Reaction of 2,4-Dichlorophenylglyoxyl-hydroximoyl Chloride with Amines as a Convenient Method for the Synthesis of Amide Oximes and Amides

L. JAROŠKOVÁ and Ľ. FIŠERA*

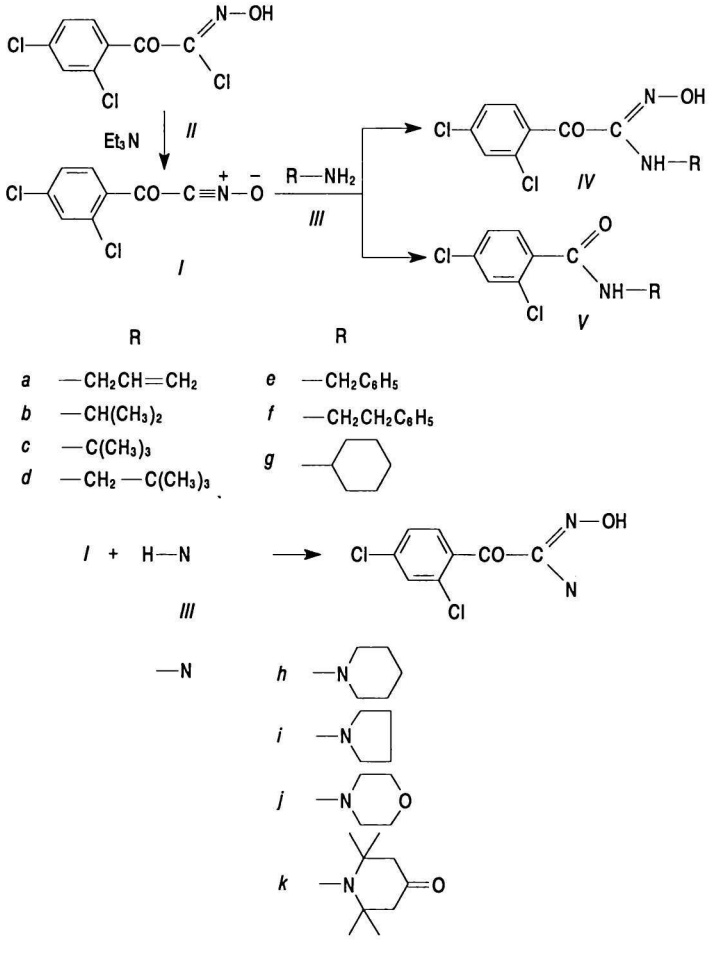
Department of Organic Chemistry, Faculty of Chemical Technology, Slovak Technical University, SK-812 37 Bratislava

Received 10 November 1992

2,4-Dichlorobenzoylnitrile oxide (*I*) generated *in situ* from the title compound reacts with amines under the condition of 1,3-dipolar cycloaddition to afford the amide oximes *IV* and amides *V*. The ratio of *IV* and *V* depends on the structure of amine. Reaction of *I* with cyclic amines gave only *IV*. The reaction mechanism is briefly discussed.

In a previous work on 1,3-dipolar cycloaddition of 2,4-dichlorobenzoylnitrile oxide (*I*) to alkenes we reported the unexpected formation of amide oxime *IVa* and amide *Va* (see Scheme 1) by the treatment with allylamine [1]. The fact that the 2,4-dichlorobenzoyl building block is a characteristic feature of some commercial agrochemicals [2] and drugs [3] and our current interest in nitrile oxides as intermediates for further studies forced us to explore the reaction of nitrile oxide *I* with amines.

The reactions are shown in Scheme 1 and the results are summarized in Table 1 and in Experimen-



Scheme 1

*The author to whom the correspondence should be addressed.

Table 1. Physicochemical Data of Compounds *IV* and *V*

Compound	Formula	M_r	w_i(calc.)/%			w_i(found)/%			Yield[a]	M.p.	$\tilde{\nu}$/cm^{-1}		
			C	H	N	C	H	N	%	°C	ν(C=O)	ν(OH)	ν(NH)
IVb	$C_{11}H_{12}Cl_2N_2O_2$	275.13	48.02	4.39	10.18	48.26	4.40	10.24	26	162—164	1705	3365	3150
Vb	$C_{10}H_{11}Cl_2NO$	232.11	51.74	4.78	6.03	51.71	4.69	6.10	15	122—123	1673	–	3330
IVc	$C_{12}H_{14}Cl_2N_2O$	289.15	49.84	4.88	9.68	49.90	4.90	9.42	20	180—182	1692	3590	3260
Vc	$C_{11}H_{13}Cl_2NO$	246.13	53.67	5.32	5.69	53.55	5.37	5.74	38	157—160	1665	–	3390
IVd	$C_{13}H_{16}Cl_2N_2O_2$	303.17	51.50	5.32	9.24	51.62	5.37	9.31	27	144—146	1690	3574	3389
Vd	$C_{12}H_{15}Cl_2NO$	260.16	55.39	5.81	5.38	55.43	5.77	5.34	14	95—96	1663	–	3449
IVe	$C_{15}H_{12}Cl_2N_2O_2$	323.15	55.75	3.74	8.67	55.67	3.74	8.57	50	91—93	1688	3573	3401
Ve	$C_{14}H_{11}Cl_2NO$	280.13	60.02	3.95	5.00	59.95	3.94	4.96	21	128—129	1664	–	3440
IVf	$C_{16}H_{14}Cl_2N_2O_2$	337.20	56.99	4.19	8.31	56.91	4.18	8.28	32	76—77	1686	3575	3410
Vf	$C_{15}H_{13}Cl_2NO$	294.17	61.24	4.45	4.76	60.97	4.19	4.66	17	88—89	1662	–	3445
IVg	$C_{14}H_{16}Cl_2N_2O_2$	315.19	53.34	5.12	8.89	53.52	5.17	8.93	38	155—157	1688	3573	3372
Vg	$C_{13}H_{15}Cl_2NO$	272.17	57.35	5.55	5.14	57.41	5.51	5.21	44	114—115	1692	–	3397
IVh	$C_{13}H_{14}Cl_2N_2O_2$	301.16	51.90	4.68	9.30	51.73	4.70	9.28	82	120—121	1705	3590,3173	–
IVi	$C_{12}H_{12}Cl_2N_2O_2$	287.14							55	Oil	1688	3568,3330	–
IVj	$C_{12}H_{12}Cl_2N_2O_3$	303.14	47.54	3.99	9.24	47.61	4.05	9.17	88	140—141	1690	3565	–
IVk	$C_{17}H_{20}Cl_2N_2O_3$	371.25	54.99	5.43	7.54	55.00	5.51	7.58	75	137—138	1709,1688	3540	–

a) Yields of the isolated compounds.

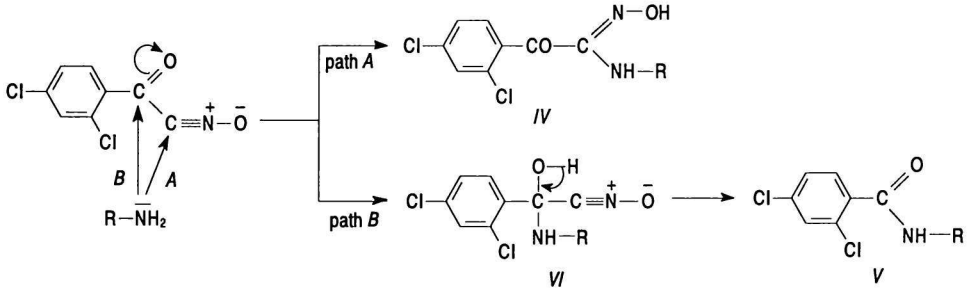
tal. The commercially available 2,4-dichloroacetophenone was chlorinated and then nitrosated to give 2,4-dichlorophenylglyoxylhydroximoyl chloride (*II*). 2,4-Dichlorobenzoylnitrile oxide (*I*) was generated *in situ* from *II* and triethylamine in ether at 0 °C. Reaction of *I* with the corresponding amine *III* at 0 °C gave amide oximes *IVb—IVg* and amides *Vb—Vg*. The NMR analysis of the crude mixture permitted determination of the ratio of the products *IV* and *V* present in the original reaction mixture (Table 2). The mass ratio of amide oximes *IV* and amides *V* strongly depends on the structure of amine *III*. In the case that R is primary alkyl the ratio was 72 : 28 in favour of amide oximes *IVa*, *IVd—IVf*. On the other hand, cyclohexylamine gave an equimolar mixture of *IVg* and *Vg* and *tert*-butylamine gave even the corresponding amide *Vc* as the major product (33 : 67). In contrast to acyclic amines the reaction of nitrile oxide *I* with cyclic amines *III* gave exclusively amide oximes *IVh—IVk*, as single products. The crude residue was chromatographically separated, and each amide oxime *IV* and amide *V* could be obtained in pure form.

Table 2. Mass Ratio of Amide Oximes *IV* and Amides *V*

Amine	*IIIa*	*IIIb*	*IIIc*	*IIId*	*IIIe*	*IIIf*	*IIIg*
IV : V	72 : 28	75 : 25	33 : 67	72 : 28	72 : 28	72 : 28	50 : 50

The assignments of the structure of the isolated products were made on the basis of the spectroscopic data. ^{1}H and ^{13}C NMR spectra show the conservation of the alkyl moiety R from the starting amine *III* in both isolated compounds *IV* and *V*. The presence of strong absorption bands of C=O and OH groups indicated that the derivatives *IV* were the open-chain *N*-substituted amide oximes. The amides *V* show the strong absorption of C=O and NH groups whereas the typical absorption bands of OH group in the IR spectrum are missing.

The typical mechanism involved in a generation of the 1,3-dipole, namely nitrile oxide *I* which reacted with amine *III* by 1,3-addition providing amide oxime *IV* depends on the experimental conditions (Scheme 2). With regard to the steric configuration of compounds *IV*, it should be noted that the synthesis according to Schemes 1 and 2 gives only one



Scheme 2

of the two possible stereoisomers. The second possible stereoisomer has not been detected in the crude reaction mixture even by ^{13}C NMR spectroscopy. Only in the case of *IVj* and *IVk* the ^{13}C NMR spectrum of the raw reaction mixture showed doubling of signals, indicating the presence of both stereoisomers.

Surprisingly, in contrast to all up-to-now investigated reactions of nitrile oxides with amines [4—6], in conformity (the compound *Va*) with our previous work [1] as has been aforementioned we have isolated the anomalous product, namely, amide *Vb—Vg*, which is not conform with 1,3-addition product. Presumably under this reaction condition the amino group can be reacted with difunctionalized compound *I* at the carbonyl group forming the second addition product *VI* and this adduct *VI* is then stabilized by elimination of fulminic acid (Scheme 2).

EXPERIMENTAL

Melting points are not corrected. ^1H and ^{13}C NMR spectra of deuterochloroform solutions were measured with Varian VXR 300 instrument, tetramethylsilane being the internal reference. ^1H NMR spectra of the raw reaction mixture were recorded on a Tesla BS 487 C (80 MHz) spectrometer. IR spectra were taken with Philips analytical PU 9800 FTIR spectrometer.

The progress of the reaction was monitored by thin-layer chromatoraphy on silica gel, impregnated by a fluorescence indicator (λ = 254 nm). 2,4-Dichlorophenylglyoxylhydroximoyl chloride (*II*) was prepared according to Ref. [7] by treating α-chloro-2,4-dichloroacetophenone by butyl nitrite in anhydrous ether in the presence of bubbling gaseous hydrochloric acid and the corresponding amines were purchased from Fluka and Aldrich.

Amide Oximes *IV* and Amides *V*

Triethylamine (13 mmol) in ether (30 cm^3) was added to a stirred solution of 2,4-dichlorophenylglyoxylhydroximoyl chloride *II* (10 mmol) in ether (30 cm^3) at 0 °C within 1 h. Then the corresponding amine *III* (10 mmol) was added during 1 h to this solution and the resulting mixture was stirred overnight at room temperature. The separated triethylammonium chloride was filtered off, the filtrate was concentrated under diminished pressure, dried, and the products were separated by chromatography on a silica gel column and purified by crystallization.

N-(1-Methylethyl)-2,4-dichlorobenzoylamide oxime (IVb). ^1H NMR spectrum, δ: 8.03 (br s, 1H, OH), 7.26—7.40 (m, 3H, H_{arom}), 4.85 (d, 1H, NH, J = 9 Hz), 4.28 (m, 1H, CH), 1.21 (d, 6H, 2 × CH_3). ^{13}C NMR spectrum, δ: 188.37 (s, C=O), 149.23 (s, C=N), 135.76, 132.68, 130.29, 129.78, 126.81 (C_{arom}), 45.09 (d, CH), 24.66 (q, CH_3).

N-(1-Methylethyl)-2,4-dichlorobenzamide (Vb). ^1H NMR spectrum, δ: 7.21—7.51 (m, 3H, H_{arom}), 6.18 (d, 1H, NH, J = 7.2 Hz), 4.25 (m, 1H, CH), 1.17 (d, 6H, 2 × CH_3). ^{13}C NMR spectrum, δ: 164.87 (s, C=O), 136.43, 133.76, 131.39, 131.00, 129.84, 127.39 (C_{arom}), 42.39 (d, CH), 22.52 (q, CH_3).

N-(1,1-Dimethylethyl)-2,4-dichlorobenzoylamide oxime (IVc). ^1H NMR spectrum, δ: 7.30—7.44 (m, 3H, H_{arom}), 1.42 (s, 9H, 3 × CH_3). ^{13}C NMR spectrum, δ: 184.35 (s, C=O), 149.32 (s, C=N), 137.10, 135.82, 132.72, 130.46, 129.91, 126.84 (C_{arom}), 52.76 (s, $C(CH_3)_3$), 31.50 (q, CH_3).

N-(1,1-Dimethylethyl)-2,4-dichlorobenzamide (Vc). ^1H NMR spectrum, δ: 7.27—7.43 (m, 3H, H_{arom}), 1.39 (s, 9H, 3 × CH_3). ^{13}C NMR spectrum, δ: 171.38 (s, C=O), 138.06, 134.92, 133.40, 131.40, 130.26, 127.04 (C_{arom}), 53.15 (s, $C(CH_3)_3$), 31.34 (q, CH_3).

N-(2,2-Dimethylpropyl)-2,4-dichlorobenzoylamide oxime (IVd). ^1H NMR spectrum, δ: 8.41 (br s, 1H, OH), 7.26—7.39 (m, 3H, H_{arom}), 5.09 (t, 1H, NH), 3.32 (d, 2H, CH_2, J = 6.6 Hz), 0.94 (s, 9H, 3 × CH_3). ^{13}C NMR spectrum, δ: 188.06 (s, C=O), 149.99 (s, C=N), 136.99, 135.67, 132.72, 130.27, 129.76, 126.74 (C_{arom}), 54.50 (s, $C(CH_3)_3$), 32.29 (t, CH_2), 26.92 (q, CH_3).

N-(2,2-Dimethylpropyl)-2,4-dichlorobenzamide (Vd). ^1H NMR spectrum, δ: 7.24—7.56 (m, 3H, H_{arom}), 6.53 (t, 1H, NH), 3.23 (d, 2H, CH_2, J = 6.0 Hz), 0.98 (s, 9H, 3 × CH_3). ^{13}C NMR spectrum, δ: 165.54 (s, C=O), 136.37, 133.77, 131.18, 131.14, 129.80, 127.30 (C_{arom}), 51.25 (s, $C(CH_3)_3$), 32.01 (t, CH_2), 27.26 (q, CH_3).

N-Benzyl-2,4-dichlorobenzoylamide oxime (IVe). ^1H NMR spectrum, δ: 8.48 (br s, 1H, OH), 7.26—7.35 (m, 8H, H_{arom}), 5.40 (t, 1H, NH), 4.68 (d, 2H, CH_2, J = 4.2 Hz). ^{13}C NMR spectrum, δ: 188.02 (s, C=O), 149.95 (s, C=N), 139.29, 137.18, 135.39, 132.77, 130.38, 129.76, 128.63, 127.49, 127.47, 126.75 (C_{arom}), 47.33 (t, CH_2).

N-Benzyl-2,4-dichlorobenzamide (Ve). ^1H NMR spectrum, δ: 7.25—7.69 (m, 8H, H_{arom}), 6.51 (t, 1H, NH), 4.66 (d, 2H, CH_2, J = 5.4 Hz). ^{13}C NMR spectrum, δ: 165.82 (s, C=O), 137.47, 136.93, 132.75, 131.52, 131.46, 130.09, 129.84, 127.90, 127.78, 127.58 (C_{arom}), 44.38 (t, CH_2).

N-(2-Phenylethyl)-2,4-dichlorobenzoylamide oxime (IVf). ^1H NMR spectrum, δ: 7.21—7.36 (m, 8H, H_{arom}), 5.17 (m, 1H, NH), 3.72 (m, 2H, CH_2), 2.88 (m, 2H, CH_2). ^{13}C NMR spectrum, δ: 187.83 (s, C=O),

150.01 (s, C=N), 138.54, 137.26, 132.85, 131.26, 130.60, 129.80, 128.81, 128.71, 128.63, 126.69, 126.55 (C_{arom}), 44.88 (t, CH_2) , 37.96 (t, CH_2).

N-(2-Phenylethyl)-2,4-dichlorobenzamide (Vf). ^{1}H NMR spectrum, δ: 7.23—7.55 (m, 8H, H_{arom}), 6.31 (br s, 1H, NH), 3.73 (m, 2H, CH_2), 2.95 (m, 2H, CH_2). ^{13}C NMR spectrum, δ: 165.44 (s, C=O), 138.54, 136.65, 133.37, 131.45, 131.18, 129.97, 128.81, 128.71, 127.43, 126.67 (C_{arom}), 41.31 (t, CH_2), 35.37 (t, CH_2).

N-Cyclohexyl-2,4-dichlorobenzoylamide oxime (IVg). ^{1}H NMR spectrum, δ: 7.26—7.40 (m, 3H, H_{arom}), 3.87 (m, 1H, CH), 1.15—1.98 (m, 10H, 5 × CH_2). ^{13}C NMR spectrum, δ: 188.04, (s, C=O), 149.20 (s, C=N), 137.17, 135.55, 132.81, 130.48, 129.82, 126.83 (C_{arom}), 51.84 (d, CH), 35.00 (t, CH_2), 25.45 (t, CH_2), 24.79 (t, CH_2).

N-Cyclohexyl-2,4-dichlorobenzamide (Vg). ^{1}H NMR spectrum, δ: 7.26—7.78 (m, 3H, H_{arom}), 5.50 (d, 1H, NH), 3.69 (m, 1H, CH), 0.82—2.03 (m, 10H, 5 × CH_2). ^{13}C NMR spectrum, δ: 162.00 (s, C=O), 138.63, 132.77, 130.82, 130.50, 127.39, 127.09 (C_{arom}), 52.54 (d, CH), 34.74 (t, CH_2), 29.68 (t, CH_2), 25.15 (t, CH_2), 24.63 (t, CH_2).

N-Piperidinyl-2,4-dichlorobenzoylamide oxime (IVh). ^{1}H NMR spectrum, δ: 8.48 (br s, 1H, NH), 7.24—7.32 (m, 3H, H_{arom}), 3.23 (s, 4H, 2 × CH_2), 1.56 (s, 6H, 3 × CH_2). ^{13}C NMR spectrum, δ: 189.98 (s, C=O), 151.58 (s, C=N), 137.38, 136.49, 133.06, 130.70, 129.74, 127.13 (C_{arom}), 49.18 (t, CH_2), 26.25 (t, CH_2), 24.29 (t, CH_2).

N-Pyrrolidinyl-2,4-dichlorobenzoylamide oxime (IVi). ^{1}H NMR spectrum, δ: 7.28—7.58 (m, 3H, H_{arom}), 5.02 (br s, 1H, OH) 3.60—3.92 (m, 4H, 2 × CH_2), 3.03—3.37 (m, 4H, 2 × CH_2). ^{13}C NMR spectrum, δ: 183.57 (s, C=O), 157.56 (s, C=N), 137.87, 135.18, 132.84, 130.69, 130.16, 126.97 (C_{arom}), 52.39 (t, CH_2), 33.44 (t, CH_2).

N-Morpholinyl-2,4-dichlorobenzoylamide oxime (IVj). ^{1}H NMR spectrum, δ: 7.27—7.53 (m, 3H, H_{arom}), 3.77 (t, 2H, OCH_2), 3.70 (t, 2H, OCH_2), 3.45 (t, 2H, NCH_2), 3.15 (t, 2H, NCH_2). ^{13}C NMR spectrum, δ: 188.26 (s, C=O), 157.84 (s, C=N), 137.64, 134.86, 133.60, 131.31, 129.74, 127.20 (C_{arom}), 67.17 (t, OCH_2), 65.94 (t, OCH_2), 48.36 (t, NCH_2), 46.16 (t, NCH_2).

N-(2,2,6,6-Tetramethyl-4-oxopiperidinyl)-2,4-dichlorobenzoylamide oxime (IVk). ^{1}H NMR spectrum, δ: 7.24—7.42 (m, 3H, H_{arom}), 2.70 (d, 2H, CH_2, J = 14.8 Hz), 2.48 (d, 2H, CH_2). ^{13}C NMR spectrum, δ: 210.34 (s, C=O), 193.30 (s, C=O), 154.50 (s, C=N), 137.83, 135.85, 131.73, 129.88, 129.63, 126.43 (C_{arom}), 58.24 (t, CH_2), 54.43 (t, CH_2), 31.57 (q, CH_3), 30.12 (q, CH_3).

REFERENCES

1. Jarošková, L. and Fišera, Ľ., *Chem. Papers 46*, 238 (1992).
2. Matocsy, G., Nádasy, M., and Adriska, V., *Pesticide Chemistry*, p. 409. Akadémiai Kiadó, Budapest, 1988.
3. Boyle, F. T., Riley, J. F., and Wilson, R. G., in *Recent Trends in the Discovery, Development and Evaluation of Antifungal Agents.* (Fromthing, R. A., Editor.) P. 131. Prous, J. R. Publishers, Barcelona, 1987.
4. Bandiera, T., Albini, F. M., and Albini, E., *J. Heterocycl. Chem. 24*, 1597 (1987).
5. Grundmann, C. and Frommeld, H. D., *J. Org. Chem. 31*, 157 (1966).
6. Caramella, P. and Finzi, P. Y., *Chim. Ind.* (Milan) *48*, 963 (1966).
7. Tegeler, J. J. and Diamond, C. J., *J. Heterocycl. Chem. 24*, 697 (1987).

Translated by Ľ. Fišera