HETEROCYCLIC REARRANGEMENTS - THE REARRANGEMENT OF 3-AROYLAMINOISOXAZOLES INTO 2-AROYLAMINOOXAZOLES

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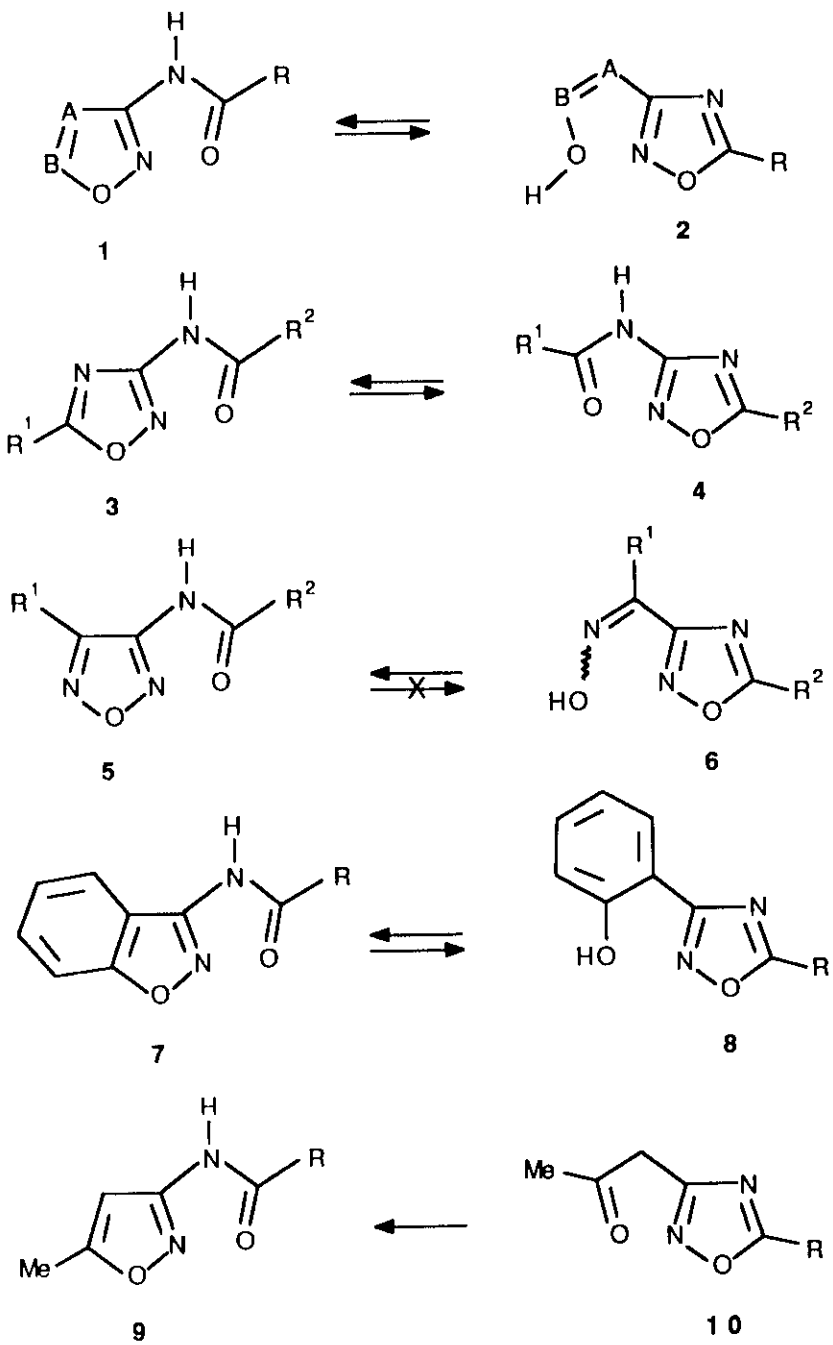
Abstract - When treated with *t*-BuOK in DMF at 110-120°C, 3-aroylamino-5-methylisoxazoles gave good yields of 2-aroylamino-5-methyloxazoles as the ring rearrangement products. The same isoxazole to oxazole ring isomerization has been also observed in a photoinduced reaction.

It is well known[1] that acylaminoazoles (**1**) are potentially rearrangeable into 1,2,4-oxadiazoles (**2**) according to a general pattern of heterocyclic rearrangements.[1,2] On the other hand, the rearrangement of the 1,2,4-oxadiazoles (**2**) into **1** could be also predicted, and several examples are known for the direct and the reverse reaction.[1] In this context, it has been reported that 3-acylamino-1,2,4-oxadiazoles furnish a thermally induced equilibrium process[3] of the *iso*-heterocyclic type **3** ⇌ **4**, which can be also degenerate[4] when $R^1 = R^2$. On the contrary, 3-acylamino-1,2,5-oxadiazoles (**5**) do not rearrange to the oxadiazoleoximes (**6**); the reverse reaction **6** ⟶ **5** does occur, indeed, according to the different stability (or reactivity) of the two heterocyclic rings.[1]

For 3-acylaminobenzisoxazoles (**7**) the base induced equilibrium process depends on the substituent R and the nature of the used base.[5] In the presence of anionic reagents, such as hydroxy or alkoxy anion, the oxadiazole (**8**) is the favoured component, owing to the stabilization of the phenolate species in **8**. On the contrary, 3-acetonyl-1,2,4-oxadiazoles (**10**; R = *i*-Pr, cyclo-C_6H_{11}, -CH_2OMe), when treated with strong bases (*t*-BuOK in THF), rearrange through the enolate anion to the corresponding 3-acylamino-5-methylisoxazoles (**9**).[6]

Scheme 1


H
N
R
A
B
O
N
O
1
A
B
N
O
H
N
O
R
2
H
N
R2
N
N
O
R1
O
3
H
N
R1
O
N
N
O
R2
4
R1
H
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R2
N
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5
R1
N
N
HO
N
O
R2
6
H
N
R
O
N
O
7
N
HO
N
O
R
8
H
N
R
O
N
Me
O
9
Me
N
O
N
O
R
10

However, the occurrence of a possible equilibrium process of the type **9** ⇌ **10**, as depending on the nature of R (which is in the acylamino moiety in **9**, but at C_5 of the oxadiazole ring in **10**) was not explored.

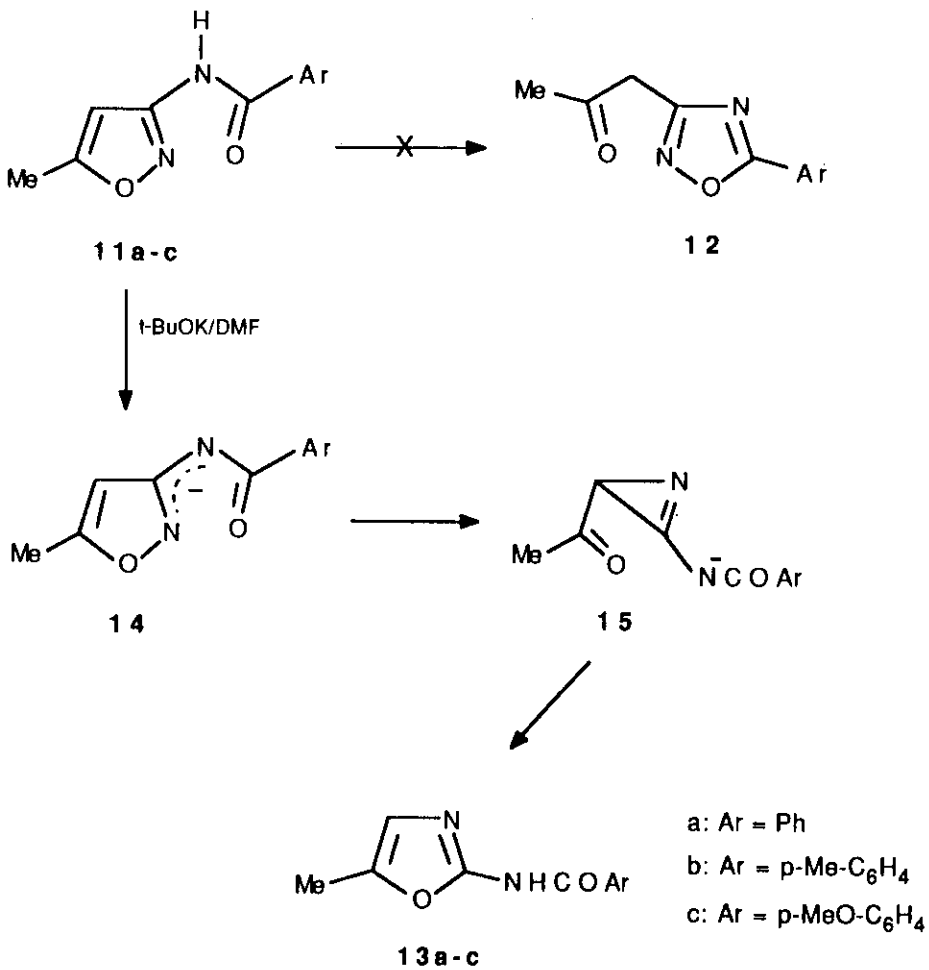
With this in mind, and in connection with our studies on heterocyclic rearrangements of five membered rings[7] and photochemical investigations on acylaminoazoles,[8] we aimed to point out an equilibrium process of this type. For this pourpose, we looked at the behaviour of 3-aroylamino-5-methylisoxazoles (**11**), from which the 5-aryl substituted oxadiazoles (**12**) (*i.e.*, an aryl-stabilized oxadiazole system) could have been expected.

Surprisingly, on reacting with *t*-BuOK in DMF at 110-120°C, compounds (**11a-c**) gave very good yields of the corresponding 2-aroylamino-5-methyloxazoles (**13a-c**) (80%) as the ring rearrangement products, whereas no traces amounts of the acetonyloxadiazoles (**12**) have been detected. The rearrangement occurs only in the presence of anionic reagents in DMF: in fact, melting alone at 160-180°C or refluxing in DMF, as well as refluxing with aqueous (10%) KOH in ethanol, left compounds (**11a-c**) essentially unchanged. As regards the oxazole structure (**13**), it was based on analytical and spectroscopic evidences, particularly on ^{13}C-nmr and mass spectra (see experimental).

The observed reaction seems to be an unusual case of a base-promoted isoxazole to oxazole rearrangement; however this type of ring isomerization represents a well documented photochemical[9] or thermal[10] reaction of the isoxazole which proceeds through a typical ring contraction - ring expansion route.[9] Therefore, we tried to verify the occurrence of an analogous photoinduced ring isomerization in the case of aroylamino compounds. We have observed that, when irradiated at 254 nm in dichlorometane solution (Rayonet apparatus) the 3-aroylaminoisoxazoles (**11a,b**) really gave the rearranged oxazoles (**13a,b**) in 10% yield (90% of starting material were recovered, however); further irradiation does not increase significantly yields of the rearranged oxazole, since subsequent photoreactions take place.[11] Clearly, the base promoted rearrangement is characterized by its simplicity and very good yields. Therefore, we are interested in recognizing a possible generalization of this reaction in the isoxazole series.

As regards the mechanistic aspect, tentatively the formation of the oxazole could be explained by assuming an anionic promoted contraction of the isoxazole ring to an azirine species, followed by an anionic assisted ring expansion of latter to the oxazole system (see Scheme 2), the dipolar aprotic solvent being a significant partner in the overall reaction.

Scheme 2


H
N
Ar
Me
O
N
O
X
Me
N
O
N
Ar
11a-c
12
t-BuOK/DMF
N
Ar
Me
O
N
O
N
Me
O
N
N C O Ar
14
15
N
Me
O
NHCOAr
13a-c
a: Ar = Ph
b: Ar = p-Me-C6H4
c: Ar = p-MeO-C6H4

EXPERIMENTAL

Melting points were determined with a Kofler hot-stage apparatus; ir spectra (nujol mulls) were determined with a Perkin-Elmer 257 instrument, ^{1}H nmr (250 MHz) and ^{13}C nmr (62MHz) spectra with a Bruker BZH 250/52 (tetramethylsilane as internal standard) spectrometer and mass spectra with a RMU 6D single focusing spectrometer (70eV). Flash chromatography was performed on Merck silica gel (0.040-0.063 mm). Light petroleum boils in the range 40-60°C. Photochemical reactions were carried out in a Rayonet RPR-100 apparatus at 254 nm (dichloromethane solution).

Table. ^{13}C nmr chemical shifts of compounds (**11a-c**) and (**13a-c**)

Compd	C_2(or C_3)	C_4	C_5	C=O	Me	Aromatic	
11a	165.24(s)	96.98(d)	158.63(s)	169.29(s)	12.05(q)	133.16(s),132.16(d)	
						128.36(2C,d)	
						128.00(2C,d)	
11b	164.99(s)	96.98(d)	158.61(s)	169.13(s)	11.97(q)	142.27(s),130.25(s)	20.87(q)
						128.84(2C,d)	(p-Me)
						127.96(2C,d)	
11c	164.48(s)	96.91(d)	158.70(s)	169.06(s)	11.97(q)	162.30(s),125.13(s)	55.28(q)
						130.00(2C,d)	(p-OMe)
						113.54(2C,d)	
13a	151.65(s)	122.24(d)	145.89(s)	165.25(s)	10.50(q)	132.65(s),132.34(d)	
						128.42(2C,d)	
						128.94(2C,d)	
13b	151.92(s)	122.35(d)	146.04(s)	165.20(s)	10.60(q)	142.64(s),129.96(s)	21.06(q)
						129.07(2C,d)	(p-Me)
						128.14(2C,d)	
13c	151.94(s)	122.21(d)	145.89(s)	164.65(s)	10.52(q)	162.64(s),124.72(s)	55.37(q)
						130.04(2C,d)	(p-OMe)
						113.68(2C,d)	

Compounds (**11a-c**) were prepared by reacting 3-amino-5-methylisoxazole (10 mmol) with the appropriate aroyl chloride (10 mmol) in anhydrous benzene (100 ml) containing equimolar amounts of pyridine (10 mmol) at room temperature for 24 h, and then working as usual.

Compound (**11a**) had mp 164°C (benzene); ir: 3250, 3210, 3140 and 3080 cm^{-1} (NH), 1680 cm^{-1} (CO); ^1H nmr (DMSO-d_6) ∂: 2.35 (s, 3H, CH_3), 6.80 (s, 1H, CH), 7.20-8.10 (m, 5H, aromatic), 11.35 (s, 1H, NH); ms m/z: 202 (M^+), 174, 160, 105, 77, 51, 43. Anal. Calcd for $C_{11}H_{10}N_2O_2$: C, 65.35; H, 4.95; N, 13.86. Found C, 65.30, H, 5.00, N, 13.85 .

Compound (**11b**) had mp 191°C (benzene); ir: 3250, 3210, 3110 and 3080 cm^{-1} (NH), 1680 cm^{-1} (CO); ^1H nmr (DMSO-d_6) ∂: 2.35 and 2.40 (2s, 6H, $2CH_3$), 6.80 (s, 1H, CH), 7.20-8.10 (m, 4H, aromatic), 11.25 (s, 1H, NH); ms m/z: 216 (M^+), 119, 91, 65. Anal. Calcd for $C_{12}H_{12}N_2O_2$: C, 66.67; H, 5.56; N, 12.96. Found C, 66.70, H, 5.50, N, 13.00 .

Compound (**11c**) had mp 182°C (benzene); ir: 3250, 3210, 3150 and 3080 cm^{-1} (NH), 1680 cm^{-1} (CO); ^1H nmr (DMSO-d_6) ∂: 2.35 (s, 3H, CH_3), 3.85 (s, 3H, OCH_3), 6.80 (s, 1H, CH), 7.00-8.00 (m, 4H, aromatic), 11.20 (s, 1H, NH); ms m/z: 232 (M^+), 190, 135, 107, 77, 43. Anal. Calcd for $C_{12}H_{12}N_2O_3$: C, 62.07; H, 5.17; N, 12.07. Found C, 62.10, H, 5.25, N, 12.00 .

Rearrangement of 3-Aroylaminoisoxazoles (**11a-c**). - General Procedure.

A mixture of the isoxazole (5 mmol), *t*-BuOK (5.1 mmol) and DMF (30 ml) was kept at 110-120°C for 4 h. The solvent was removed under reduced pressure, and the residue was worked with water. Acidification with acetic acid and filtration of the precipitate gave the rearranged products which were purified by chromatography by using mixtures of light petroleum - ethyl acetate in varying ratios as eluent.

Compound (**13a**) had mp 134°C (benzene)(80%); ir: 3300, 3230, and 3120 cm^{-1} (NH), 1700 cm^{-1} (CO); ^1H nmr (DMSO-d_6) ∂: 2.30 (s, 3H, CH_3), 6.80 (s, 1H, CH), 7.40-8.10 (m, 5H, aromatic), 11.30 (s, 1H, NH); ms m/z: 202 (M^+), 105, 77, 51, 43. Anal. Calcd for $C_{11}H_{10}N_2O_2$: C, 65.35; H, 4.95; N, 13.86. Found C, 65.30, H, 5.00, N, 13.80 .

Compound (**13b**) had mp 140°C (benzene)(80%); ir: 3220, 3140 and 3120 cm^{-1} (NH), 1700 cm^{-1} (CO); ^1H nmr (DMSO-d_6) ∂: 2.30 and 2.40 (2s, 6H, $2CH_3$), 6.80 (s, 1H, CH), 7.20-8.10 (m, 4H, aromatic), 11.25 (s, 1H, NH); ms m/z: 216 (M^+), 188, 119, 91, 65. Anal. Calcd for $C_{12}H_{12}N_2O_2$: C, 66.67; H, 5.56; N, 12.96. Found C, 66.60, H, 5.60, N, 12.90 .

Compound (**13c**) had mp148-150°C (benzene)(80%); ir: 3250, 3210, 3150 and 3080 cm^{-1} (NH), 1680 cm^{-1} (CO); ^1H nmr (DMSO-d_6) ∂: 2.25 (s, 3H, CH_3), 3.85 (s, 3H, OCH_3), 6.80 (s, 1H, CH), 7.00-8.10 (m, 4H, aromatic), 11.20 (s, 1H, NH); ms m/z: 232 (M^+), 135, 107, 77, 64. Anal. Calcd for $C_{12}H_{12}N_2O_3$: C, 62.07; H, 5.17; N, 12.07. Found C, 62.00, H, 5.20, N, 12.10 .

Photochemical Reactions.

A solution of the isoxazole (5 mmol) in dichloromethane (200 ml), portioned in four quartz tubes, was irradiated in a Rayonet apparatus RPR-100 at 254 nm. The solvent was removed under reduced pressure and the residue was chromatographed by using light petroleum - ethyl acetate in varying ratios as eluent.

*Irradiation of compound (**11a**) for 30 min gave the starting material (90%), and compound (**13a**) (10%).*

Irradiation of compound (**11b**) for 60 min gave the starting material (90%), and compound (**13b**) (10%).

ACKNOWLEDGEMENTS

The authors thank the MURST (Rome) for financial support.

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11 In the irradiation of **11c** we are not able to isolate the oxazole (**13c**), owing to the formation of subsequent photoproducts.

Received, 5th June, 1991