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Serendipitously Discovered Diazomethane-Mediated Novel Molecular Rearrangements of Norbornyl α-Ketohemiketals

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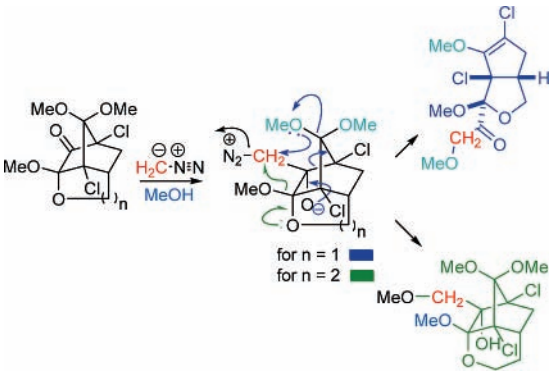
ABSTRACT



Unprecedented molecular rearrangements during diazomethane-mediated reaction of norbornyl α-ketohemiketals leading to novel molecular entities are presented. A dramatic change in the reaction outcome was noted for five- and six-membered α-ketohemiketals: the former predominantly furnished rearranged bicyclic products involving migration of the γ-alkoxy group, and the latter furnished the oxetane derivative as the major product. Interestingly, six-membered *O*-methyl-ketal yielded a product arising from the migration of the vicinal alkoxy group.

In its journey of more than 100 years, diazomethane has found a place as a versatile and indispensable one-carbon reagent in the arsenal available for methylation of functional groups possessing an acidic hydrogen such as the carboxylic group, phenols, enols, etc.[1] The reagent is particularly useful for advanced intermediates in a multistep sequence that possess groups which are sensitive to other methylating agents. It is also a convenient one-carbon reagent for chain homologation or ring expansion of carbonyl compounds.[2] In addition, diazomethane is routinely employed for preparing α-diazoketones and transition-metal-catalyzed cyclopropanation of alkenes.[3] The toxicity and explosive nature of diazomethane, a yellow gas at room temperature, were the principal deterrents for its industrial use for almost a century. However, recent technological advancements allow safe, large-scale commercial production and use of diazomethane in complex, multistep processes, particularly in the pharmaceutical industry.[4]

In this account, we wish to disclose serendipitously observed molecular rearrangements during the reaction of diazomethane with norbornyl α-ketohemiketals. In connection with our interest in tricyclic core skeleton **1** present in

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(2) (a) Krow, G. R. *Tetrahedron* **1987**, *43*, 3. (b) Black, T. H. *Aldrichimica Acta* **1983**, *16*, 3.

(3) (a) Kottwitz, J.; Vorbrüggen, H. *Synthesis* **1975**, 636. (b) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49.

(4) Proctor, L. D.; Warr, A. J. *Org. Process Res. Dev.* **2002**, *6*, 884.

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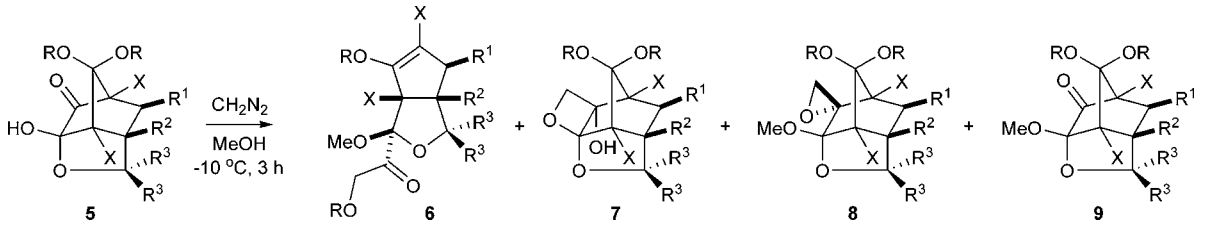
Table 1. Reaction of **5** with Diazomethane

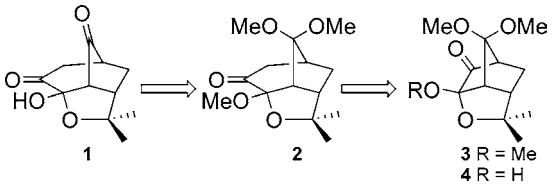


entry	substrate	R	X	R^1–R^3	product, isolated yield (%)			
1	**5a**	Me	Cl	R^1–R^3 = H	**6a**, 44	**7a**, 26	**8a**, 19	**9a**, --
2[a]	**5a**	Me	Cl	R^1–R^3 = H	**6a**, 42	**7a**, 26	**8a**, 23	**9a**, --
3[b]	**5a**	Me	Cl	R^1–R^3 = H	**6a**, 38	**7a**, 30	**8a**, --	**9a**, 23
4	**9a**	Me	Cl	R^1–R^3 = H	**6a**, 57	**7a**, --	**8a**, 28	
5	**5b**	Me	Br	R^1–R^3 = H	**6b**, 40	**7b**, 12	**8b**, --	**9b**, 22
6[a]	**5b**	Me	Br	R^1–R^3 = H	**6b**, 43	**7b**, 19	**8b**, --	**9b**, 36
7[b]	**5b**	Me	Br	R^1–R^3 = H	**6b**, 41	**7b**, 12	**8b**, --	**9b**, 44
8	**5c**	Me	Cl	R^1–R^2 = H; R^3 = Me	**6c**, 39	**7c**, 29	**8c**, 6	**9c**, 14
9	**5d**	Me	Br	R^1–R^2 = H; R^3 = Me	**6d**, 40	**7d**, 29	**8d**, 2[c]	**9d**, 15[c]
10	**5e**	Me	Cl	R^1 = H; R^2–R^3 = Me	**6e**, 43	**7e**, 14	**8e**, --	**9e**, 20
11	**5f**	Me	Cl	R^2 = H; R^1 = R^3 = Me	**6f**, 52	**7f**, 12	**8f**, 2[c]	**9f**, 18[c]
12	**5g**	Et	Cl	R^1–R^3 = H	**6g**, 26	**7g**, 25	**8g**, 8[c]	**9g**, 18[c]

[a] Reaction temperature: rt. [b] Reaction temperature: −78 °C. [c] Calculated from ^{1}H NMR (400 MHz) integration of the inseparable mixture of **8** and **9**.

elisapterosin A, a terpenoid isolated from *Pseudopterogorgia elisabethae*,[5] we sought ring expansion of α-ketoketal **3** as depicted in retrosynthetic Scheme 1. We have recently

Scheme 1. Retrosynthetic Analysis



reported a novel reaction of diazomethane with norbornyl α-diketones in MeOH as solvent leading regioselectively to α-ketoketals.[6] On the basis of this result, we surmised that α-ketohemiketal **4** would first form the α-ketoketal **3** followed by its ring expansion to **2**. Acid-catalyzed hydrolysis of **2** under mild conditions would eventually furnish **1** (Scheme 1). With this plan in mind, we first selected simple hemiketals **5a**,**b** as the model substrates to evaluate the feasibility of diazomethane-mediated one-carbon ring expansion.

The substrate **5a**,[7] dissolved in methanol, was treated with an ethereal solution of diazomethane at −10 °C and allowed to stand for 3 h. The results are summarized in Table 1. To our surprise, a novel, unexpected bicyclic derivative **6a** was formed via a hitherto unprecedented molecular rearrangement as one of the components. The absence of one of the halogen-substituted bridgehead resonances and the appearance of a pair of olefinic carbons at 147.3 and 111.3 ppm in the ^{13}C NMR spectrum strongly pointed toward a major skeletal change and were fitting with the assigned structure. Unequivocal proof for the structural assignment was established through single-crystal X-ray analysis of a related compound at a later stage.[8] The second component **7a** also turned out be an interesting oxetane derivative and showed a diagnostic pair of signals at 5.12 and 4.43 ppm in the ^{1}H NMR spectrum for the methylene group in the oxetane ring. We could not trace any literature precedent where preparatively useful amounts of this type of product in a diazomethane-mediated reaction have been isolated. However, in a spectacular and meticulously carried out work, Baumann and co-workers first observed the formation of such an unusual oxetane derivative as one of the 11 byproducts in 0.3% yield (92 mg from 30 g!) in the reaction of 23-membered ascomycin with diazomethane.[9] The formation of **8a** was not surprising, and the assignment was based on the recognition of the characteristic epoxy-methylene proton resonances and a comparison with related well-characterized epoxy ketones formed from the corresponding α-diketones.[6] The outcome of the reaction did

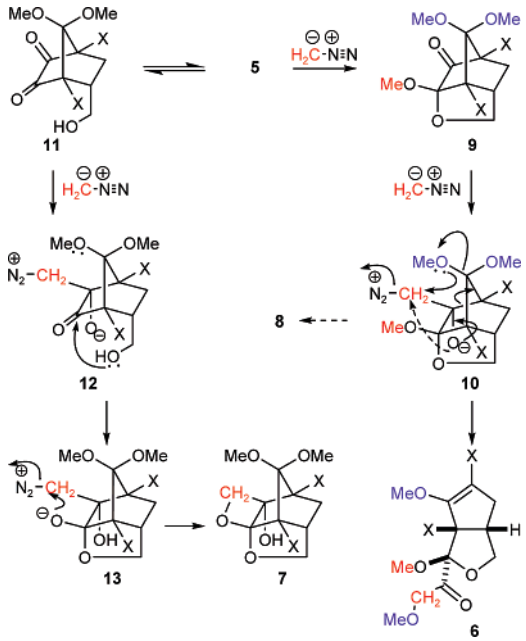
(5) Rodríguez, A. D.; Ramírez, C.; Rodríguez, I. I.; Barnes, C. L. *J. Org. Chem.* **2000**, *65*, 1390.
(6) Khan, F. A.; Satapathy, R.; Sudheer, Ch.; Rao, Ch. N. *Tetrahedron Lett.* **2005**, *46*, 7193.
(7) Khan, F. A.; Dash, J.; Sahu, N.; Sudheer, Ch. *J. Org. Chem.* **2002**, *67*, 3783.
(8) The data were collected on a Bruker SMART APEX diffractometer. The structure was solved using SIR-92 and refined using SHELXL-97. CCDC 624833 (**7d**) and CCDC 624832 (**6f**).
(9) Baumann, K.; Hoegenauer, K.; Knapp, H.; Bacher, M.; Steck, A.; Wagner, T. *Tetrahedron* **2005**, *61*, 4819.

not alter noticeably when it was carried out at room temperature (Table 1, entry 2).

The reaction of **5a** was then carried out at −78 °C to intercept any intermediate en route to observed products. The α-ketoketal **9a** which is the actual precursor for **6a** and **8a** was isolated in 23% yield along with 38% of **6a** and 30% of oxetane derivative **7a** when the reaction was allowed to stand at −78 °C for 3 h (entry 3). The intermediacy of **9a** was further confirmed by separately treating it with diazomethane at −10 °C for 3 h to obtain **6a** and **8a** in 57 and 28% yield, respectively (entry 4). The substrate **5b** showed similar results except that the epoxide derivative **8b** was not detected at −10 °C nor at room temperature. When substrates **5c**,**d**[7] with dimethyl substituents in the tetrahydrofuran moiety were treated with diazomethane at −10 °C for 3 h, the rearranged products **6c**,**d** were obtained in 39−40% yield and the yield of oxetane derivatives **7c**,**d**[8] was enhanced to 29%. The yield of minor products **8** and **9** is shown in Table 1 (entries 8 and 9).

A plausible mechanism for the formation of **6**−**9** is depicted in Scheme 2. We believe that the presence of an

Scheme 2. Proposed Mechanism for the Formation of **6**−**9**



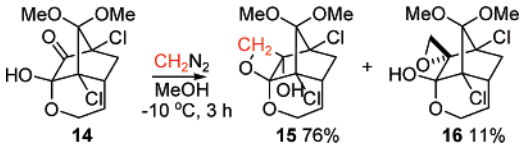
α-carbonyl moiety renders hemiketal **5** acidic enough to be methylated directly by diazomethane, leading to **9**. The addition of a second molecule of diazomethane to **9** occurs from the *exo*-face to furnish the intermediate **10**. The tetrahedral betaine intermediate **10** is responsible for the unusual molecular rearrangement, leading to **6**. Collapse of this type of intermediate usually results in ring expansion via concomitant migration of either of the two σ bonds attached to the tetrahedral carbon to give two regioisomeric products or gives epoxide **8** (dotted arrow, Scheme 2). However, the presence of a methoxy group in close proximity triggers the cascade of events, shown with solid arrows, leading to unprecedented product **6**. On the other hand, formation of oxetane derivative **7** may be rationalized by the regio- and stereoselective addition of diazomethane to the keto form **11** of hemiketal **5** from the *exo*-face to give intermediate **12**. This intermediate is susceptible to form hemiketal and after the proton shift gives **13**. The proximity of nucleophilic oxygen in this rigid system culminates in ring closure to give oxetane **7**.

It is interesting to note that a vicinal methoxy group is present in **10** at a matching distance for migration, as evident from pathway **13** to **7**, but the nonavailability of a subsequent fragmentation pathway prevents its relocation. We, therefore, anticipated that the formation of products **6** and **7** would be sensitive to subtle changes in the molecular geometry. We considered **5e**[10] and **5f**[7] as suitable substrates possessing innocuous substituents remote from the reaction site to evaluate this aspect. The results, summarized in Table 1 (entries 10 and 11), indicate that the remote substituents have little influence on the reaction outcome. The bicyclic rearranged products **6e**,**f**[8] were formed in 43 and 52% yield, respectively, whereas the yield of oxetane derivatives **7e**,**f** was decreased to 12−14%. The other products, **8f** and **9e**,**f**, were formed as shown in Table 1.

To prove that it is indeed one of the methoxy groups of the dimethyl ketal moiety in **10** that is migrating, an interesting experiment was set up. Substrate **5g**[10] with the diethyl ketal moiety was treated with diazomethane under usual conditions to obtain the corresponding products **6g** (with OEt attached to methylene) and **7g** in 26 and 25% yield, respectively, along with minor epoxide **8g** as well as **9g** (Table 1, entry 12).

Another variant to probe the influence of molecular geometry is to change the ring size of the hemiketal unit. Accordingly, hemiketal **14** with six rings was prepared[10] and subjected to diazomethane. To our astonishment, oxetane product **15** was formed in 76% yield (Scheme 3). The

Scheme 3. Reaction of **14** with Diazomethane



bicyclic rearranged product was not detected, whereas, unlike earlier cases, epoxide product **16** without methylation of hemiketal hydroxyl was formed in 11% yield.

The influence of the hemiketal ring size is rather dramatic: the five-membered hemiketal in **5** predominantly gave bicyclic rearranged products **6**, and the six-membered hemiketal in **14** furnished mainly oxetane derivative **15**. As depicted in Scheme 2, the former products are derived from the hemiketal form through intermediate **10** and the latter products originate via the keto form of the type **11**. That

(10) For the preparation of **5e**, **5g**, **14**, and **17**, see Supporting Information.

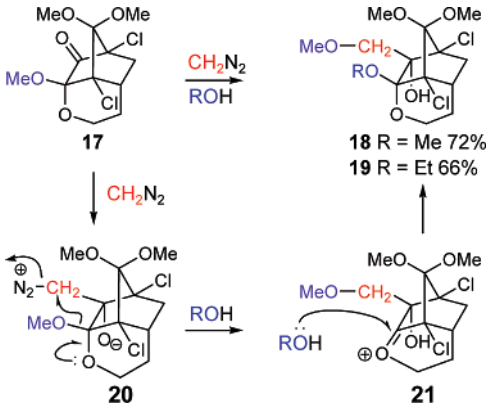
means the six-membered hemiketal in **14** is relatively more susceptible to exist in the keto form compared to the five-membered hemiketal in **5**. We looked at the B3LYP/6-31G(d) optimized geometries of **5a** and **14** to gain further insight.[11] The results indicate that hemiketal forms are more stable compared to keto forms in both the cases. However, intramolecular hydrogen bonding which provides additional incentive for the existence of hemiketal forms is relatively weaker for **14** and is probably one of the most likely factors for the formation of products derived solely through the keto form similar to **11**.

To further unravel the intriguing reactivity difference of the hemiketals with ring size, we decided to prepare and study the reaction outcome for the *O*-methyl-ketal **17** of six-membered hemiketal **14**.[10] Unlike in five-membered hemiketal **5**, *O*-methyl-ketal **17** is not formed during diazomethane reaction of **14**. Interestingly, **17** on treatment with diazomethane furnished **18** resulting from the migration of the methoxy group from the vicinal position in intermediate **20**. The stabilized oxocarbenium ion **21** thus formed is then quenched by the solvent MeOH leading to **18**, as shown in Scheme 4. The best chemical proof for the mechanism illustrated in Scheme 4 was established when the *O*-ethyl-ketal **19** was obtained in 66% yield upon changing the solvent to EtOH. Because the formation of an oxocarbenium ion similar to **21** is not possible in the case of five-membered hemiketals **5** due to high strain, an alternative pathway as depicted in Scheme 2 is operative.

In conclusion, serendipitously discovered diazomethane-mediated novel rearrangements of α-ketohemiketals leading to rearranged bicyclic products and unusual oxetane derivatives are described. The influence of molecular geometry on the course of the reaction outcome was probed by placing innocuous remote substituents and by altering the ring size of the hemiketal. The five-membered hemiketals **5** predominantly gave bicyclic rearranged products **6** involving migration of the γ-alkoxy group, whereas six-membered hemiketal **14** furnished mainly the oxetane derivative. Interestingly, *O*-methyl-ketal **17** furnished a novel product **18** resulting from migration of the α-methoxy group.

(11) For details of theoretical calculations, see Supporting Information.

Scheme 4. Reaction of Ketal **17** with Diazomethane



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Supporting Information Available: Experimental procedures, spectroscopic data, copies of ^{1}H and ^{13}C spectra, details on the X-ray structures (**6f** and **7d**), and computational methodology. This material is available free of charge via the Internet at http://pubs.acs.org.

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