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RING ENLARGEMENT OF DIAZIRIDINONE: PYRAZOLINE-FORMING REACTION WITH α-METALATED NITRILE

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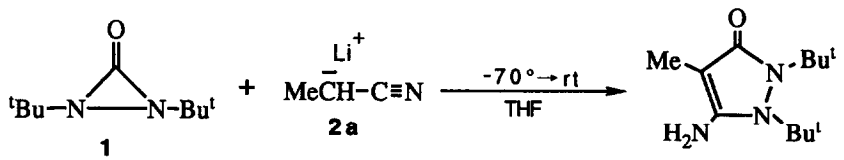
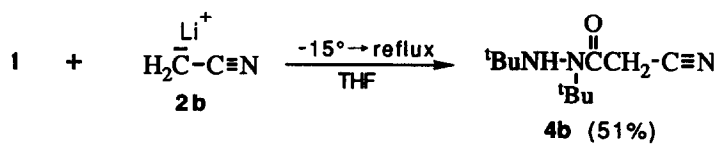
Summary: Reaction of *N,N'*-di-*tert*-butyldiaziridinone (**1**) with α-lithiopropionitrile or α-sodiobenzylcyanide caused ring enlargement of **1** to give functionalized five-membered heterocycles such as aminopyrazolinone and/or iminopyrazolidinone.

Diaziridinone is of great interest because of high and specific reactivity.[1] Especially ring enlargement reaction such as cycloaddition provides us with facile preparative methods for functionalized poly-nitrogen heterocycles. Most of the reported cycloadditions of diaziridinone are based on its 1,3-dipolar property according to large ring strain and polar bonds.[2] While electrophilic nature of the carbonyl carbon of diaziridinone is well known,[1,3] few ring enlargement reactions initiated by nucleophilic attack to the ring carbon are reported.[2c] Here we report pyrazoline-forming ring enlargement of diaziridinone by reaction with α-metalated nitriles (*i.e.*, α-cyanocarbanions).

Reactions of *N,N'*-di-*tert*-butyldiaziridinone (**1**) with α-metalated aliphatic nitriles were studied first. α-Lithiopropionitrile (**2a**) reacted with diaziridinone **1** to afford a 1:1 adduct, pyrazolinone **3a**, in an almost quantitative yield as a result of N-C bond fission of **1** and ring enlargement.



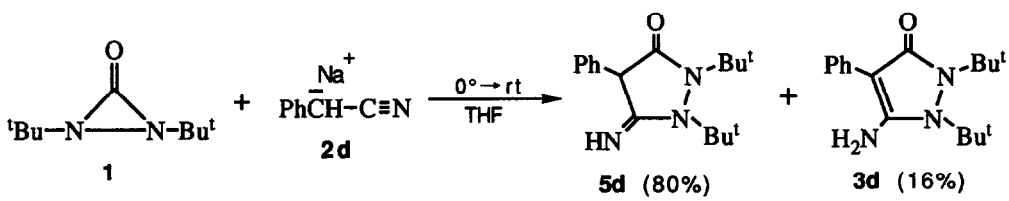
Effect of the substituent of nitrile was remarkable. While α-lithioacetonitrile (**1b**) caused ring opening of **1**, no ring enlargement product but an acyclic 1:1 adduct, cyanoaceto-hydrazide derivative **4b**, was isolated (51%). In the case with α-lithioisobutyronitrile (**2c**), a considerable amount (41%) of *N,N'*-di-*tert*-butylurea was obtained[4] instead of the addition product correponding to **3a** or **4b**.



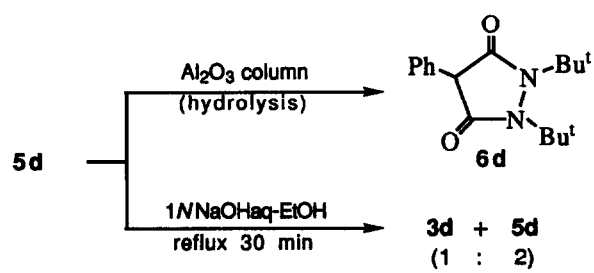
A typical reaction procedure is as follows. A solution of propionitrile (1.10 g, 20 mmol) in THF (5 ml) was added dropwise at -70 °C to a solution of *in-situ* generated lithium diisopropylamide (LDA: 20 mmol) in THF (30 ml). After stirring for 2 h, a THF solution (5 ml) of **1** (3.40 g, 20 mmol) was added dropwise and the mixture was stirred for another hour at -70 °C. The temperature was then gradually raised to room temperature. Water (10 ml) was added to quench the reaction and the mixture was concentrated and extracted (Et_2O). The organic layer was dried (Na_2SO_4) and concentrated to give orange oily residue which afforded 4.2 g (93%) of crystalline 5-amino-1,2-di-*tert*-butyl-4-methylpyrazolin-3-one (**3a**) upon standing overnight after addition of a small amount of ether.

The structures of aminopyrazolinone **3a** and hydrazide **4b** were determined by spectral data and elemental analyses.[5] In the IR spectrum of **3a**, an absorption band of the carbonyl group was observed at 1620 cm^{-1}. The D_2O exchangeable singlet at δ 6.20 in NMR spectrum (in d_6-DMSO) was ascribed to the amino group. Molecular ion peak observed at *m/z* 225 in MS and elemetal analysis were also in good agreement with the structure.

Similar pyrazolinone-forming reaction was also found for benzylcyanide. Treatment of diaziridinone **1** with *in-situ* generated α-sodiobenzylcyanide (**2d**, from sodium hydride and benzylcyanide) in THF at 0 °C gave iminopyrazolidinone **5d** (crude yield 80 %) along with aminopyrazolinone **3d** (16 %) corresponding to **3a**. Under the same conditions, α-sodiodiphenylacetonitrile (**2e**) gave no adduct with **1** and *N,N'*-di-*tert*-butylurea (71%) was obtained similarly to the reaction of α-lithioisobutyronitrile (**2c**).[4]

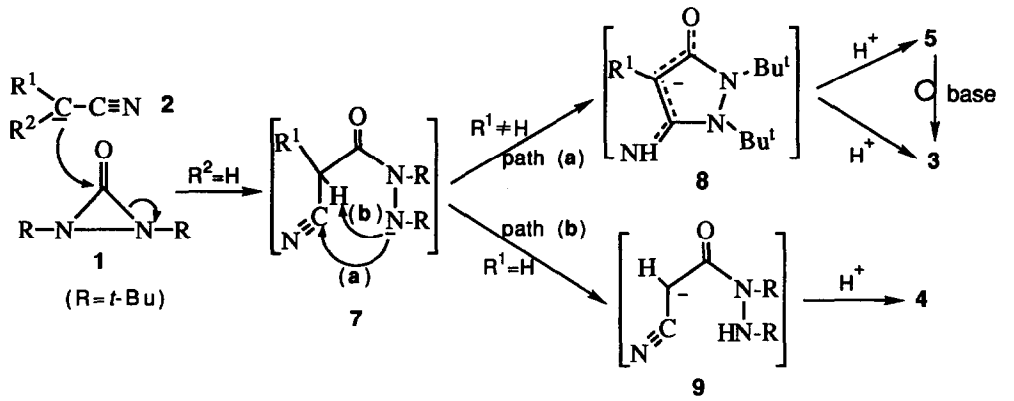


One of the features of the spectra of **5d** is the existence of a methine proton (δ 4.76) in ^1H nmr and an sp^3 carbon (d, 62.8 ppm) and an imino carbon (s, 157.8 ppm) in ^{13}C nmr.[5] Pyrazolidinone **5d** was obtained as pale orange oil whose crystallization was not so easy and chromatographic treatment of the oil on an Al_2O_3 column caused hydrolysis forming pyrazolidinedione **6d** (51 %) along with unidentified materials. Iminopyrazolidinone **5d** is considered to be the precursor of aminopyrazolinone **3d** since 37% of **5d** was converted to **3d**

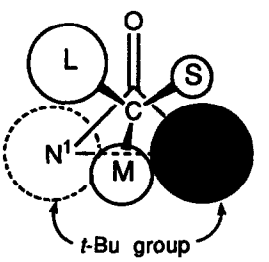


when **5d** was heated in refluxing mixture of 1*N* NaOHaq and EtOH (1:10) for 30 min.

The reaction path of the present ring enlargement reaction is considered as follows. Nucleophilic attack of cyanocarbanion **2** to the ring carbon of diaziridinone **1** causes N-C bond cleavage to release large ring strain of **1**. The resulted intermediate **7** recyclizes to the stabilized anion **8** via path (**a**) followed by protonation to give aminopyrazolinone **3** or iminopyrazolidinone **5**. When R^1 is hydrogen, amide ion of **7** abstracts proton via path (**b**) leading to the stabilized anion **9** which gives the acyclic adduct **4** upon protonation.



Since proton abstraction via path (**b**) was not observed for the more acidic hydrogen of the adduct of α-sodiobenzylcyanide (**2d**) and **1** (**7**: R^1 = Ph), there must be some steric reasons. One of the possibilities is the following assumption. Taking into account of a model of a transition state leading to **7** and the bulky *t*-butyl substituents (see the figure on the right), the cyano group of **2a** (R^1=Me) or **2d** (R^1=Ph) should take the place of "M" which is located near the anion-forming nitrogen "N^1" and the hydrogen should be "S" which is far from "N^1". On the contrary, the hydrogens of **2b** (R^1=H) must take the places of "S" and of "M" which is near to the hydrogen-abstracting nitrogen "N^1". Tertiary carbanions such as α-lithioisobutyronitrile (**2c**) and α-sodiodiphenylacetonitrile (**2e**) did not give adducts probably because of steric hindrance against approach of **2** to **1** as well as of that the cyano group should be oriented opposite to the nitrogen "N^1". In this case, reduction of **1** to *N*,*N*'-di-*tert*-butylurea seems to become predominant similarly to the reduction by *tert*-butyllithium via electron transfer process.[4]



S, M, L : size of substituents

All the hitherto known isolable diaziridinones are, unfortunately, those having two tertiary alkyl substituents. However, tert-butyl group on nitrogen atom is often eliminated under acidic conditions,[6] which renders protective nature to the butyl moiety. To have better insight into the specific nature of diaziridinones and to generalize the present reaction, further study on preparation of various types of diaziridinones as well as on de-*tert*-butylation of these products are under investigation.

References and Notes

1) E. Schmitz, "Three-membered Rings with Two Heteroatoms and Fused-ring Derivatives," in "Comprehensive Heterocyclic Chemistry: Vol.8," Ed. by W. Lwowski, Pergamon Press, Oxford, 1984; H. W. Heine, "Diaziridines, 3*H*-Diazirines, Daiziridinones, and Diaziridineimines," in "Chemistry of Heterocyclic Compounds: Vol. 42 (Small Ring Heterocycles: Part 2.), " Ed. by A. Weissberger and E. C. Taylor, John Wiley & Sons, New York, 1983.

2) a) Y. Ohshiro, M. Komatsu, Y. Yamamoto, K. Takaki, and T. Agawa, *Chem. Lett.*, **1974**, 383, b) C. A. Renner and F. D. Greene, *J. Org. Chem.*, **41**, 2813 (1976), c) T. Hirao, T. Masunaga, Y. Ohshiro, and T. Agawa, *Synthesis*, **1983**, 477.

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4) Reduction of the diaziridinone **1** to the urea with *tert*-butyllithium or sodium naphthalenide is reported: F. D. Greene, W. R. Bergmark, and J. F. Pazos, *J. Org. Chem.*, **35**, 2813 (1970).

5) **3a**: mp 163.5-165°C (colorless needles from benzene); ir (Nujol, cm^{-1}) 3450, 3240 (NH), 1620 (C=O), 1595 (C=C); ^{1}H-nmr (DMSO-d_6, δ) 1.15 (s, 18H, 2 t-Bu), 1.43 (s, 1H, Me), 6.20 (s, 2H, NH_2, D_2O exchangeable); MS (70eV, *m/z*) 225 (M^+); Anal. Calcd for $C_{12}H_{23}N_3O$: C, 63.96; H, 10.29, N, 18.65. Found: C, 64.03; H, 10.25; N, 18.50.

4b: mp 93.5-94.5°C (colorless needles from benzene-hexane); ir (Nujol, cm^{-1}) 3350 (NH), 2250 (CN), 1640 (C=O); ^{1}H-nmr ($CDCl_3$, δ) 1.20 (s, 9H, t-Bu),1.48 (s, 9H, t-Bu), 3.71 (d, *J*=18.0 Hz, 1H, C*H*H), 3.80 (s, 1H, NH, D_2O exchangeable), 3.87 (d, *J*=18.0 Hz, 1H, CH*H*); MS (70eV, *m/z*) 211 (M^+); Anal. Calcd for $C_{11}H_{21}N_3O$: C, 62.52; H, 10.02; N, 19.89. Found: C, 62.38; H, 10.08; N, 19.99.

3d: mp 168-170.5°C (colorless needles from benzene-hexane); ir (Nujol, cm^{-1}) 3480, 3280-3160 (NH), 1640 (C=O), 1600 (C=C); ^{1}H-nmr ($CDCl_3$, δ) 1.28 (s, 9H, t-Bu), 1.30 (s, 9H, t-Bu), 4.9 (s, 2H, NH_2), 7.0-7.4 (m, 5H, Ph); MS (70eV, *m/z*) 287 (M^+); Anal. Calcd for $C_{17}H_{25}N_3$: C, 71.04; H, 8.77; N, 14.62. Found: C, 71.28; H, 8.91; N, 14.65.

5d: mp 88-89°C (colorless granules from ether-hexane); ir (Nujol, cm^{-1}) 3270, 1720 (C=O), 1645 (C=N); ^{1}H-nmr ($CDCl_3$, δ) 1.28 (s, 9H, t-Bu), 1.66 (s, 9H, t-Bu), 4.76 (s, 1H, CH), 6.51 (s, 1H, NH), 7.33 (s, 5H, Ph); ^{13}C-nmr ($CDCl_3$, ppm) 28.6 (q, 2 Me), 56.5 and 55.2 (s, CMe_3), 62.8 (d, CH), 125.0 (d), 128.4 (d), 129.2 (d), 140.1 (s), 157.8 (s, C=NH), 165.4 (s, C=O) ; MS (70eV, *m/z*) 287 (M^+). Elemental analysis was not satisfactory probably because of its high sensitivity toward hydrolysis.

6d: mp 132.5-133.5°C (colorless needles from benzene-hexane); ir (Nujol, cm^{-1}) 1760 and 1700 (C=O); ^{1}H-nmr ($CDCl_3$, δ) 1.30 (s, 9H, t-Bu), 1.57 (s, 9H, t-Bu), 4.70 (s, 1H, CH), 7.27 (s, 5H, Ph); MS (70eV, *m/z*) 288 (M^+); Anal. Calcd for $C_{17}H_{24}N_2O_2$: C, 70.80; H, 8.39; N, 9.71. Found: C, 70.69; H, 8.36; N, 9.68.

6) One or both of the *tert*-butyl groups incorporated into heterocyles are eliminated in the presence of $AlCl_3$ or BF_3·OEt_2[2a] or on acidic hydrolysis (unpublished data).

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