New Route to Cyclic Azomethine Imines

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Cyclic azomethine imines, in which the ring is four-membered, have been synthesized by thermal decomposition of the readily available 2-hydrazono-Δ^3-1,3,4-oxadiazolines. Possible mechanisms, involving the intermediacy of an iminooxirane, are discussed.

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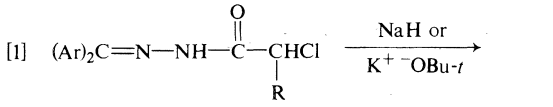
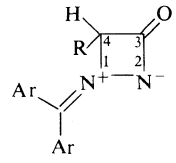
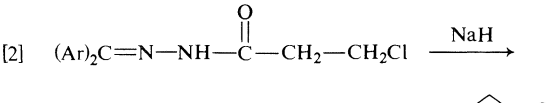
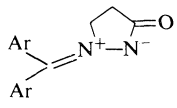
On a synthétisé des azométhines imines cycliques contenant un cycle à quatre par la décomposition thermique des hydrazono-2 Δ^3-oxadiazolines-1,3,4 facilement accessibles. On discute de différents mécanismes possibles impliquant la formation d'un iminooxyranne comme intermédiaire. [Traduit par le journal]

Azomethine imine ylids are readily available through a variety of routes including hydrogen abstraction from *N*-amino pyridinium salts (1, 2), photochemical ring contraction of a phthalazine to an isoindole ylid (3), reaction of azocyanides (4) or azocarbonyl compounds (5) with diazoalkanes, and reaction of 3-pyrazolidones with ketones (6–8). Cyclic azomethine imines, containing a four- or five-membered ring, were reported in 1968 by Greenwald and Taylor (9, 10), who prepared them according to eqs. 1 and 2. Such compounds are useful in synthesis of other heterocyclic









molecules (10, 11). Moreover, the four-membered ylid (eq. 1) has interesting structural features; the X-ray crystal structure showing an ortho hydrogen of the *Z*-oriented aromatic ring within hydrogen bonding distance from N-2 (12).

We report a new synthesis of 4,4-disubstituted, cyclic, azomethine imines (**3**), which complements the previous route (eq. 1) (10, 11) and which extends to new members of the family, particularly 4,4-disubstituted systems, not available by the previous route (11).

Results and Discussion

Scheme 1 illustrates the sequence of reactions by which carbonyl compounds and carbohydrazide are converted to 2-hydrazono-Δ^3-1,3,4-oxadiazolines (**2**) and to 3-oxo-1,2-diazetidinium hydroxide inner salts (**3**).

Table 1 lists some compounds (**2**) which were synthesized in connection with the present work. Oxidative cyclization of carbohydrazones (Scheme 1) gave only one of the configurations possible at the exocyclic double bond (13). Such selectivity has been observed also in oxidative cyclization of 4-substituted semicarbazones of ketones (14), which leads to 2-imino-Δ^3-1,3,4-oxadiazolines with the *Z*-configuration at the exocyclic double bond (15). Compounds **2** are tentatively assigned the *Z*-configuration by analogy.

Table 2 lists the new dipolar compounds (**3**) which have been synthesized by thermolysis of **2**. The scope of Scheme 1 for the synthesis of **3** is currently limited to the following substituent types: R_1, R_2 = aryl; R_2 = H, R_1 = aryl; and R_3, R_4 = alkyl. The spirocyclic compound **2***i* (Table 1) decomposed to a complex mixture containing the appropriate product **3** (n.m.r. evidence) but a pure sample could not be isolated. In the case of **2***h* (Table 1), the pyrolysis mixture was again complex and there was no evidence that it contained the expected

TABLE 1. 2-Hydrazono-Δ^3-1,3,4-oxadiazolines (**2**)[a]

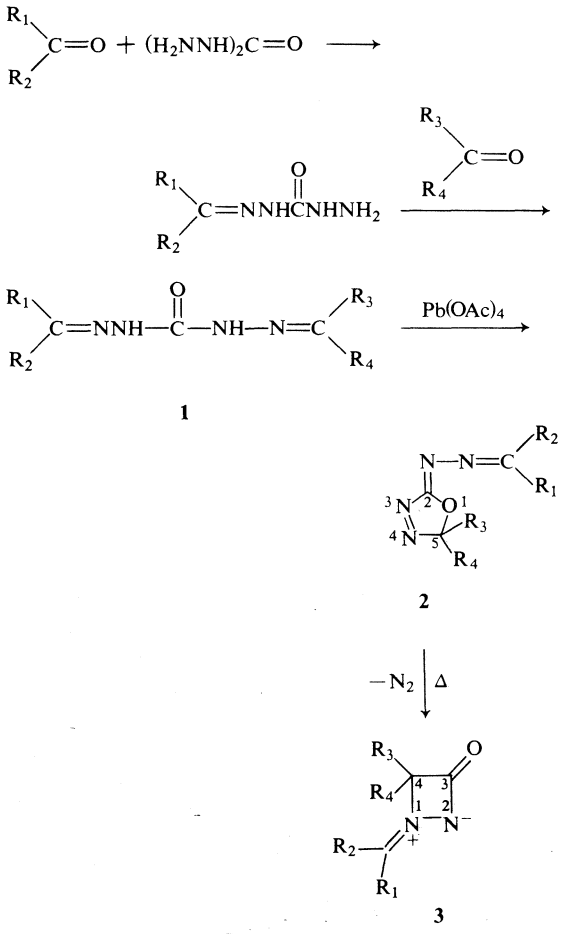
Compound	R_1	R_2	R_3	R_4	Melting point (°C)	%C Calcd.	%C Found	%H Calcd.	%H Found	%N Calcd.	%N Found
2*a*	C_6H_5	C_6H_5	CH_3	CH_3	110–112		[b]		[b]		[b]
2*b*	*p*-C_6H_4Cl	*p*-C_6H_4Cl	CH_3	CH_3	143–145 (dec)	56.53	56.48	3.91	4.11	15.50	15.39[d]
2*c*	*p*-C_6H_4Br	*p*-C_6H_4Br	CH_3	CH_3	173–174 (dec)	45.36	45.29	3.14	3.30	12.45	12.41[e]
2*d*	C_6H_5	CH_3	CH_3	CH_3	115–116	62.59	62.66	6.13	6.50	24.33	24.30
2*e*	C_6H_5	H	CH_3	CH_3	95	61.10	60.95	5.59	5.78	25.91	25.90
2*f*	*p*-$C_6H_4CH_3$	H	CH_3	CH_3	108–110	62.59	62.67	6.13	6.23	24.33	24.19
2*g*	C_6H_5	H	CH_3	CH_2CH_3	44[c]						
2*h*	C_6H_5	H	$(CH_2)_5$		Oil[c]						
2*i*	C_6H_5	H	$(CH_2)_4$		104	64.45	64.25	5.82	5.80	23.12	23.35

[a]Yields were in the range 57–78%, based on amounts isolated. Some of the oxidations have been carried out only once and in no case was optimization of the yield attempted.
[b]Previously reported (13).
[c]This low-melting material was not obtained analytically pure. Its n.m.r. and i.r. spectra (13) were consistent with the assigned structure and it gave the expected molecular weight (mass spectrometric).
[d]%Cl: calcd., 19.62; found, 19.51.
[e]%Br: calcd., 35.50; found, 35.39.

TABLE 2. Azomethine imine ylids (**3**)[a]

Compound	R_1	R_2	R_3	R_4	Melting point (°C)	%C Calcd.	%C Found	%H Calcd.	%H Found	%N Calcd.	%N Found
3*a*	C_6H_5	C_6H_5	CH_3	CH_3	171–173	77.27	77.22	6.06	6.15	10.61	10.65
3*b*	*p*-C_6H_4Cl	*p*-C_6H_4Cl	CH_3	CH_3	200–201	61.27	61.27	4.23	4.26	8.41[b]	8.46[b]
3*c*	*p*-C_6H_4Br	*p*-C_6H_4Br	CH_3	CH_3	210–211		[c]				
3*d*	C_6H_5	H	CH_3	CH_3	191	70.21	69.76	6.38	6.53	14.89	14.76
3*f*	*p*-$C_6H_4CH_3$	H	CH_3	CH_3	211	71.29	70.81	6.93	7.20	13.86	13.47
3*g*	C_6H_5	H	CH_3	CH_2CH_3	154	71.29	71.33	6.93	7.07	13.86	13.80

[a]Yields of pure material were in the range 32–36% in all cases listed.
[b]%Cl: calcd., 21.27; found, 20.98.
[c]This material was not analyzed. Its identity was established by means of an X-ray crystal structure (16).



SCHEME 1

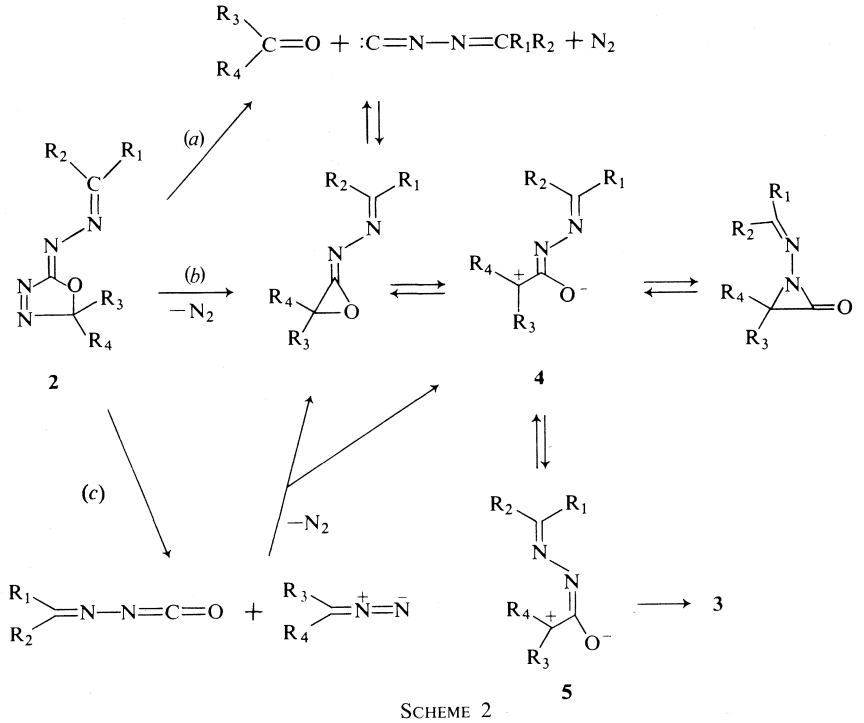
azomethine imine. The small C-3, C-4, N-1 bond angle (81°) of the azomethine imines (12, 16) would tend to enlarge the angle between exocyclic bonds to C-4, a geometry that could be mildly resisted in spiranes of the type under consideration. Whether strain at C-4 is a cause of the very low yields of such spiranes is not clear at this time.

Attempts to prepare **3** with R_1 and/or R_2 = alkyl have been unsuccessful to date, possibly because such products undergo subsequent reactions involving proton transfer from the allylic positions of the imminium function. Compounds **3** with R_3 = H and/or R_4 = H are also not available via Scheme 1 because the required precursors (**2**, R_3 = H and/or R_4 = H) undergo rapid azo–hydrazone tautomerism, precluding their isolation. Fortunately, the site selectivity in oxidation of unsymmetric carbohydrazones (**1**, $R_3 = R_4$ = alkyl; $R_1 = R_2$ = aryl or R_1 = aryl, R_2 = H) is just that depicted in Scheme 1 (13), placing alkyl substituents at C-5 of the ring and aryl substituents (or aryl and H) at the exocyclic hydrazono function of **2**. Thus the new synthetic route nicely complements Taylor's method (eq. 1), which cannot be adapted to the synthesis of 4,4-disubstituted members of the family **3** because tertiary chloroacyl hydrazones give only products of elimination on treatment with NaH or *t*-BuO^-K^+, and which also does not lead to systems **3** in which R_2 = H (11).

Two configurations of **3** are possible if $R_1 \neq R_2$. In the cases studied to date, we have obtained only the *Z*-isomers (R_2 = H, R_1 = aryl). Assignment of the configuration is based on the finding that diaryl compounds ($R_1 = R_2$ = aryl) have proton magnetic resonance (p.m.r.) spectra in which the chemical shift of two aryl protons is 8.0 δ while eight aryl protons (for the diphenyl system) absorb near 7.4 δ. The lower-field signal has been assigned to the two *ortho* protons of the *Z*-oriented phenyl group (11), since these are in close proximity to the negative amido nitrogen. All compounds **3** of Table 2, which have only one aryl group at the imminium carbon, have a two-proton signal near 8.0 δ. They must therefore be the *Z*-isomers.

The crystal structures of two members of the family **3** ($R_3 = R_4 = CH_3$, $R_1 = R_2$ = *p*-C_6H_4X, X = Cl, Br) have been determined (16). These not only confirm the assigned structure but also the close proximity between one ortho hydrogen of the *Z*-oriented aryl group and negative ring nitrogen, which has been described as a hydrogen bond (12, 16). In solution that interaction, if the term hydrogen bond is appropriate, is quite small. At −90°, in CH_2Cl_2, the n.m.r. spectrum of **3***a* showed two *ortho* hydrogens in equivalent environments, at 8.0 δ.

Several mechanisms can be envisioned for the formation of **3** from **2** (Scheme 2). There is precedent for decomposition of 2-imino oxadiazolines both to ketone and isonitrile (path *a*, Scheme 2) and to isocyanate and diazoalkane (path *c*) (17). Reactions of isocyanides with ketones are known (Passerini reaction) and an iminooxirane intermediate has been proposed (18). Evidence against operation of path *a* in the present system was obtained by decom-



SCHEME 2

position of **2** ($R_3 = R_4 = CH_3$, $R_1 = R_2 = C_6H_5$) in 2-butanone, which was not incorporated. Path *c*, involving isocyanate and diazoalkane as primary intermediates from a retro 1,3-dipolar cycloaddition has not been ruled out. Those products could recombine with loss of nitrogen to form an iminooxirane or the latter could arise more directly from **2** (path *b*). Iminooxiranes have never been isolated but there is evidence that they can undergo thermolysis to isocyanides and carbonyl compounds (19) and that they are interconvertible with α-lactams (20), probably through a dipolar intermediate analogous to that involved in polymerization of α-lactones (21).

The dipolar intermediate in the present system has available a third ring closure option, to form **3**. Such closure is not possible, however, until the amido nitrogen has inverted configuration. Inversion of that configuration could occur via the α-lactam, in which resonance (22) would give the amido nitrogen's lone pair more p-character, or it could occur in the zwitterion, which must have C—N bond orders below two because of conjugation. Once the amido nitrogen is inverted the azine system has the unstable *s-cis* configuration. It could either return to **4** or else the second nitrogen could invert to achieve another *s-trans* configuration (**5**), which is geometrically suited for closure to **3**. Inversion of the second nitrogen, however, converts from the *E*-configuration ($R_1 = C_6H_5$, $R_2 = H$) of aldazine **2** (23), or of iminooxirane, to the *Z*-configuration. Thus the mechanism can account for the apparent selectivity of ring closure to the *Z*-isomers of **3***d*–**3***g*. The stereoselectivity, it should be emphasized, is not firmly established at this time for the stability of corresponding (unknown) *E*-isomers to the reaction conditions has not been demonstrated.

The mechanism of formation of **3** is under investigation.

Experimental

Carbohydrazones were synthesized according to Scheme 1; the aldehyde or aryl ketone moiety being introduced first and the aliphatic ketone last. Yields in these straightforward condensations were in the range 65–90% for each step. A typical synthesis is described below. The procedures for oxidative cyclization of carbohydrazones and for thermolysis of oxadiazolines are also described below. Properties and analyses of compounds are gathered in Tables 1–2. Melting points are uncorrected.

*Benzaldehyde-4-aminosemicarbazone (**6**)*

Carbohydrazide (5.0 g, 0.056 mol) and benzaldehyde (4.5 g, 0.042 mol) in 50 ml of absolute ethanol were heated at the reflux temperature for 1 h. The product which separated on cooling was filtered, washed with hot water, and recrystallized from ethanol: m.p. 165° (lit. (24) m.p. 173°); 86% yield.

*Crossed Carbohydrazone of Acetone and Benzaldehyde (**7**)*

A solution of **6** (20 g) in excess acetone (80 ml) was refluxed for 3 h. The solution was concentrated to 20 ml and the crystals which separated on cooling were filtered: yield 82%; m.p. 188–191°.

*5,5-Dimethyl-2-(benzylidenehydrazono)-Δ^3-1,3,4-oxadiazoline (**2e**)*

A solution of lead tetraacetate (LTA, 6.0 g, 0.0135 mol) in 25 ml of methylene chloride was cooled with ice. Gradual addition of **7** (2.0 g, 0.0092 mol) with stirring, was completed in 10 min; the temperature in the reaction vessel remaining below 5°. Stirring was continued for 15 min before ice water (50 ml) was added. After stirring for 10 min more, the dark brown slurry was filtered through Celite and the pale yellow organic layer was separated, washed with cold water (3 × 50 ml), with saturated sodium bicarbonate (50 ml), with cold water (3 × 50 ml), and dried with $MgSO_4$. Filtration and evaporation left a yellow solid (65%) which was recrystallized from petroleum ether: m.p. 95°; p.m.r. ($CDCl_3$) δ 1.8 (s, 6), 7.5 (m, 5), 8.5 (s, 1). All aldehyde derivatives **2** (R_1 = H) showed a one-proton singlet near 8.5 δ. All compounds **2** gave infrared spectra characteristic of 2-alkylidenehydrazono-Δ^3-1,3,4-oxadiazolines (13). Melting points and analyses are in Table 1.

*1-((Z)-phenylmethylene)-4,4-dimethyl-3-oxo-1,2-diazetidinium Hydroxide, Inner Salt (**3d**)*

A solution of **2e** (0.20 g, 1.05 × 10^{-3} mol) in chlorobenzene (10 ml) was refluxed for 24 h. About 7 ml of the solvent was distilled out. Cooling of the residual solution and addition of petroleum ether caused separation of a white solid which was filtered, washed with petroleum ether, and recrystallized from petroleum ether – chloroform to yield **3d** (37%): m.p. 191°; p.m.r. ($CDCl_3$) δ 1.74 (s, 6), 7.1 (s, 1), 7.45 (m, 3), 8.05 (m, 2); m.s. 188 (molecular ion). Melting points and analyses of members of the family **3** synthesized by analogous procedures, are in Table 2.

2-Methoxy-2-methyl-N-(diphenylmethylenimino)-propionamide

2-Methoxy-2-methylpropanoic acid (25) was esterified with methanol and sulfuric acid (25). The ester (2.95 g, 0.022 mol) was heated on the steam bath for 5 h with hydrazine hydrate (99%, 1.55 g, 0.031 mol). Evaporation of liquid in a rotary evaporator at 80° left 1.63 g (55%) of crude 2-methoxy-2-methylpropanoic acid hydrazide as a colorless oil. The hydrazide (1.63 g, 0.0123 mol) was heated with benzophenone (4.5 g, 0.025 mol) in 20 ml of ethanol for 17 h before the alcohol was removed at the water pump (65°). Washing of the solid residue with petroleum ether and recrystallization from ethyl ether in petroleum ether gave 0.34 g (10%) of the title compound: m.p. 125–126°; p.m.r. (CCl_4) δ 1.30 (s, 6, CH_3), 2.97 (s, 3, OCH_3), 7.13–7.73 (m, 10, phenyl); i.r. 3345 cm^{-1} (N—H), 1710 cm^{-1} (CO). This product was identical to that obtained from heating **3a** with methanol in a sealed tube at 150° for 30 h.

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1. R. Gosl and A. Neuwsen. Chem. Ber. **92**, 2521 (1959).
2. W. Schneider and W. Riedel. Ber. Dtsch. Chem. Ges. **74**, 1252 (1941).
3. B. Singh. J. Am. Chem. Soc. **91**, 3670 (1969).
4. R. Huisgen, R. Fleischmann, and A. Eckell. Tetrahedron Lett. 1 (1960).
5. G. F. Bettinetti and L. Capretti. Gazz. Chem. Ital. **95**, 33 (1965).
6. W. O. Godtfredsen and S. Vangedal. Acta Chem. Scand. **9**, 1498 (1955).
7. J. C. Howard, G. Gever, and P. Wei. J. Org. Chem. **28**, 868 (1963).
8. H. Dorn and A. Otto. Angew. Chem. Intern. Ed. Engl. **7**, 214 (1968).
9. R. B. Greenwald and E. C. Taylor. J. Am. Chem. Soc. **90**, 5272 (1968).
10. R. B. Greenwald and E. C. Taylor. J. Am. Chem. Soc. **90**, 5273 (1968).
11. N. F. Haley. Ph.D. Thesis, Princeton University, 1971; Diss. Abstr. **32**, 3851-B (1972).
12. C. J. Fritchie, Jr. and J. L. Wells. Chem. Commun. 917 (1968).
13. P. R. West and J. Warkentin. J. Org. Chem. **33**, 2089 (1968).
14. A. M. Cameron, P. R. West, and J. Warkentin. J. Org. Chem. **34**, 3230 (1969).
15. A. Prakash, C. Calvo, A. M. Cameron, and J. Warkentin. J. Cryst. Mol. Struct. **3**, 71 (1973).
16. C. Calvo, P. C. Ip, N. Krishnamachari, and J. Warkentin. Can. J. Chem. **52**, 2613 (1974).
17. P. R. West and J. Warkentin. J. Org. Chem. **34**, 3233 (1969).
18. T. Saegusa, N. Taka-ishi, and H. Fujii. Tetrahedron **24**, 3795 (1968).
19. K. Bott. Tetrahedron Lett. 3323 (1968).
20. (*a*) J. C. Sheehan and I. Lengyel. J. Am. Chem. Soc. **86**, 746 (1964); (*b*) J. C. Sheehan and I. Lengyel. Angew. Chem. Intern. Ed. **7**, 25 (1968).
21. (*a*) P. D. Bartlett and L. B. Gortler. J. Am. Chem. Soc. **85**, 1864 (1963); (*b*) R. Wheland and P. D. Bartlett. J. Am. Chem. Soc. **92**, 6057 (1970); (*c*) W. Adam and R. Rucktäschel. J. Am. Chem. Soc. **93**, 557 (1971). (*d*) O. L. Chapman, P. W. Wojtkowksi, W. Adam, O. Rodriquez, and R. Rucktäschel. J. Am. Chem. Soc. **94**, 1365 (1972).
22. E. R. Talaty, A. E. Dupuy, Jun., and T. H. Golson. Chem. Commun. 49 (1969).
23. J. Elguero, R. Jacquier, and C. Marzin. Bull. Soc. Chim. Fr. 1374 (1969).
24. A. C. Brown, E. C. Pickering, and F. J. Wilson. J. Chem. Soc. 107 (1927).
25. C. H. Weizmann, M. Sulzbacher, and E. Bergmann. J. Am. Chem. Soc. **70**, 1153 (1948).