Oxidative cyclization of carbonyl derivatives. 5-Imino-Δ^1-1,2,4-triazolines from alkylideneimino guanidines

LUBOMIRA M. CABELKOVA-TAGUCHI AND JOHN WARKENTIN

Department of Chemistry, McMaster University, Hamilton, Ont., Canada L8S 4M1

Received February 10, 1978

LUBOMIRA M. CABELKOVA-TAGUCHI and JOHN WARKENTIN. Can. J. Chem. **56**, 2194 (1978).

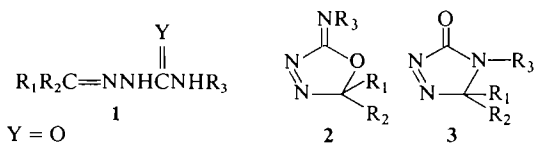
Treatment of 2-propylideneimino guanidinium acetate with lead tetraacetate, in methylene chloride containing solid sodium carbonate, afforded the previously unknown 3,3-dimethyl-5-imino-Δ^1-1,2,4-triazoline. Similarly, *N,N'*-diphenyl-*N''*-(2-propylideneimino)guanidinium acetate afforded *Z*-4-phenyl-5-phenylimino-Δ^1-1,2,4-triazoline as the major oxidation product and the corresponding *E* isomer as a minor product. Stereochemistry was established spectrophotometrically and also by isomerizing the minor (*E*) isomer to the major (*Z*) isomer.

LUBOMIRA M. CABELKOVA-TAGUCHI et JOHN WARKENTIN. Can. J. Chem. **56**, 2194 (1978).

La réaction de l'acétate de propylidèneimino-2-guanidinium avec le tétraacétate de plomb dans le chlorure de méthylène contenant du carbonate de sodium solide conduit à la diméthyl-3,3 imino-5 Δ^1 triazoline-1,2,4 qui était inconnue. De la même manière, l'acétate du *N,N'*-diphényl *N''*-(propylidèneimino-2) guanidinium conduit à la phényl-4 phénylimino-5 Δ^1 triazoline-1,2,4(*Z*) comme produit d'oxydation majeur alors que l'isomère *E* correspondant est le produit mineur. On a établi la stéréochimie d'une façon spectrophotométrique et aussi par isomérisation de l'isomère (*E*) en isomère majeur (*Z*).

[Traduit par le journal]

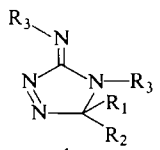
Oxidation of ketone semicarbazones (**1***a*), either with lead tetraacetate (LTA) (1) or by air in the presence of neutral alumina (2), leads to cyclization products **2** and **3**, respectively. Analogous oxidation



1

a Y = O
b Y = O, R_3 = —N=CR_1R_2
c Y = NR_3

2 **3**



4

a $R_1 = R_2 = CH_3$, R_3 = H
b $R_1 = R_2 = CH_3$, $R_3 = C_6H_5$
c *E* isomer of **4***b*

of carbohydrazones (**1***b*) yields **2** (R_3 = —N=CR_1R_2) (3) which are of some interest as precursors of diazetidinium hydroxide inner salts (4, 5). As part of a continuing study of the chemistry of cyclic azo systems (5–9), we investigated the oxidation of alkylideneimino guanidines (guanyl hydrazones) (**1***c*) to iminotriazolines **4**, which were unknown. Other Δ^1-1,2,4-triazoline systems were scarce too[1] although there were many examples of 1,2,4-triazoles in the literature. Moreover, we were interested in the stereochemistry of cyclization of **1***c* to **4** because of our earlier finding that **1***a* is oxidized selectively to the *Z* isomer of **2** (10).

Results and Discussion

Oxidation of 2-propylideneimino guanidine[2] (**1***c*, $R_1 = R_2 = CH_3$, R_3 = H) with LTA in CH_2Cl_2 gave 5-imino-3,3-dimethyl-Δ^1-1,2,4-triazoline (**4***a*) in 28% yield. Oxidation with bromine in acetic acid gave the same product in 17% yield. In either case there were numerous by-products which were not identified. The gross structure of **4***a* was established from analytical and spectral data; the strong ir band at 1680 cm^{-1}, characteristic of the exocyclic C=N function (11), was taken as evidence for the imine structure rather than the tautomeric amine structure. Attempts to detect and to separate both *E* and *Z* isomers of **4***a* were unsuccessful. Iminotriazoline **4***a* is readily decomposed by dilute acid or by water to yield acetone. We were unable to find **3**[3] ($R_1 = R_2 = CH_3$, R_3 = H) or the amino tautomer of **4***a*[4] among the products.

Oxidation of *N,N'*-diphenyl-*N''*-(2-propylidene-

[1]The only examples that we were able to find were 1,2,4-triazolinones (**3**) (2).

[2]We assume that it is the free guanidine, not the guanidinium ion, which is oxidized.

[3]Our experience with **3** ($R_1 = R_2 = CH_3$, $R_3 = C_6H_5$), suggests that **3** ($R_1 = R_2 = CH_3$, R_3 = H) would have survived the procedure.

[4]The formation of this tautomer as an intermediate is not precluded, of course, for it may undergo rapid subsequent reactions.

imino)guanidine (**1***c*, $R_1 = R_2 = CH_3$, $R_3 = C_6H_5$) with LTA in CH_2Cl_2 afforded **4***b* (40%) and its *E* isomer (1%). These isomers have indistinguishable ^{1}Hmr and ^{13}Cmr spectra and both have ir bands at 1680 (C=N) and 1590 (N=N) cm^{-1}. Assignment of stereochemistry was based on their uv spectra and on the result of an isomerization experiment.

The uv spectra, λ_{max} (95% ethanol) 410 and 395 nm, for the major and minor isomers, respectively, indicate that the latter is less conjugated than the former. Nonbonded interactions between proximate phenyl groups of the *E* isomer, forcing them out of the plane of the triazoline ring, is the only obvious conjugation-inhibiting feature. The minor isomer was therefore assigned the *E* geometry and the major isomer the *Z* geometry (**4***b*, as drawn).

Partial inhibition of resonance because of steric hindrance between phenyl groups of the *E* isomer should mean that its ground state energy is higher than that of the *Z* isomer. Treatment of the minor isomer with aniline–anilinium buffer converted it (50% yield) to the major isomer, under conditions which left a trace of the minor isomer. Thus, the minor isomer is less stable, thermodynamically, than the major isomer and the assignment based on uv data is supported.

Experimental

3,3-Dimethyl-5-imino-Δ^1-1,2,4-triazoline

LTA Method

2-Propylideneimino guanidinium acetate, mp 221–222°C (lit. (12) mp 222°C) was prepared in 78% yield from aminoguanidine bicarbonate (12). To the acetate (1.7 g, 0.01 mol) in 75 ml of ice-cold dichloromethane was added anhydrous sodium carbonate (2.1 g, 0.025 mol) and the mixture was stirred under nitrogen for 3 h. Lead tetraacetate (2.2 g, 5 mmol, washed with petroleum ether) was added and the resulting yellow slurry was stirred for 10 min before a cold solution of sodium bicarbonate (5.0 g in 20 ml of water) was added. The brown slush which formed was stirred for 15 min and then filtered through Celite. The organic layer was separated and washed three times with ice water before it was dried over magnesium sulfate. Evaporation of dichloromethane at ca. 10°C in a rotary evaporator left a crude solid from which **4***a* (0.25 g, 28%) was obtained by sublimation at room temperature and 10^{-2} Torr: mp 70°C (d); ir 3550, 3490 (NH), 1680 (C=N) cm^{-1}; ^{1}Hmr δ: 1.5, s; uv, λ_{max} (95% ethanol): 285 (2.375). *Anal.* calcd. for $C_4H_8N_4$: C 42.86, H 7.16, N 50.00; found: C 42.80, H 7.09, N 50.11.

Br_2 Method

2-Propylideneimino guanidinium acetate (1.7 g, 0.01 mol) in 50 ml of anhydrous methanol was stirred with anhydrous sodium carbonate (2.1 g, 0.025 mol) for 1 h at ice bath temperature. Bromine (0.60 g, 7.5 mmol) was added dropwise and the yellow solution was stirred for 15 min after addition of Br_2 was complete. Filtration and evaporation of the solvent left a solid which was dissolved in water (25 ml). Extraction with ether (25 ml), washing with water, drying, removal of the ether, and sublimation of the solid residue as described above gave **4***a* (0.15 g) in 17% yield.

3,3-Dimethyl-4-phenyl-5-phenylimino-Δ^1-1,2,4-triazolines (4b and the E *Isomer)*

Acetone-4-phenylthiosemicarbazone (**5**) (13) was methylated by a procedure modelled after Kirsten and Smith's methylation of thioureas (14). To an ice-cold solution of **5** (21 g, 0.1 mol) in 200 ml of absolute ethanol was added methyl iodide (15 g, 0.1 mol) and the resulting solution was stirred for 3 h at ice temperature and subsequently for 12 h at room temperature. During this time, a white suspended solid dissolved leaving a clear yellow solution. Most of the ethanol was evaporated with a rotary evaporator and the resulting viscous, yellow oil was chromatographed on silica gel (80–200 mesh) with 1:1 petroleum ether in CCl_4. From the second fraction was obtained, after recrystallization from alcohol, *N*-phenyl-*N'*-(2-propylideneimino)-*S*-methylisothiouronium iodide (**6**) (16.5 g, 79%) as white crystals: mp 43–44°C; ^{1}Hmr δ: 2.05 (s, 3H), 2.10 (s, 3H), 2.40 (s, 3H), 7.25 (s, broad, 5H), 8.20 (s, broad, 1H).

The salt **6** (18 g, 0.05 mol) was heated on a steam bath under an air condenser with aniline (4.65 g, 0.05 mol, freshly distilled) in 50 ml of dry benzene. When the evolution of methanethiol was no longer detectable by odour (about 24 h), the benzene was removed with a rotary evaporator to leave *N,N'*-diphenyl-*N''*-(2-propylideneamino)guanidinium iodide (**7**) as a syrup (87% yield). This product was used directly in the next step.

The procedure for oxidation of **7** with LTA was analogous to that described above. Evaporation of dichloromethane in the work-up procedure left a dark brown oil which was stirred for 12 h with 50 ml of 1:1 petroleum ether in ether. The orange solvent layer was decanted and the extraction was repeated twice more. Evaporation of the combined extracts left a gummy orange residue which was chromatographed on silica gel (80–200 mesh) using petroleum ether (30–60°C) in ether (4:1) as eluent. Crystallization of the main orange fraction afforded 1.2 g (40%) of **4***a* as orange crystals: mp 89.5–90°C (dec.); ^{1}Hmr δ: 1.66 (s, 6H), 7.16 (s, broad, 5H), 7.3 (s, broad, 5H); ^{13}Cmr δ: 156.11, 147.53, 135.79, 129.55, 128.44, 127.40, 126.78, 123.73, 123.37, 102.60, 24.06; ir: 1680 (s, C=N), 1590 (m, N=N) cm^{-1}; uv λ_{max} (95% ethanol): 410 (3.38), 345 (3.67), 235 (4.11) nm; ms: 264 (molecular ion). *Anal.* calcd. for $C_{16}H_{16}N_4$: C 72.73, H 6.10, N 21.19; found: C 72.97, H 6.45, N 20.97.

A yellow to orange lead fraction from the column gave yellow crystals of **4***c* (0.03 g, 1%): mp 93–94°C; ir ^{1}Hmr, and ^{13}Cmr data identical to those listed above; uv λ_{max} (95% ethanol): 395 (3.88), 338 (3.93), 230 (4.69) nm; ms: 264 (molecular ion). *Anal.* calcd. for $C_{16}H_{16}N_4$: N 72.73, H 6.10, N 21.19; found: C 72.75, H 6.38, N 20.86. Mixture mp (**4***a* and **4***b*): 85–87°C.

Isomerization of 4c *to* 4b

To freshly distilled aniline (10 ml) were added 3 drops of concentrated HCl and **4***c* (0.08 g). The solution was kept at ca. 45°C for 4 h, together with a control sample containing only aniline and HCl. The uv spectrum of a portion of the first solution showed a new absorption band at 410 nm which was not present in the uv spectrum of the control sample. Vacuum distillation of the aniline from the test solution and thin layer chromatography of the residue showed that compounds with the R_f values of **4***b* and **4***c* were present. Column chromatography on silica gel afforded **4***b* (0.041 g, 50%): mp 89–90°C; spectra identical to those of **4***a* obtained by oxidation of **7**.

Acknowledgement

The authors wish to thank the National Research

Council of Canada for a grant in support of this work.

1. (*a*) A. M. CAMERON, P. R. WEST, and J. WARKENTIN. J. Org. Chem. **34**, 3230 (1969); (*b*) S. L. LEE, G. B. GUBELT, A. M. CAMERON, and J. WARKENTIN. Chem. Commun. 1074 (1970); (*c*) S. L. LEE, A. M. CAMERON, and J. WARKENTIN. Can. J. Chem. **50**, 2326 (1972).
2. J. K. LANDQUIST. J. Chem. Soc. (C), 63 (1970).
3. P. R. WEST and J. WARKENTIN. J. Org. Chem. **33**, 2089 (1968).
4. K. RAMAKRISHNAN, J. B. FULTON, and J. WARKENTIN. Tetrahedron, **32**, 2685 (1976).
5. P. C. IP, K. RAMAKRISHNAN, and J. WARKENTIN. Can. J. Chem. **52**, 3671 (1974).
6. S. L. LEE, P. KNITTEL, and J. WARKENTIN. Can. J. Chem. **50**, 3248 (1972).
7. (*a*) P. KNITTEL and J. WARKENTIN. Can. J. Chem. **53**, 2275 (1975); (*b*) P. KNITTEL and J. WARKENTIN. Can. J. Chem. **54**, 1341 (1976).
8. D. C. FROST, N. P. C. WESTWOOD, N. H. WERSTIUK, L. M. CABELKOVA-TAGUCHI, and J. WARKENTIN. Can. J. Chem. **55**, 3677 (1977).
9. P. R. WEST and J. WARKENTIN. J. Org. Chem. **34**, 3233 (1969).
10. A. PRAKASH, C. CALVO, A. M. CAMERON, and J. WARKENTIN. J. Cryst. Mol. Struct. **3**, 71 (1973).
11. (*a*) H. NAJER, J. MENIN, and J. F. GIUDICELLI. C. R. Acad. Sci. **258**, 4579 (1974); (*b*) H. NAJER, J. MENIN, and J. F. GIUDICELLI. C. R. Acad. Sci. **259**, 2868 (1964); (*c*) J. F. GUIDICELLI, J. MENIN, and H. NAJER. C. R. Acad. Sci. **260**, 4538 (1965); (*d*) H. NAJER, R. GIUDICELLI, J. MENIN, and J. LOISEAU. C. R. Acad. Sci. **254**, 2175 (1964); (*e*) G. L. SCHMIR and B. A. CUNNINGHAM. J. Am. Chem. Soc. **87**, 5693 (1965); (*f*) H. PETER, M. BRUGGER, J. SCHREIBER, and A. ESCHENMOSER. Helv. Chim. Acta, **46**, 577 (1963); (*g*) M. KURHARA and N. YODA. Tetrahedron Lett. 2597 (1965).
12. F. BAIOCCHI, C. C. CHENG, W. J. HAGGERTY, JR., L. R. LEWIS, T. K. LIAO, W. H. NYBERG, D. E. O'BRIEN, and E. G. PODREBARAC. J. Med. Chem. **6**, 431 (1963).
13. F. J. WILSON and R. BURNS. J. Chem. Soc. **121**, 871 (1922).
14. G. W. KIRSTEN and G. B. L. SMITH. J. Am. Chem. Soc. **58**, 800 (1936).