, Hal = Cl
b $R^1 = C(O)NHBn$, R^2 = Ph, Hal = Cl
c $R^1 = R^2$ = Ph, Hal = Cl
d R^1 = Ph, R^2 = Me, Hal = Cl
e $R^1 = C(O)NHBn$, R^2 = Ph, Hal = Br

Scheme 1

Table 1 Ammonolysis of **2a–d** (MeOH, 20 °C).[a]

Compound	Time/h	Conversion (%)	Yields, %		
			1	**3**	**4**
2a	48	97	96.8	0.2	–
2b	48	95	98.2	0.3	–
2c	72	54	72	18	10
2d	48	100	–	2	97

[a]Yields on converted **2a–d** (measured from NMR spectra of the evaporated reaction mixtures). For experimental details, see Online Supplementary Materials.

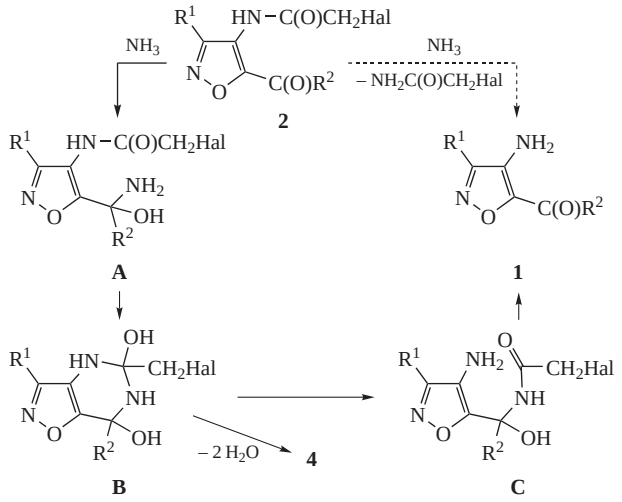
It seems reasonable to assume that unusually high rate of N-deacetylation in case of aminoisoxazoles bearing carbamoyl substituents results from the low electron density on the nitrogen atom of amide group. In order to confirm this hypothesis, we measured the basicities of these compounds spectrophotometrically (Table 2). Basicities measured could be compared with pK_a of 4-amino-3,5-dimethylisoxazole (+3.8),[11] unsubstituted isoxazole (–2.28),[11] 4-nitroaniline (+1.0),[12] and 2,4-dinitroaniline (–4.25).[13]

As established from UV spectra[11(a)] of 3-, 4- and 5-amino-isoxazoles and then confirmed by ^{15}N NMR spectroscopy,[11(b)] there is a significant difference in the site of the first protonation and of the metal ion coordination.[3] 3-Amino and 5-amino-isoxasoles are protonated at the isoxazole ring nitrogen. In contrast, 4-aminoisoxazoles are monoprotonated at the amino group. 4-Aminoisoxazoles bearing electron-withdrawing groups are considerably weaker bases than 4-nitroaniline and alkyl-substituted 4-aminoisoxazoles. Low basicities of the amino group and low electron densities in chloroacetamide moiety correlate

Table 2 Basicities of aminoisoxazoles **1a**,**c**,**d** in sulfuric acid solutions.[a]

Compound	UV spectrum in MeOH [λ/nm (ε)]	UV spectrum in H_2SO_4[b] [λ/nm (ε)]	pK_a
1a	360 (13700) 262 (7700)	286 (16000)	–1.9±0.05
1c	358 (15900) 259 (11900) 227 (19600)	284 (16600)	–1.8±0.1
1d	331 (8700) 225 (14400)	230 (15600)	–1.2±0.05

[a]H_0 values for different concentrations of sulfuric acid were taken from ref. 14. [b]60% H_2SO_4 for **1a**, **1c** and 50% H_2SO_4 for **1d**.



Scheme 2

with high rates of deacetylation, but in case of the direct nucleophilic attack of ammonia on carbonyl group of the chloroacetyl moiety one should expect approximately equal rates of deacetylation because the basicities of aminoisoxazoles are not different in fact. However, ammonolysis affords fundamentally different products at relatively small changes in the amino group basicities.

Based on these findings we assume that the main reaction pathway (Scheme 2) includes a rapid nucleophilic attack of ammonia on the ketone group with the formation of the intermediate hemiaminal **A** (aminal group is not strongly electron-withdrawing). Next, the key intermediate **B** is formed, which is favoured by the presence of 3-positioned electron-withdrawing group (*e.g.*, carbamoyl) in the isoxazole ring. Further cleavage of the amide bond results in deacylation to give aminoisoxazoles **1**. When R^1 is phenyl, elimination of two water molecules is preferential to produce isoxazolopyrimidine **4**. Since ketone group is more electrophilic than carbamoyl one, a direct ammonia-assisted cleavage of amide bond does not make a considerable contribution in total yields of aminoisoxazoles **1**. In case of electron-rich rings such as benzene, thiophene and similar rings, the ketone group is insufficiently electrophilic and a halogen substitution proceeds more quickly than the addition of ammonia to the ketone group.

The bromoacetylated compound **2e** and iodoacetylated compound **5b** affords predominantly diazepine **3b** (Scheme 3, Table 3).† Iodoacetylated compounds **5a**–**d** were prepared by the Finkelstein reaction in acetonitrile and isolated before the cyclization.

When the Finkelstein reaction and treatment with ammonia were conducted sequentially in the same vessel without isolation of iodoacetylated compound **5b**, the parent aminoisoxazole **1b** was predominantly formed (Table 3, run 2). On the other hand, when the process was carried out in liquid ammonia, iodides gave lower yields than bromides.[16]

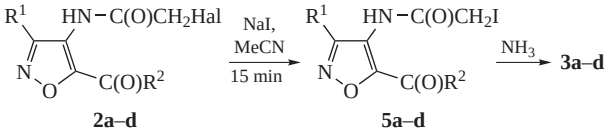
Attempts to obtain diazepine **3b** by other synthetic schemes were less successful. A condensation of aminoisoxazole **1b** with glycine ethyl ester hydrochloride leads to diazepine **3b** in very low yield (3%). An attempt to use hexamethylenetetramine (hexamine) instead of ammonia under the conditions previously published[6,17] affords isoxazolodiazepine **3b** contaminated with side products. As previously reported,[17] in reaction with hexamine, formed formaldehyde produces isoxazolones and dihydropyrimidines. Hence,

† *General procedure for the preparation of isoxazolo[4,5-e][1,4]diazepines* **3a**–**d**. 5% Methanolic ammonia (4–8 ml) was added to 1 mmol of haloacetylated aminoisoxazoles **5a**–**d** or **2e**. After 1–2 days, volatiles were evaporated under vacuum and chromatography on a dry column[15] with a mixture of benzene and ethyl acetate (10:1, then 1:1) as eluent gave, after recrystallization from ethanol (methanol), the colourless analytical sample of **3a**–**d**.

Table 3 Preparation of **3b** at room temperature.

Run	Time/h	Conversion (%)	Ratio **1b**:**3b**
1: **2b** + NH_3	48	95	490:1
2: **2b** + NaI[a] + NH_3	24	85	4.1:1
3: **2e** + NH_3	24	100	1:3.1
4: **5b** + NH_3	24	100	1:9.9

[a] Equimolar amount of NaI was added.



Scheme 3

in case of deactivated and/or sterically hindered systems, iodoacetylated derivatives provide better yields of the fused diazepines than analogous chloroacetylated or bromoacetylated ones.

Other diazepines **3a**,**c**,**d** were synthesised under the conditions for preparation of **3b**. Isoxazolodiazepine **3d** was obtained in good yield from iodoacetylated compound **5d**. 5-Iodomethyl- or 5-aminomethylisoxazolo[4,5-*d*]pyrimidine similar to **4d** was not detected.

The structures of the prepared compounds were confirmed by microanalysis, HRMS, ^{1}H NMR and UV spectral data (see Online Supplementary Materials).

The procedure developed can be recommended for the preparation of similar isoxazolo[4,5-*e*][1,4]diazepin-5-ones from the corresponding deactivated electron-poor isoxazole derivatives.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2012.03.011.

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