REACTION OF AMIDOXIMES WITH α-CHLOROACID CHLORIDES: NOVEL SYNTHESIS OF 1,2,4-OXADIAZIN-5-ONES

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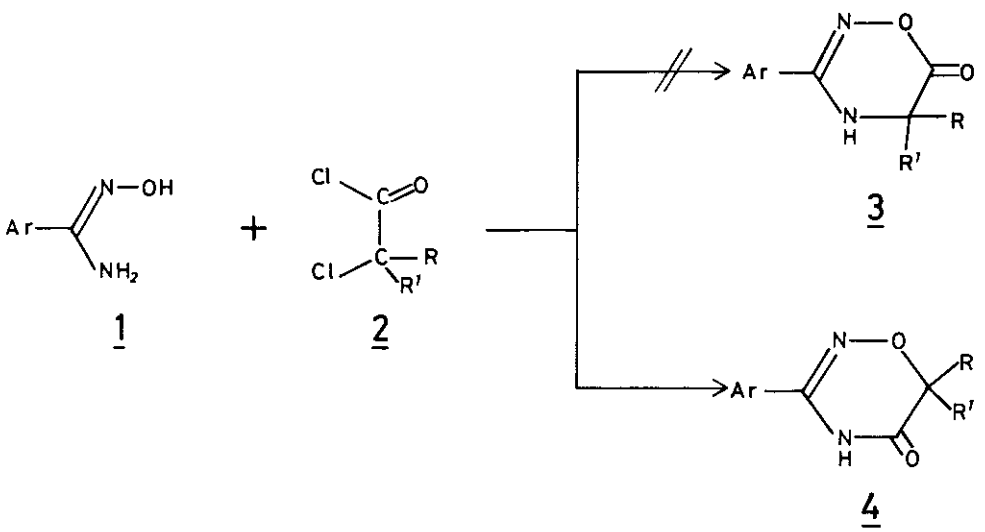
Abstract — The reaction of amidoximes with α-chloroacid chlorides gives under thermal reaction conditions 5-(1-chloroalkyl)-1,2,4-oxadiazoles. In presence of a strong base, the reaction follows a different path leading to the formation of 4H-1,2,4-oxadiazin-5(6H)-ones (4). This latter transformation, involving O → N acyl migration, constitutes a new convenient route to compounds 4.

1,2,4-Oxadiazin-6-ones (3) have been synthesized for the first time by us[1] from the reaction of nitrile oxides and α-amino esters. Shortly thereafter, Ajzert and Takacs[2] described a related, but less convenient method for synthesis of compounds 3 by ring expansion of (4-ethoxycarbonylmethyl)-Δ^2-1,2,4-oxadiazol-5-ones, accessible from amidoximes through a multi-step reaction. Both methods suffer, however, from certain limitations and, in some cases, the reported yields are rather low. This prompted us to explore a new synthetic route for this type of heterocycles, which complements existing synthetic methods. We envisage that the reaction of amidoximes (1) with α-chloroacid chlorides (2) could directly yield the desired heterocycles 3 (Scheme 1). Hence, this latter reaction is investigated in the present study.

When a solution of the amidoxime (1) in dry tetrahydrofuran (THF) was treated with an α-chloroacid chloride (2), in the presence of two equivalents of sodium hydride, an immediate exothermic reaction took place. Work up of the reaction mixture gave, surprisingly, good yields of the 1,2,4-oxadiazin-5-ones (4), but none of the desired 1,2,4-oxadiazin-6-ones (3) (Scheme 1).

The structure of compounds 4 is elucidated from elemental analysis and spectral data (Table 1). These new compounds are characterized by infrared absorption bands in the range 3080-3280 and 1705-1725 cm^{-1}, assigned respectively to the N-H

Scheme 1



and C=O bond stretching modes. The latter lactam carbonyl absorption occurs, as expected, at a significantly lower frequency than does the lactone carbonyl in the isomeric 1,2,4-oxadiazin-6-ones.[1,2] ^{1}H-nmr spectra of compounds 4a-i ($CDCl_3$) exhibit a broad singlet (1 H) in the range δ 9.55-9.65 attributed to the amide N-H proton, which disappears upon addition of deuterium oxide. The C_6-protons appear as a sharp singlet in compounds 4a-e, and as a quartet in compounds 4f-i. The absence of mutual coupling between C_6-H and N_4-H, thus indicated, is in agreement with the assigned structure 4, in which these protons are separated by the carbonyl group. In contrast, such coupling is apparent in the isomeric structure 3[1,2] in which the above mentioned protons are vicinal. Structure 4 is fruther substantiated by mass spectral data. In addition to intense peaks corresponding to the correct molecular ions, other prominent fragment ions are also observed (Table 2). These characteristic fragment ions $[A]^+ - [D]^+$ are produced by bond fissions as postulated in Scheme 2. The occurrence of ion $[M\text{-}RR\ CO]^+$, though of low abundance, conforms with structure 4, but not with the

Table 1. Physical and Spectral Data of Compounds 4a-j[a]

Compd	Ar	R	R'	Yield(%)	mp(°C)	ir (cm^{-1}) N - H	ir (cm^{-1}) C=O	ir (cm^{-1}) C=N	^{1}H-nmr (δ) Ar	^{1}H-nmr (δ) R,R'	^{1}H-nmr (δ) NH
4a	C_6H_5	H	H	68	148-150	3280-3140	1710	1610	7.47(2H,m) 7.70(3H,m)	4.40(2H,s)	9.60(1H,br)
4b	p-$NO_2C_6H_4$	H	H	75	226-228	3260-3080	1725	1590	8.17(2H,d) 7.91(2H,d)	4.33(2H,s)	11.36(1H,br)
4c	p-BrC_6H_4	H	H	82	178-179	3280-3100	1710	1615	7.47(4H,s)	4.34(2H,s)	9.30(1H,br)
4d	p-$CH_3C_6H_4$	H	H	76	151-152	3280-3140	1725	1610	7.60(2H,d), 7.20(2H,d) 2.40(CH_3,s)	4.40(2H,s)	9.65(1H,br)
4e	o-$CH_3C_6H_4$	H	H	50	98-100	3280-3160	1710	1620	7.20(4H,s) 2.37(CH_3,s)	4.27(2H,s)	9.57(1H,br)
4f	C_6H_5	H	CH_3	66	129-130	3290-3140	1715	1615	7.75(2H,m) 7.44(2H,m)	4.34(1H,q) 1.52(3H,d)	9.55(1H,br)
4g	p-$NO_2C_6H_4$	H	CH_3	78	258-260	3230-3100	1720	1585	8.27(2H,d) 8.03(2H,d)	4.32(1H,q) 1.53(3H,d)	11.50(1H,br)
4h	p-BrC_6H_4	H	CH_3	85	186-187	3280-3160	1715	1615	7.73(2H,d) 7.53(2H,d)	4.26(1H,q), 1.48(3H,d)	11.20(1H,br)
4i	p-$CH_3C_6H_4$	H	CH_3	75	154-155	3260-3120	1720	1610	7.58(2H,d), 7.17(2H,d) 2.38(CH_3,s)	4.32(1H,q), 1.55(3H,d)	9.60(1H,br)
4j	p-$CH_3C_6H_4$	C_6H_5	C_6H_5	75	210-212	3260-3100	1710	1610	7.54-6.98(14H,m) 2.26(CH_3,s)		9.46(1H,br)

(a) Nmr spectra of 4b,g,h were taken in DMSO-d_6.

Scheme 2

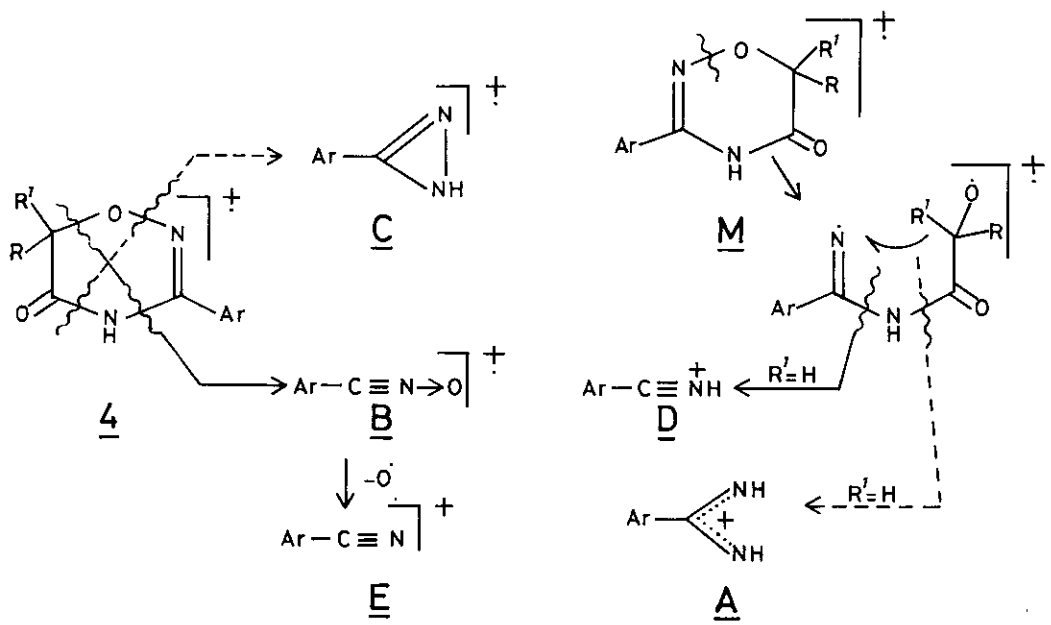


Table 2. Mass Spectral Data for Compounds 4a-j (m/z values, relative intensity[a] in parenthesis)

Compd	$[M]^+$	$[M-RR'CO]^+$	$[A]^+$ or $[B]^+$	$[C]^+$	$[D]^+$	$[E]^+$
4a	176(90)	146(2)	119(6)	118(12)	104(100)	103(22)
4b	221(100)	191(2)	164(2)	163(26)	149(68)	148(7)
4c	256/254(98)	226/224(4)	199/197(5)	198/196(16)	184/182(100)	183/181(18)
4d	190(80)	160(2)	133(8)	132(26)	118(100)	117(20)
4e	190(74)	160(3)	133(9)	132(100)	118(52)	117(66)
4f	190(61)	146(2)	119(20)	118(64)	104(90)	103(100)
4g	235(100)	191(3)	164(26)	163(18)	149(96)	148(8)
4h	270/268(92)	226/224(2)	199/197(22)	198/196(88)	184/182(86)	183/181(100)
4i	204(81)	160(1)	133(45)	132(69)	118(100)	117(77)
4j	342(4)	160(2)	133(97)	132(90)	118(100)	117(92)

(a) Rel. abundance for 4c and 4h belongs to the lighter isotope.

structure 3. A striking difference between these isomeric structures lies in the fragment ion [M-RR'CNH]$^+$, which predominates in the mass spectra of 1,2,4-oxadiazin-6-ones (3),[1] but is not observed for the 5-ones (4).

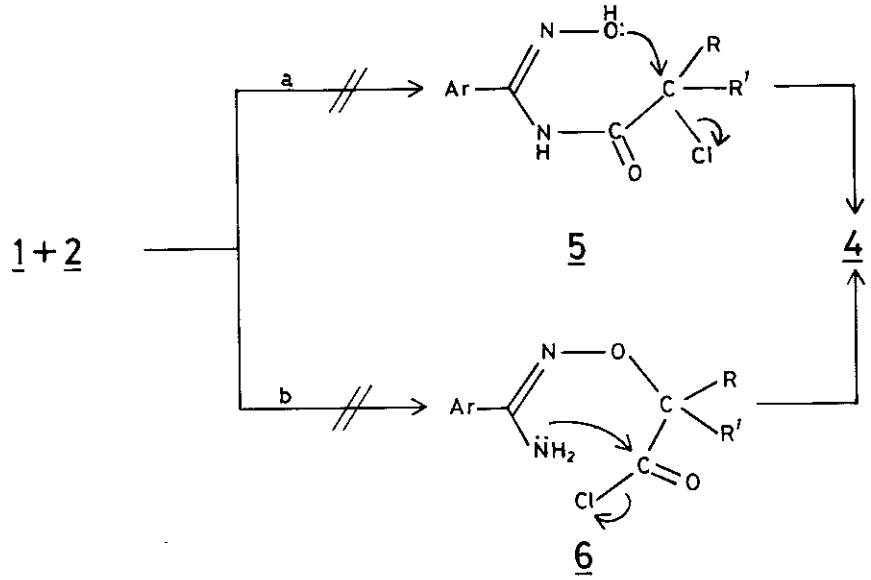
The formation of compounds 4 via the intermediacy of N-acylamidoxime derivatives 5 (Scheme 3, path a) is refuted, since acylation and alkylation of amidoximes is well known to take place exclusively at the oxygen atom.[3] An alternative mechanism via formation of O-alkylamidoxime derivatives 6 (Scheme 3, path b) is also excluded; this is because in the α-chloroacid chloride (2), the chlorinated sp^3-carbon is unlikely to compete with the acyl sp^2-carbon towards nucleophiles.

A more plausible reaction mechanism involves acylation of the amidoximes at the oxygen cite to yield the O-acylamidoximes 7, which rearrange, under the basic reaction conditions, to the isomeric N-acyl derivatives 9 prior to the cyclization (Scheme 4). This O → N acyl migration results from an intramolecular nucleophilic attack by the aza-anion 8 at the acyl carbon, in preference to attack at the chlorinated sp^3-center. In this manner, anion 8 is transformed to more stable oxy-anion 9, which then cyclizes to compounds 4. This mechanism is supported by the isolation of the compounds 7 (Table 3) from the reaction of amidoximes (1) and α-chloroacid chlorides (2) in presence of triethylamine, instead of NaH, as a base. Upon treatment with NaH, these O-acylamidoximes (7) undergo ring closure readily yielding the oxadiazin-5-ones (4). Thus, the reaction of amidoximes with α-chloroacid chlorides constitutes a convenient one-pot synthetic route to 1,2,4-oxadiazin-5-ones, and competes favourably with other reported methods[4,5] for the synthesis of these compounds, of which only few examples are known. These 6-oxa-5-pyrimidone derivatives are currently receiving increasing attention since they exhibit certain biological activities.[6]

Although the reaction between 1 and 2 has long been described in the literature,[7] yet the reaction conditions employed sofar favoured thermal dehydration of the intermediate O-acylamidoximes to 1,2,4-oxadiazoles. We also found, in the present study, that compounds 7, under similar condition, cyclize to the corresponding 1,2,4-oxadiazoles 10 (Scheme 5, Table 3).

In view of the preceeding discussion, it is evident that the fate of the intermediate O-(α-chloroacyl)amidoximes (7), formed from the reaction of amidoximes and acylating agent, is solely determined by the reaction conditions employed. Thermal condensation of compounds 1 and 2 leads to 1,2,4-oxadiazoles, whereas in

Scheme 3



Scheme 4

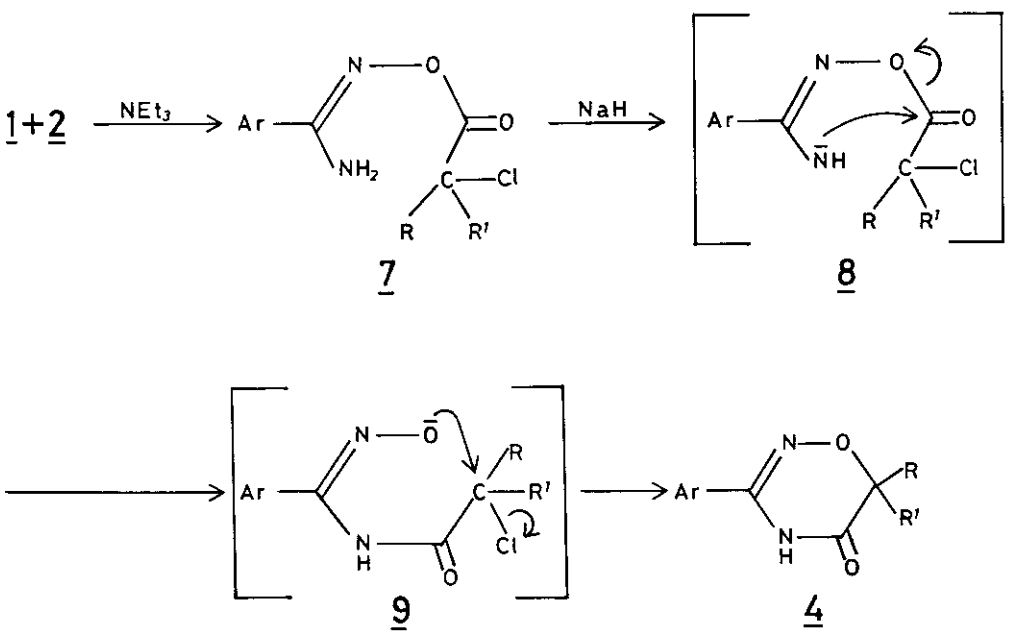
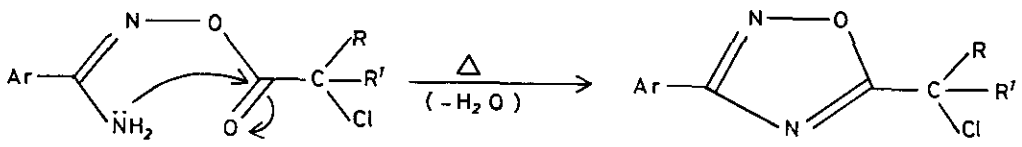


Table 3. Physical and Spectral Data for Compounds 7a-j

Compd	Ar	R	R'	Yield(%)	mp(°C)	ir (cm^{-1}) NH_2	ir (cm^{-1}) C=O	ir (cm^{-1}) C=N	^{1}H-nmr (δ) Ar	^{1}H-nmr (δ) R,R'	^{1}H-nmr (δ) NH_2
7a	C_6H_5	H	H	55	69-70	3480,3360	1745	1620	8.13-7.87(2H,m) 7.54-7.33(3H,m)	4.72(2H,s)	5.18(2H,br)
7b	p-$NO_2C_6H_4$	H	H	82	126-127	3490,3345	1755	1630	8.24(2H,d) 7.96(2H,d)	4.34(2H,s)	5.27(2H,br)
7c	p-BrC_6H_4	H	H	70	122-124	3490,3360	1745	1615	7.90(2H,d) 7.50(2H,d)	4.70(2H,s)	5.24(2H,br)
7d	p-$CH_3C_6H_4$	H	H	74	120-122	3485,3360	1745	1615	7.33(2H,d) 7.17(2H,d) 2.38(CH_3,s)	4.30(2H,s)	5.13(2H,br)
7e	o-$CH_3C_6H_4$	H	H	72	82-83	3490,3340	1750	1625	7.39-7.10(4H,m) 2.40(CH_3,s)	4.23(2H,s)	5.07(2H,br)
7f	C_6H_5	H	CH_3	62	80-81	3480,3350	1745	1620	7.70-7.22(5H,m)	4.55(1H,q) 1.75(3H,d)	5.26(2H,br)
7g	p-$NO_2C_6H_4$	H	CH_3	85	114-115	3450,3340	1745	1630	8.14(2H,d) 7.76(2H,d)	4.54(1H,q) 1.78(3H,d)	5.35(2H,br)
7h	p-BrC_6H_4	H	CH_3	78	129-130	3460,3340	1745	1630	7.56(2H,d) 7.38(2H,d)	4.53(1H,q), 1.58(3H,d)	6.14(2H,br)
7i	p-CH_3H_4	H	CH_3	70	118-119	3500,3370	1740	1620	7.52(2H,d) 7.12(2H,d) 2.37(CH_3,s)	4.56(1H,q), 1.78(3H,d)	5.07(2H,br)
7j	p-$CH_3C_6H_4$	C_6H_5	C_6H_5	80	121-122	3500,3360	1740	1620	7.60-6.90(14H,m),2.27(CH_3,s)		4.87(2H,br)

Scheme 5



7 → 10

Table 4. Physical and Spectral Data of Compounds 10a-i

Compd	Yield(%)	mp(°C)	ms(m/z) [M]+	^{1}H-nmr (δ) Ar	R,R'
10a	82	33-34	194/196	8.14-7.87(2H,m) 7.54-7.30(3H,m)	4.72(2H,s)
10b	65	80-82	239/241	8.30(4H,s)	4.77(2H,s)
10c	62	55-56	272/274/276	7.90(2H,d) 7.56(2H,d)	4.68(2H,s)
10d	80	40-41	208/210	7.90(2H,d), 7.20(2H,d) 2.37(CH_3,s)	4.68(2H,s)
10e	60	Oil	208/210	7.42-7.08(4H,m) 2.43(CH_3,s)	4.60(2H,s)
10f	85	Oil	208/210	8.20-8.00(2H,m) 7.64-7.40(3H,m)	5.23(1H,q), 2.04(3H,d)
10g	75	115-117	253/255	8.30(4H,s)	5.27(1H,q), 2.02(3H,d)
10h	85	27-28	286/288/290	7.93(2H,d) 7.57(2H,d)	5.22(1H,q), 1.98(3H,d)
10i	90	Oil	222/224	7.86(2H,d), 7.22(2H,d) 2.40(CH_3,s)	5.20(1H,q), 2.02(3H,d)

presence of a strong base (such as NaH) a new reaction pathway leading to 1,2,4-oxadiazin-5-ones is established. Further investigation of the generality and scope of this reaction are underway.

EXPERIMENTAL

Melting points were determined on a Philip-Harris melting point apparatus and are uncorrected. IR spectra (KBr pellets) were recorded on a Perkin Elmer 577 Spectrophotometer. ^{1}H-NMR spectra were measured on a Varian T-60 spectrometer using $CDCl_3$ (unless otherwise noted) as a solvent and tetramethylsilane as an internal reference. A Varian MAT 112 Mass Spectrometer was used to obtain the mass spectra by electron-impact ionization. Satisfactory elemental analyses (C,H,N) were obtained for all new compounds of type 4, 7, and 10. Amidoximes were prepared from the corresponding nitriles following Lit.[8] procedures. Chloroacetyl and chloropropionyl chlorides were commercially available reagents (Fluka). Diphenylchloracetyl chloride was prepared from diphenylacetic acid and phosphorus pentachloride.[9]

Preparation of O-acylamidoximes (7).

A solution of the chloroacid chloride (2) (0.05 mol) in chloroform (10 ml) was dropwise added to a stirred solution of the appropriate amidoxime (0.05 mol) in chloroform (30 ml). After completion of the exothermic reaction, triethylamine (0.06 mol) in chloroform (20 ml) was added dropwise with continuous stirring. The reaction mixture was then extracted with water (2 x 20 ml) and the organic layer was separated, dried over anhydrous sodium sulfate and the solvent evaporated in vacuo. The remaining solid residue was finally recrystallized from chloroform-petroleum ether (bp 40-60°).

Preparation of 1,2,4-Oxadiazin-5(4H)-ones (4).

a) To a stirred solution of the O-acylamidoxime 7 (0.02 mol) in dry THF (30 ml) was added, in small portions, enough sodium hydride until hydrogen evolution ceased. Stirring was continued for 1 h and the mixture was cautiously acidified with acetic acid. The solvent was then evaporated in vacuo leaving a solid residue which was washed with water (10-15 ml), dried and recrystallized from chloroform-petroleum ether (bp 40-60°).

b) A solution of the chloroacid chloride (0.02 mol) in dry THF (10 ml) was added to a stirred solution of the amidoxime (0.02 mol) in dry THF (20 ml). After the reaction mixture was stirred for 0.5 h at room temperature, it was cooled (ice-bath) and cautiously treated with sodium hydride (0.06 mol). The reaction mixture was stirred for 1 h at room temperature and then acidified with acetic acid. The solvent was evaporated in vacuo and the solid residue washed with water (10-15 ml), dried and recrystallized.

Preparation of 1,2,4-Oxadiazoles (10).

The particular O-acylamidoxime 7 (0.01 mol) was refluxed 2-3 h in xylene (10 ml). The solvent was then removed in vacuo and the residue recrystallized from benzene-pentane. In case the product was an oil, it was purified on preparative silica gel TLC plates using hexane as the developing solvent.

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