AN UNEXPECTED REACTION OF 3-PHENYL-3-CHLORO-2-OXOPROPANOIC ACID DERIVATIVES WITH SODIUM AZIDE. A NOVEL SYNTHESIS OF HIGHLY FUNCTIONALIZED OXAZOLINES

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Abstract - The reaction of 3-phenyl-3-chloro-2-oxopropanoic acid derivatives with sodium azide proceeded unexpectedly with the formation of oxazolines via intermediately forming α-azido- and/or α-imino ketones.

It is well known that reactions of α-halo ketones with sodium azide under mild conditions produce corresponding α-azido ketones, which undergo the loss of nitrogen to give imidazoles and α-imino ketones when heated from 180 to 240 °C in an inert solvent.[1] According to the analysis of both literature data and our own results, the path of the reaction with mono-[2] and polynucleophiles[3] are expected to be affected by the functional groups in α-chloro ketone moiety, and also by the halogen atom. During our investigations on the chemistry of 3-aryl-3-chloro-2-oxopropanoic acid derivatives, which are easily available from Darzens condensation of dichloroacetates and aromatic aldehydes,[4] we have elaboratedseveral different methods for the synthesis of various heterocyclic compounds such as thiazoles,[5] quinoxalines,[6] thiazolo[3,4-*a*]quinoxalines,[7] oxatiin, ditiines,[8] thiadiazines.[9] These methods

[#] On leave from the affiliation (b) as a guest scientist of the Japan Society for the Promotion of Science (JSPS) fellowship for research.

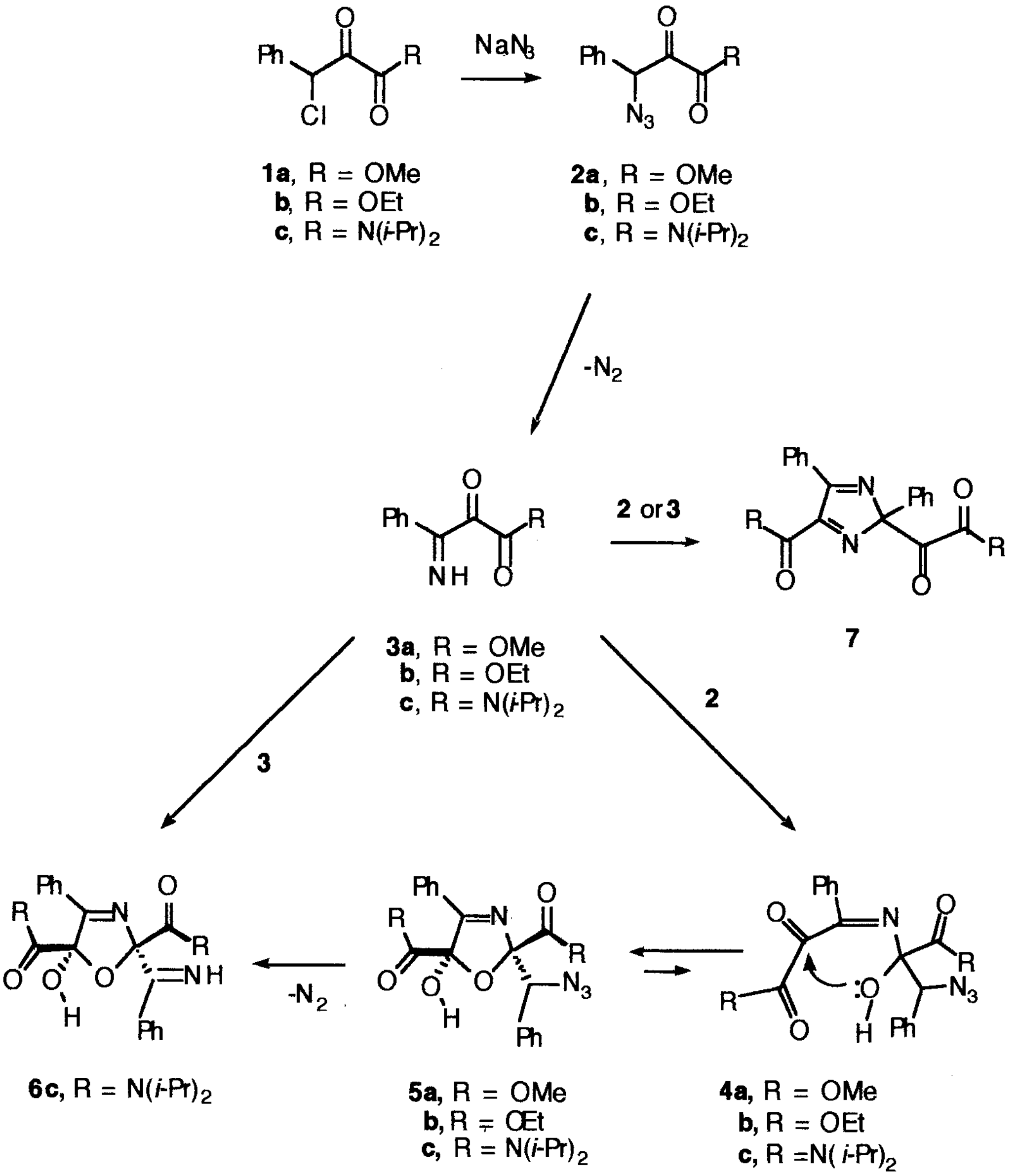
are based mainly on the esters and amides of 3-phenyl-3-chloro-2-oxopropanoic acid, which undergo smooth cyclocondensation reactions with various binucleophiles having the same or different nucleophilic centers. As a further development of our program, we report here a study on the reaction of 3-phenyl-3-chloro-2-oxopropanoic acid derivatives (**1**) with sodium azide. Alkyl azides with electron-withdrawing groups in α-position will give promising intermediates in the synthesis of various heterocycles. Azido moiety reacts as a dipolar as well as an imine group depending on the experimental conditions and on the character of the reagents used.

The reaction of α-chloro ketones with sodium azide was carried out according to the method described by Boyer and Straw.[1] In contrast to the known reactions reported,[1] the present reactions of 3-phenyl-3-chloro-2-oxopropanoic acid derivatives with sodium azide gave final products possessing four nitrogen atoms (for **5a** and **5b**): one nitrogen atom of heterocycle and three others of azido group. Their IR spectra show the presence of N_3 (2102-2110 cm^{-1}), and OH (3214-3748 cm^{-1}) groups side by side with esters (1750-1755 cm^{-1}), amide (1715 cm^{-1}), and imino groups (1600, 1570 cm^{-1}) in the composition of the products. In the ^1H and ^{13}C NMR spectra of the crude products the doubling of all signals occurs, the ratio of signal intensities depending on the reaction time and solvents used. On the basis of these data the reaction is suggested to proceed along the pathway shown in the Scheme 1.

The structure (**5a**) was unambiguously confirmed by single crystal X-Ray diffraction study (Figure 1). The system of H-bonding in crystals is also shown in Figure 2.

It is interesting to note that in the case of amide derivative (**1c**) (R = N(*i*-Pr)$_2$, the final product of the reaction is 2-(α-iminobenzoyl)oxazoline (**6c**) and not 2-(α-azidobenzyl)oxazoline (**5c**). The physical properties (mp, IR, NMR spectra) of oxazoline (**6c**) are identical with those of the sample obtained from the dimerization of pure α-imino ketone (**3c**).

It should be pointed out that in the boiling solution of methanol or benzene in the presence of catalytic amount of sulfuric acid, oxazoline (**5a** or **5b**) converts into open-chain tautomeric form **4** until the equilibrium between the two tautomers is established, although compound (**4**) was not isolated. The evidence for this fact was obtained from the signals of the NMR spectrum of the sample obtained after approximately one hour boiling of the solution containing **5a** or **5b**. Further boiling of the solution does not cause any changes in the ratio of NMR signals.



Scheme 1

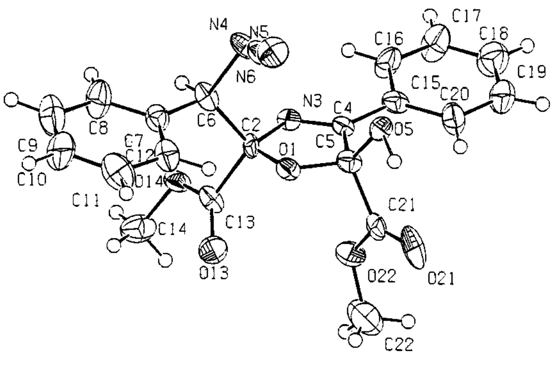


Figure 1. ORTEP view of oxazonline (**5a**)

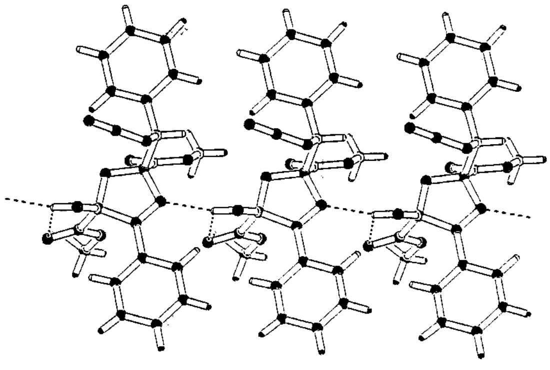


Figure 2. The system of H-bonding in crystals.

Thus, in contrast to the cases described in literature[1] which indicated that the reactions of α-chloro ketones with sodium azide lead to the formation of imidazolo derivative (**7**),[10] this study demonstrates the new direction in the reaction of α-chloro ketones with azide anion, leading to the formation of **5a**, **5b**, and **6c**.

EXPERIMENTAL

Infrared spectra (IR) were recorded on a PT/IR-5000 spectrometer. ^1H and ^{13}C NMR spectra were recorded from $CDCl_3$ solutions on Varian Gemini 200 (1H: 199.98 MHz, ^{13}C: 50.23 MHz) spectrometer. The solvent ($CDCl_3$) signal was used as internal standard, which was related with δ 7.26 ppm for 1H and 77.0 ppm for ^{13}C. Melting points were determined on a Mel-Temp-II hot stage microscope and are uncorrected. Elemental analyses were performed at the YANACO CHN-Corder MT-3.

General Procedure for the Preparation of 1,3-Oxazolines (5).

To an ice cooled solution of α-chloro ketone (**1**)[4] (0.1 mol) in 75 mL of ethanol and 12 mL (0.2 mol) of glacial acid, a cold solution of 13.0 g (0. 2 mol) of sodium azide in 2 mL of water was added and the resulting mixture was placed into refrigerator for 5 days with intermittent shaking. The mixture was evaporated under reduced pressure and the residue was poured into ice-cooled water (150 mL). The mixture was extracted with $CHCl_3$ (4 x 50 mL) and combined extracts were washed with water, dried ($MgSO_4$), and evaporated under reduced pressure. The residue was recrystallized giving pure 1,3-oxazoline (**5**).

2,5-Bismethoxycarbonyl-2-(α-azidobenzyl)-4-phenyl-5-hydroxy-1,3-oxazoline-3 (5a): mp 192-194 °C (*ⁱ*PrOH-MeOH), yield 83%. ^{1}H-NMR ($CDCl_3$): 3.69 (3H, s, CH_3), 3.76 (3H, s, CH_3), 4.70 (1H, s, OH), 5.38 (1H, s, CH), 7.35-7.98 (10H, m, $2C_6H_5$). *Anal.* Calcd for $C_{20}H_{18}N_4O_6$: C, 58.56; H, 4.39; N, 13.65. Found: C, 58.63; H, 4.41; N, 13.54.

X-Ray Analysis of 5a

Empirical formula $C_{20}H_{18}N_4O_6$, formula weight 410.2, mp 192-194 °C (*ⁱ*PrOH-MeOH), crystal system triclinic at 20 °C, unit cell dimensions (from 25 high angle reflections) lattice parameters: a=6.066(2), b=7.822(2), c=10.861(1) Å, α=73.90(2), β=83.43(2), γ=81.95(2)°, V=489(2) Å^3, $d_{(cal.)}$=1.39 g/cm^3, Z=1, space group P1. The unit cells parameters an intensities of 1484 reflections were measured on a automatic four circle diffractometer "Enraf-Nonius CAD" (λMoKα, graphite-monochromator (w/2Θ scaning, Θ<26.3°). The structure was solved by the direct method using the SIR program and refined initially in the isotropic approximation, and then anisotropic approximation. All of the H-atoms were identified from the differential series, and their contributions to structural amplitudes were taken into account in the final cycles of the refinement with fixed positional and isotropic thermal parameters. The final value of the residual factor: R=0.059 (R_w=0.076) over 1231 reflections with $F^3>3s$ (the unit weight scheme was used). All of the calculations were carried out on a DEC Alpha Station 200 computer with MolEN program complex.

All of atomic parameters, bond length and angles, torsion angles are collected in Tables 1 and 2.

2,5-Bisethoxycarbonyl-2-(α-azidobenzyl)-4-phenyl-5-hydroxy-1,3-oxazoline-3 (5b): mp 154-155 °C (*ⁱ*PrOH), yield 74%. ^{1}H-NMR ($CDCl_3$): 1.25(3H, t, *J* =7 Hz, CH_3), 1.28 (3H, t, *J* =7 Hz, CH_3), 4.129 (1H, q, *J*=7 Hz, one proton of CH_2), 4.136 (1H, q, *J* =7 Hz, one proton of CH_2), 4.223 (1H, q, *J* =7 Hz, one proton of CH_2), 4.226 (1H, q, *J*=7 Hz, one proton of CH_2), 4.71 (1H, s, OH), 5.35 (1H, s, CH), 7.35-7.98 (10H, m, $2C_6H_5$). *Anal.* Calcd for $C_{22}H_{22}N_4O_6$: C, 60.29; H, 5.02; N, 12.78. Found: C, 60.16 H, 5.23; N, 12.64.

2,5-Bis-(*N,N*-diisopropylcarbamoyl)-2-(α-iminobenzylidene)-4-phenyl-5-hydroxy-1,3-oxazoline-3 (6c): mp 179-181 °C (MeOH), yield 74%. IR (KBr): 3255 (OH), 3010-3100, 1640, 1630 (amide C=O), 1600 , 1570 (C=N), 1330, 1285, 1210, 1110, 1085, 1045, 1000, 840, 790, 770 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 0.549 (3H, d, *J*=6.4 Hz, CH_3), 0.827 (3H, d, *J*=6.6 Hz, CH_3), 0.876 (3H, d, *J*=6.6 Hz, CH_3), 1.057 (3H, d, *J*=6.2 Hz, CH_3), 1.086 (3H, d, *J*=5.6 Hz, CH_3), 1.343 (3H, d, *J*=6.8 Hz, CH_3), 1.367 (3H, d, *J*=6.6 Hz, CH_3), 1.473 (3H, d, *J*=6.8 Hz, CH_3), 3.161 (1H, sept, *J*=6.8 Hz, CH), 3.411 (1H, sept, *J*=6.6 Hz, CH), 3.928 (1H, sept, *J*=6.4 Hz, CH), 4.202 (1H, sept, *J*=6.4 Hz, CH), 7.32-8.48 (10H, m, $2C_6H_5$), 10.91 (1H, br s, NH). ^{13}C-NMR ($CDCl_3$): 18.63, 18.87, 18.98, 19.06, 19.13, 19.18, 21.17, 21.37 (CH_3x8), 46.90, 47.73, 48.41, 48.89 (CHx4), 104.01 (C_2), 112.13 (C_5), 127.95, 128.26, 128.58 (C_i),128.69, 129.0, 130.81, 132.28, 134.91 (C_i) (aromatics), 164.30 (C=O), 164.70 (C=O), 126.55 (C=NH), 170.85 (C_4). *Anal.* Calculated for $C_{30}H_{40}N_4O_4$: C, 69.25; H, 7.69; N, 10.76. Found: C, 69.54 H, 7.41; N, 10.43.

***N,N*-Diisopropylamide-3-imino-2-oxo-3-phenylpropionamide (3c)**. To the ice cooled solution of α-chloro ketone(**1c**)(0.1 mol) in DMF (50 mL) and MeOH (50 mL) was added a solution of NaN_3 (0.2 mol) in 5 mL of H_2O. After 4 h at 0-5 °C the cooling bath was removed and the solution was further stirred overnight. The solution was diluted with 150 mL of $CHCl_3$, washed with water, the organic layer was dried over anhydrous $MgSO_4$ and evaporated in *vacuo*. The residual oil became crystal, after recrystallization from hexane was obtained compound (**3c**): mp 164-166 °C (Hexane), yield 81%. ^1H-NMR ($CDCl_3$): 0.69 (3H, d, J=6.4 Hz, CH_3), 0.861 (3H, d, J=6.4 Hz, CH_3), 1.181 (3H, d, J=6.8 Hz, CH_3), 1.427 (3H, d, J=6.8 Hz, CH_3), 3.276 (1H, sept, J=6.8 Hz, CH), 3.891 (1H, sept, J=6.4 Hz, CH), 6.869 (1H, s, NH), 7.318-8.105 (5H, m, $2C_6H_5$). ^{13}C-NMR ($CDCl_3$): 19.01, 19.07, 19.98, 20.09 (CH_3x4), 47.50, 48.58 (CHx2), 127.13 (C=NH), 128.10 (C_o), 128.49 (C_m), 131.11 (C_p), 134.50 (C_i), 166.30, 166.94 (C=Ox2). *Anal.* Calcd for $C_{15}H_{20}N_2O_2$: C, 69.25; H, 7.69; N, 10.76. Found: C, 69.47; H, 7.76; N, 10.49.

The Dimerization of Imine (3c): The solution of 2.6 g (0.01 mol) of imine (**3c**) in 50 mL MeOH was refluxed for 1 h, then allowed to cool to room temperature. The forming crystal was filtrated and dried, giving 2.4 g (92%) of oxazoline (**6c**).

REFERENCES

1. J. H. Boyer and D. Straw, *J. Amer. Chem. Soc.*, 1952, **74**, 4506; J. H. Boyer and D. Straw, *J. Amer, Chem. Soc.*, 1953, **75**, 1642; S. Patai, *The Chemistry of the Azido Group*, Interscience Publishers, London-New York-Sydney-Toronto, 1971, 367.
2. V.A. Mamedov, I.A. Litvinov, A.T.X. Lenstra, Yu.Ya. Efremov, V.A. Naumov, and I.A. Nuretdinov, *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1991, 1427; V.A. Mamedov, I.A. Nuretdinov, and V.L. Polushina, *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1989, 1395.
3. V.A. Mamedov, E.A. Berdnikov, V.N. Valeeva, I.E.Ismaev, I.Ch. Rizvanov, L.A. Antokhina, I.A. Nuretdinov, and P.P. Chernov, *Russian Chem. Bull.* , 1993, **42**, 1690.
4. S. Tsuboi, H. Furutani, and A. Takeda, *Synthesis* , 1987, 292; V.A. Mamedov and I.A. Nuretdinov, *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1992, 1690, A. Takeda, S. Wada, M. Fujii, and H. Tanaka, *Bull. Chem. Soc. Jpn.*, 1970, **43**, 2997; A. Takeda and S. Tsuboi, *Bull. Chem. Soc. Jpn.*, 1975, **48**, 1067.
5. V.A. Mamedov, I.A. Nuretdinov, and F.G. Sibgatullina, *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1991, 2832; V.A. Mamedov, I.A. Nuretdinov, and F.G. Sibgatullina, *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1992, 679; A. Takeda, S. Tsuboi, S. Wada, and H. Kato, *Bull. Chem. Soc. Jpn.*, 1972, **45**, 1217.
6. V.A. Mamedov, I.A. Nuretdinov, and F.G. Sibgatullina, *Bull. Acad. Sci. USSR, Div. Chem. Sci.*,

1989, 1412; V.A. Mamedov, V.L. Polushina, F.F. Mertsalova, I.A. Nuretdinov, and A.Kh. Plyamovatyi, *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1991, 1660.

7. V.A. Mamedov and Ya.A. Levin, *Chem. Heterocycl. Comp.*, 1996, 1005.
8. V.A. Mamedov, F.G. Sibgatullina, V.P. Gubskaya, R.M. Gaynullin, R.R. Shagidullin, and A.V. Il'yasov, *Chem. Heterocycl. Comp.*, 1994, 1196.
9. V.A. Mamedov, L.V. Krokhina, E.A. Berdnikov, and Ya.A. Levin, *Chem. Heterocycl. Comp.*, 1996, 1266.
10. The formation of **7** from the reaction of **3** with **2** or **3** was suggested by the results of the literature (ref. 1), however it was not obtained.

Received, 2nd August, 1999