NEW ENTRY TO 2-AZA-2,4-CYCLOPENTADIENONE BY RING EXPANSION OF 4-AZIDO-2-CYCLOBUTENONE

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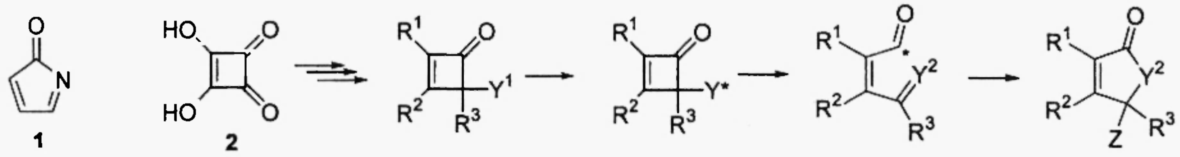
Abstract : Thermal decomposition of 4-azido-3,4-diethoxy-2-phenyl-2-cyclobutenone obtained by phenylation, acetalization and azidation of squaric acid ethyl ester gave rise to a polysubstituted 2-aza-2,4-cyclopentadienone through the combined process of nitrogen extrusion and ring expansion. Anti-aromatic yet resonance-stabilized nature of this product allowed easy isolation and further cyclization with binucleophilic reagents to nitrogen heterocycles.

Similar to 2,4-cyclopentadienone, 2-aza-2,4-cyclopentadienone 1 is an intrinsically unstable compound because of an antiaromatic 4π-electrons system.[1] Nevertheless, some substituents on the ring enhance stability kinetically and/or thermodynamically to allow handling under isolable conditions. While much less attention has been paid for this aza-analog, the prototype (unsubstituted system) was demonstrated to have the life time of ca. 2 s at 30 °C by Gaviña,[2] and alternatively, stabilized types were reported for some derivatives which are substituted with *t*-butyl, 3-indolyl, and heteroatom groups.[3]

We have been interested in chemistry of squaric acid **2**, especially centering on ring-transformation of its cyclobutenone derivatives triggered by reactive intermediates.[4,5] Radical, cation, and carbene intermediates generated at the position adjacent to an unsaturated four-membered ring are all possible to initiate ring-expansion reactions to five-membered rings including 2(*5H*)-furanones and cyclopentene-1,3-diones. In these cases, fruitful results were obtained by virtue of effective interaction of the reactive intermediates with the cyclobutenone ring and relief of strain existing in this ring (Scheme 1).

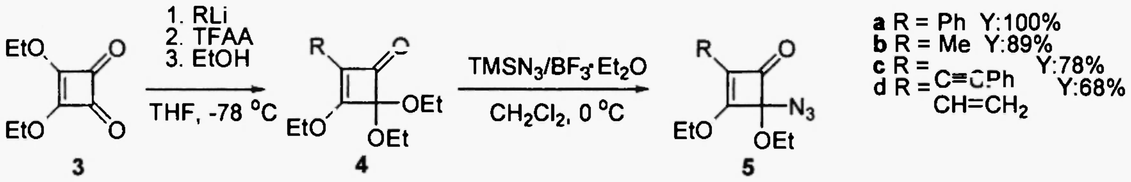


Y*: Reactive Intermediate (radical, cation, carbene)

Scheme-1

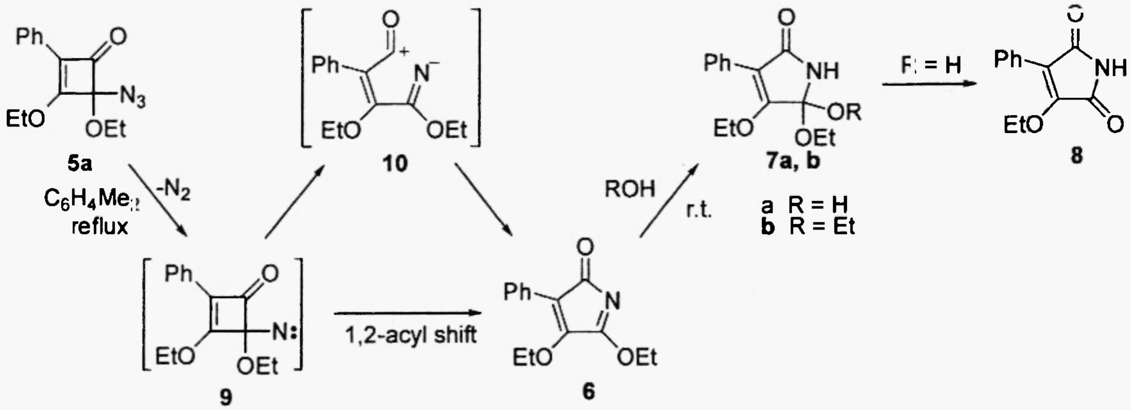
Along this line, it is reasonable to consider that the nitrene intermediate[6] induces the analogous pattern of reaction to produce five-membered nitrogen heterocycles; on the basis of a related mechanism (Scheme 1, Y*=N:), 1,2-acyl shift to the positive nitrene possibly leads to polysubstituted 2-aza-2,4-cyclopentadienones. We now wish to report such a new ring-transformation reaction and utilization of the resulting ring-expansion product.

Azide function was selected as a source of the nitrene intermediate in this experiment.[6] Introduction of the azide group was carried out by an organosilicon method developed by us.[4,5] Thus, substituted cyclobutenedione monoacetals **4**, which were prepared by successive treatment of ethyl squarate **3** with organolithium reagents and ethanol/trifluoroacetic anhydride,[7] were allowed to react with trimethylsilyl azide under $BF_3 \cdot Et_2O$-catalyzed conditions at 0 °C for 1 h (Scheme 2). After usual work-up and purification by silica gel chromatography, 4-azidation products **5** were obtained in good yields.[8] The structure was confirmed by spectral characteristics showing azide and carbonyl groups (2115 and 1765 cm^{-1}) in IR, and one 3-ethoxy group and another diastereotopic 4-ethoxy group (dq coupling pattern) in ^{1}H-NMR, and a cyclobutenone ring (requisite three sp^2-carbons and one sp^3-carbon) in ^{13}C-NMR.[9]



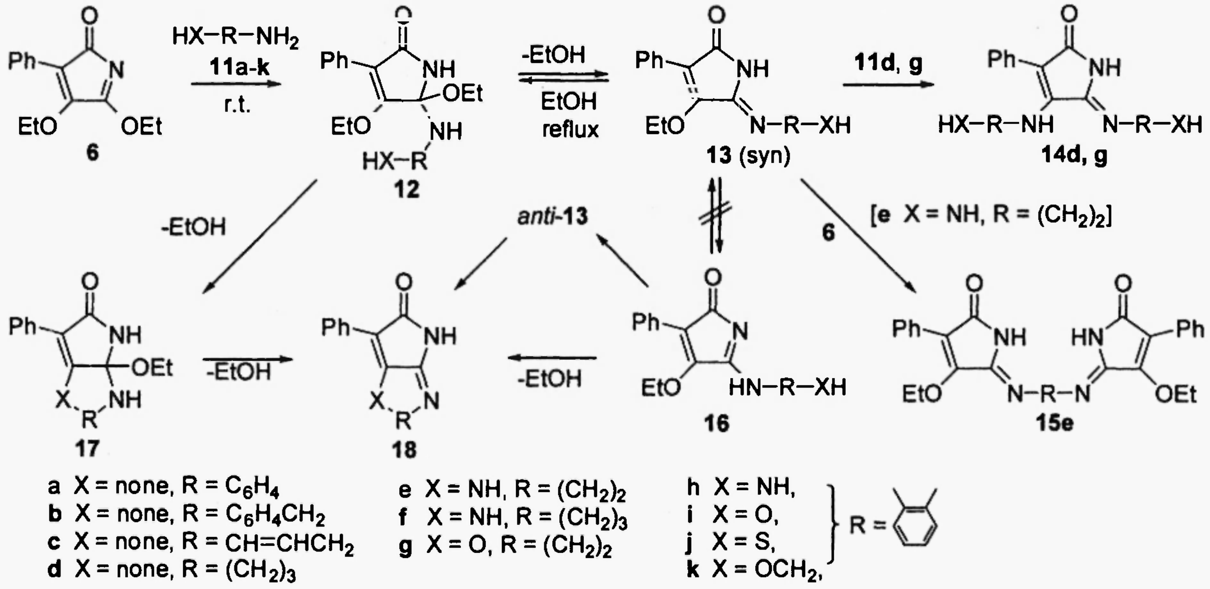
Scheme-2

For the next thermal decomposition reaction to generate the aimed nitrene intermediate, the best suited 2-phenyl-substituted case was examined. Thus, **5a** was heated in dry *p*-xylene at reflux temperature under a nitrogen atmosphere, and smooth decomposition was found to occur within 30 min to give a yellow solution. After direct treatment of the crude product with $H_2O/NaHCO_3$, maleimide 8 was obtained in 95% yield.[10] Similar treatment with ethanol gave acetal **7b** (R = Et) in 79% yield. Obtained were indeed ring-expansion products following the expected mechanism with the participation of nitrene intermediate **9**. Thus, these results suggest a new entry to 2-aza-2,4-cyclopentadienone by ring expansion of 4-azidocyclobutenone. The scrutinized mechanism may be delineated with two possible routes (Scheme 3): straightforward 1,2-acyl shift to the nitrene center in concertedness (**9**→**6**), or more sophisticatedly, ring-opening of cyclobutenone induced by electron-deficient nature of the nitrene and recombination of the resulting acyl cation and iminyl anion (*via* **10**).[11] Importantly, the above experiment indicates that "polysubstituted" 2-aza-2,4-cyclopentadienone **6** can survive even at higher temperature. In fact, without addition of water or ethanol, the solution was concentrated and cooled to give **6** itself as yellow crystals (mp **118-119** °C). The spectral data of isolated **6** was compatible with the expected structure; MS and IR showed the molecular ion peak at *m*/e 245 and absorptions at 1730 and 1584 cm^{-1} due to carbonyl and imine groups with no absorption due to an azide group, respectively. Also, ^{1}H NMR showed the required signals due to two ethyl groups one of which was no longer diastereotopic, indicating loss of the chiral center of 4-position, and ^{13}C NMR showed the signals due to ring carbons all of which were sp^{2}-carbons, consistent with the 2-aza-2,4-cyclopentadienone ring.[12] The enhanced stability of **6** is apparently attributed to double resonance between carbonyl and both ethoxy groups besides phenyl-conjugation.



Scheme-3

Thus, the polysubstituted 2-aza-2,4-cyclopentadienone **6** is much different in stability from parent **1**, yet the LUMO level of **6** is estimated to be considerably low (**1**: -1.323 eV, **6**: -1.206 eV by AM1 calculation). Therefore, **6** is anticipated to accept nucleophiles with ease; conveniently, ethoxy groups are feasible in some cases as a leaving group. The reactions with water and ethanol as seen above are informative. Likewise monoamines **11a-d** (1.5 equiv.) underwent smooth substitution with crude **6** to give amidines **13a-d** in 71-76% yields as a result of *exo*-elimination of ethanol from primary adducts **12a-d** (Scheme-4). The excess use (5 equiv.) of a reagent advanced the second substitution at 4-position for the case of **11d** to give 1:2 adduct **14d** (47%). This result suggests that heterocyclization is to occur with diamines through an intramolecular version. Typically, ethylenediamine **11e** was examined. However, the reaction of crude **6** with this binucleophile (1.5 equiv.) gave 1:2 adduct **15e** in 35% yield together with cyclized **18e** in 19% yield, although **18e** was obtainable in 45% yield by the excess use of **11e** (5 equiv.) to suppress the reaction of primary adduct **13e** with another **6**. Yet the same cyclization with excess1,3-propanediamine **11f** resulted in low yield of **18f** (12%) and a similar reaction with ethanolamine **11g** gave not **18g** but **13g** (81%) or **14g** (43% after prolonged time). Chemical behavior in these attempted cyclizations was intuitively unusual, since the second substitution seemed to differ only in an intramolecular process. However, it is essential not to overlook that even substituted 2-aza-2,4-cyclopentadienones preserve antiaromaticity. Equilibration in amidine tautomerism **13** $\rightleftarrows$ **16** is in effect disfavored; the aimed cyclization necessitates the form of **16** but it is anti-aromatic.[13] This forces the cyclization process more or less ineffective. For the problem encountered in this ring system, a reasonable way is to utilize another equilibrium **12** $\rightleftarrows$ **13**. This permits intramolecular substitution at 4-position prior to *exo*-elimination (*via* **17**), and thereby the cyclization is no longer interrupted. Actually, appropriate reaction conditions were realized by using ethanol as a solvent. Thus, the crude product **13f** once obtained with **11f** was heated in refluxing ethanol for 12 h to improve the yield of **18f** to 55% (based on **5**). For the isolated product **13g** from **11g**, the expected cyclization was performed with the aid of DBU in ethanol (reflux 7 h, 74% yield), but in vain in DMF (90 °C, 7 h); this difference rationalized the proposed cyclization mechanism. With these results in hand, binucleophilic anilines **11h-k** with NH_2, OH, SH, CH_2OH groups at o-position were subjected to the above established two-step conversion to give tricyclic azaheterocycles **18h-k** in 19-76% yields (based on **5**).[14]



a X = none, R = C_6H_4
b X = none, R = $C_6H_4CH_2$
c X = none, R = CH=CHCH_2
d X = none, R = $(CH_2)_3$
e X = NH, R = $(CH_2)_2$
f X = NH, R = $(CH_2)_3$
g X = O, R = $(CH_2)_2$
h X = NH,
i X = O,
j X = S,
k X = OCH_2,
R =

Scheme-4

In summary, ethyl squarate **3** was converted into 4-azidocyclobutenones **5** by BF_3-catalyzed azidation of its acetal **4** with $(CH_3)_3SiN_3$, and the 2-phenyl derivative **5a** was shown to undergo thermal ring expansion reaction possibly *via* a nitrene intermediate, giving maleimide after hydrolysis. Owing to resonance-stabilization, the phenyl-substituted **5a** was utilized for isolation of polysubstituted 2-aza-2,4-cyclopentadienone **6** and it was applied for further addition reactions. Among them, heterocyclization with binucleophilic reagents was effected by equilibrated conditions in ethanol (to avoid anti-aromatic nature of this ring system). These reactions constitute a new method for heterocycles synthesis based on squaric acid.

References and Notes

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8. General procedure for **5**: To a solution of **4** (0.61 mmol) and trimethylsilyl azide (142 mg, 1.23 mmol) in dry CH_2Cl_2 (2 mL), was added $BF_3 \cdot Et_2O$ (0.093 mL, 0.74mmol) dropwise with a syringe at 0 °C under a nitrogen atmosphere, and the solution was stirred for 1 h. After treating with 10% aq. $NaHCO_3$ for 10 min, the mixture was extracted with Et_2O (3 X 10 mL), washed with brine (10 mL), and dried (Na_2SO_4). Evaporation of the solvent left the residue, which was chromatographed on a silica gel column (hexane/AcOEt 15/1) to give **5** as oil.
9. NMR data of **5a** ($CDCl_3$): ^1H NMR δ 1.30 (3 H, t, J = 7.0 Hz), 1.55 (3 H, t, J = 7.0 Hz), 3.86 and 3.94 (each, 1 H, dq, J = 9.2, 7.0 Hz), 4.60 (2 H, q, J = 7.0 Hz), 7.28-7.81 (5 H, m); ^{13}C NMR δ 15.3, 15.5, 63.4, 70.6, 104.6, 127.7, 128.1, 129.0, 129.3, 129.8, 178.3, 185.5.
10. Patented compound, mp 127.5-129.5 °C (cf. Umio, S.; Kariyone, K.; Nishida, M. *Chem. Abstr.* **71**, 12859 (1969): observed mp 127.5-129.5 °C.
11. On the other hand, depending on the timing of nitrogen extrusion, it is not ruled out that a 1,2,3-triazepin-7-one ring might be formed advantageously by tandem electrocyclic ring-opening/ring-closure reactions,[4,5] and this intermediate could undergo ring contraction to **6** with loss of N_2.
12. NMR data of **6** ($CDCl_3$): ^1H NMR δ 1.33 (3 H, t, J = 7.0 Hz), 1.52 (3 H, t, J = 7.0 Hz), 4.23 (2 H, q, J = 7.0 Hz), 4.67 (2 H, q, J = 7.0 Hz), 7.31-7.62 (5 H, m); ^{13}C NMR δ 14.2, 15.3, 68.5, 69.4, 114.1, 128.50, 128.54, 129.4, 129.9, 155.7, 182.5, 183.3.
13. Heat of formation was compared for a case of R = Pr (**13d** and **16d**) by AM1 calculation; **13d** is slightly more stable (0.5 kcal/mol) in *syn*-form (as is depicted in Scheme 4) than in *anti*-form, and much more stable (8.5 kcal/mol) than antiaromatic form of **16d**. These results suggest that the *syn*-form is likely stereochemistry of **13**, and **16** is unlikely tautomer (if not so, the cyclization would have proceeded without difficulty).
14. All of the products (**7**, 8, **13**-**15**, **18**) derived from **6** gave satisfactory spectral data. A typical procedure and spectral data were as follows: A solution of **5a** (80 mg, 0.3 mmol) in dry *p*-xylene (5 mL) was refluxed for 30 min under a nitrogen atmosphere, and the product was cooled and treated directly with **11e** (0.1 mL, 1.5 mmol) at room temperature for 1 h. After evaporation of the solvent, the residue was chromatographed on a silica gel column (hexane/AcOEt 5/1) to give **18e** (30 mg, 45%); IR (KBr) 1685, 1625 cm^{-1}; ^1H NMR (DMSO-d_6)δ 3.19 (2 H, dt, J = 6.4, 2.0 Hz), 3.65 (2 H, t, J = 6.4 Hz), 7.15-7.78 (5 H, m), 7.78 (1 H, br s), 9.74 (1 H, br s); ^{13}C NMR (DMSO-d_6) δ 38.7, 45.5, 97.7, 125.6, 127.1, 128.3, 131.8, 138.3, 153.3, 172.2; MS (EI) *m/e* (rel. intensity) 213 (M^+, 100), 212 (49), 184 (11), 157 (10), 129 (10).

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