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Tetrahedron Letters 46 (2005) 7193–7196

Tetrahedron Letters

A new reaction of diazomethane with norbornyl α-diketones

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Received 29 June 2005; revised 8 August 2005; accepted 17 August 2005
Available online 6 September 2005

Abstract—A new reaction of diazomethane with norbornyl α-diketones in MeOH as solvent leading regioselectively to ketals is described. The mechanistic details of this intriguing reaction were investigated employing d_4-MeOH, EtOH and d_6-EtOH. The surprising observation of complete deuterium incorporation in the diazomethane-derived methoxy group was accounted for by sequential deuterium exchange between the initially formed hemiketal d_4-**18** and diazomethane in the presence of d_4-MeOH as solvent.

Over the last century, diazomethane has emerged as one of the most versatile and indispensable one-carbon reagents in organic synthesis.[1] The commercial availability of stable solid precursors and apparatus to generate diazomethane safely, a yellow gas at room temperature, is perhaps an indicator of its widespread use.[2] It is routinely used for methylation and is a convenient reagent for one-carbon chain elongation/ring expansion.[3]

Although a large number of examples of diazomethane reactions with ketones are documented in the literature, its reactions with α-diketones are limited. The reaction of camphorquinone is known to give a mixture of β-methoxyketones resulting from ring expansion followed by methylation of the two possible enols.[3,4] A literature search revealed that for ketones with electron withdrawing substituents, which possess a tendency to form stable hydrates or hemiketals in the presence of moisture or alcohol (e.g., methanol), exclusive formation of epoxide products was reported. Eistert's pioneering work on reactions of diazomethane demonstrated that chloroquinone gave the corresponding epoxide.[5] Lemal et al. have reported an interesting example where treatment of tetrafluorocyclopentadiene with diazomethane in methanol as solvent gave exclusively a spiro-epoxide.[6] The formation of the corresponding dimethyl ketal was clearly ruled out. In a very recent article, Haufe and co-workers reported the formation of spiro-epoxides from polyfluorinated cyclohexa-2,5-dienones.[7] In a study of solvent effects on the reactivity of 1,10-phenanthroline-5,6-dione towards diazomethane, Antkowiak and Sobczak reported the formation of 5,6-methylenedioxy-1,10-phenanthroline as the only product when an aprotic medium such as THF, ether or CH_2Cl_2 was used while protic solvents such as 2-propanol or ethanol resulted in the formation of the corresponding dispiro-epoxide as the main product. Surprisingly, MeOH as solvent furnished dimethyl 2,2′-bipyridine-3,3′-dicarboxylate resulting from cleavage of the C_5–C_6 bond as the only product, although in a very low (10%) yield.[8]

We have recently reported, a ruthenium catalyzed novel and efficient conversion of the dihaloalkene moiety in tetrahalonorbornyl derivatives to the corresponding α-diketones.[9] In connection with our interest to elaborate norbornyl α-diketones to ring enlarged bicyclic systems, we became interested in studying the reaction of diazomethane with these compounds. We herein report, the observation of a new reaction of norbornyl α-diketones with diazomethane which furnished, in the majority of cases, predominantly ketals when the reaction was carried out by adding ethereal solution of diazomethane to the substrate dissolved in methanol. On the other hand, when ether was used as the solvent, stereo- and regio-selective formation of spiro-epoxides was observed (Scheme 1).

Since a small amount of methanol as co-solvent is known to suppress the formation of spiro-epoxide side-products,[1] we initially carried out the reaction by

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Keywords: Diazomethane; α-Diketones; Ketal; Regioselectivity; Oxiranes.

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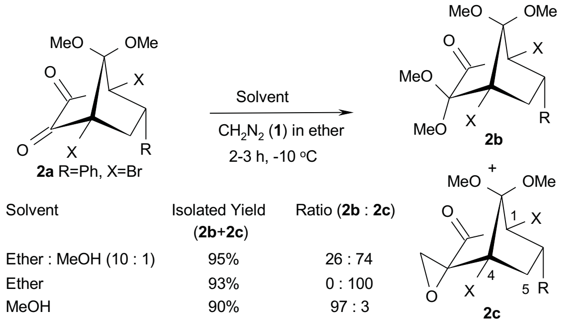
0040-4039/$ - see front matter © 2005 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2005.08.087



Solvent	Isolated Yield (2b+2c)	Ratio (2b : 2c)
Ether : MeOH (10 : 1)	95%	26 : 74
Ether	93%	0 : 100
MeOH	90%	97 : 3

Scheme 1. Preferential formation of ketal **2b** or epoxide **2c** depending on the solvent used.

adding a freshly distilled ethereal solution of diazomethane **1** to α-diketone **2a** in ether–methanol (10:1) at −10 °C. We were astonished to observe the formation of an unexpected product in 21% isolated yield which was characterized as ketal **2b**. However, the major product isolated in 74% yield from this reaction turned out to be the spiro-epoxide **2c**. In the subsequent run, when the solvent for **2a** was changed to ether, epoxide **2c** was formed as the sole product. Surprisingly, when methanol was used as the solvent, ketal **2b** was formed as the principal product with only traces of **2c**. This, to our knowledge, is the first example where selective ketal formation under diazomethane reaction conditions has been observed.

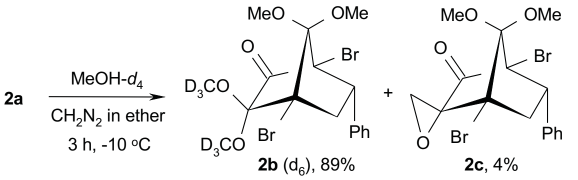
Intrigued by the observation of the formation of ketals, we extended our study to a variety of monosubstituted norbornyl α-diketones to probe the mechanistic details of this new reaction. Our results are summarized in Table 1. The ketal is the major product in all cases except for the bromoethyl and trimethylsilyl substituted derivatives **9a** and **11a** (entries 7 and 9) when the reactions were carried out by dissolving the substrates in MeOH followed by the addition of an excess of an ethereal solution of diazomethane at −10 °C. The reactions were highly regioselective and gave a single regioisomer with ketalization occurring at the carbonyl carbon diagonally opposite to the substituent R. This unambiguous structural assignment is based on a single crystal X-ray analysis of **2b** and internal consistency in the ^{1}H as well as the ^{13}C spectra across the entire series.[10] On the other hand, when ether was used as the solvent in place of MeOH, spiro-epoxides **3**–**14c** were formed in high yield (86–99%) as the sole products in all cases. Once again, a single regioisomer resulting from attack of the reagent on the carbonyl carbon diagonally opposite to the substituent R was formed. Furthermore, the attack of diazomethane took place stereoselectively from the *exo*-face. The remarkable deshielding effect of the *endo*-oxygen of the epoxide moiety on the *endo*-proton of the methylene group (C-5) in the ^{1}H NMR (400 MHz) of **2**–**14c** provided structural proof which was further confirmed by NOESY and HMBC experiments (500 MHz) on **3c**.

Table 1. Reaction of diazomethane with monosubstituted norbornyl α-diketones in MeOH as solvent

Entry	Substrate	X	R	Product	Yield[a] (%)	Ratio (**b**:**c**)[b]
1	**3a**	Cl	Ph	**3b**,**c**	91	67:33
2	**4a**	Cl	OAc	**4b**,**c**	89	63:37
3	**5a**	Cl	CO$_2$Me	**5b**,**c**	83	68:32
4	**6a**	Cl	OEt	**6b**,**c**	94	66:34
5	**7a**	Cl	CH$_2$Cl	**7b**,**c**	89	74:26
6	**8a**	Cl	CH$_2$Br	**8b**,**c**	88	80:20
7	**9a**	Cl	CH$_2$CH$_2$Br	**9b**,**c**	90	45:55
8	**10a**	Cl	CH$_2$OAc	**10b**,**c**	82	70:30
9	**11a**	Cl	SiMe$_3$	**11b**,**c**	88	23:77
10	**12a**	Br	OAc	**12b**,**c**	90	66:34
11	**13a**	Br	CO$_2$Me	**13b**,**c**	92	74:26
12	**14a**	Br	OEt	**14b**,**c**	90	68:32

[a] Isolated yield of analytically pure samples.

[b] Determined from ^{1}H NMR integration of reaction mixtures.

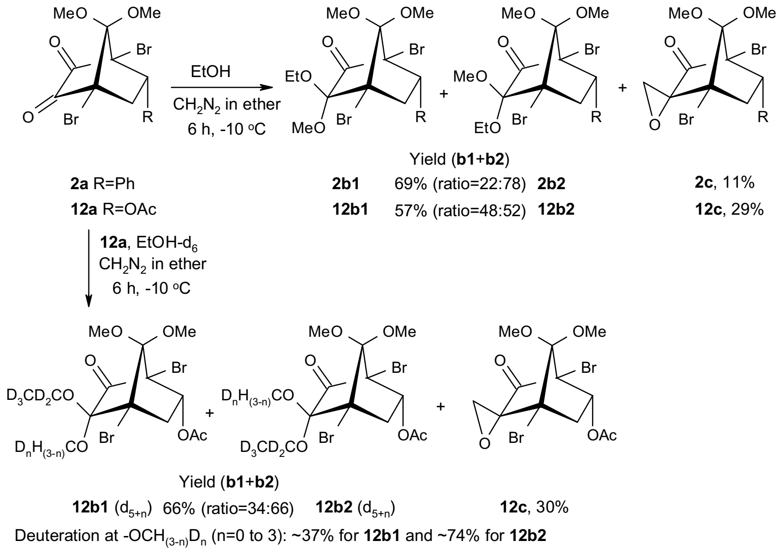


(1)

In order to gain mechanistic insight, the reaction of **2a** was carried out using deuterated methanol as the solvent. Surprisingly, both the OMe groups of the newly formed ketal moiety in **2b** were completely deuterated as evidenced from the complete disappearance of the corresponding diagnostic singlets from the ^{1}H NMR spectrum (400 MHz). Spiro-epoxide **2c**, isolated in 4% yield, showed little incorporation of deuterium as indicated by the almost unaltered integral of the oxirane methylene protons in the ^{1}H NMR spectrum (Eq. 1). It appeared, at this stage, as though both the OCD$_3$ groups of the newly formed ketal were derived from the solvent (d_4-MeOH) unless there existed an efficient mechanism for deuterium exchange such that the diazomethane completely exchanged deuterium before methylating the intermediate leading to d_6-**2b**.

To settle the issue, absolute ethanol was used as the solvent in place of MeOH and the results obtained with **2a** under these conditions are shown in Scheme 2. Interestingly mixed ketals **2b1**,**b2** were formed but could not be separated for unambiguous characterization. Therefore **12a** was used for the same transformation which gave the mixed ketals **12b1**,**b2** along with 29% of spiro-epoxide **12c**. Fortunately, the mixed ketals derived from **12a** were resolvable on preparative HPLC to afford pure **12b1**,**b2** which were characterized thoroughly. A single crystal X-ray analysis of **12b2** established the structure unequivocally.[10] This experiment clearly demonstrated that one of the alkoxy moieties in the newly formed ketal was derived from the solvent alcohol while the other originated from diazomethane. Furthermore, unlike d_4-MeOH, a varying amount of deuteration of the diazomethane-derived OMe group was observed when d_6-EtOH was used as the solvent (Scheme 2) clearly indicating that the efficiency of the exchange mechanism was different in the two cases.

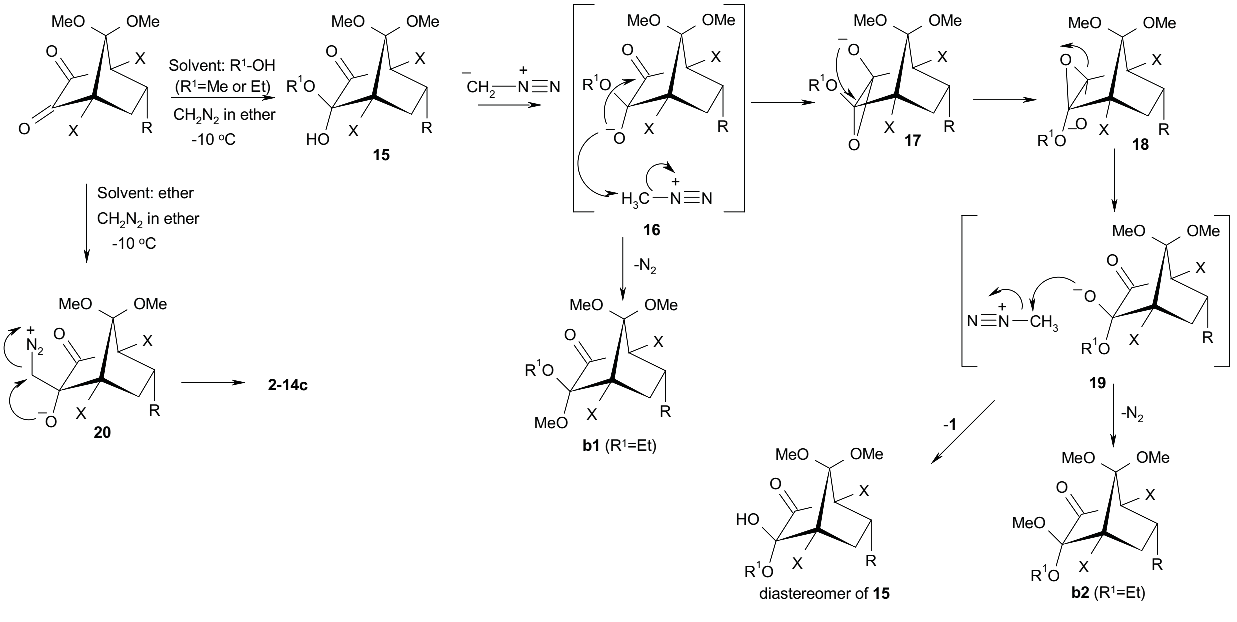
Formation of diastereomer **b2** was quite surprising because initial nucleophilic attack of a reagent is preferred



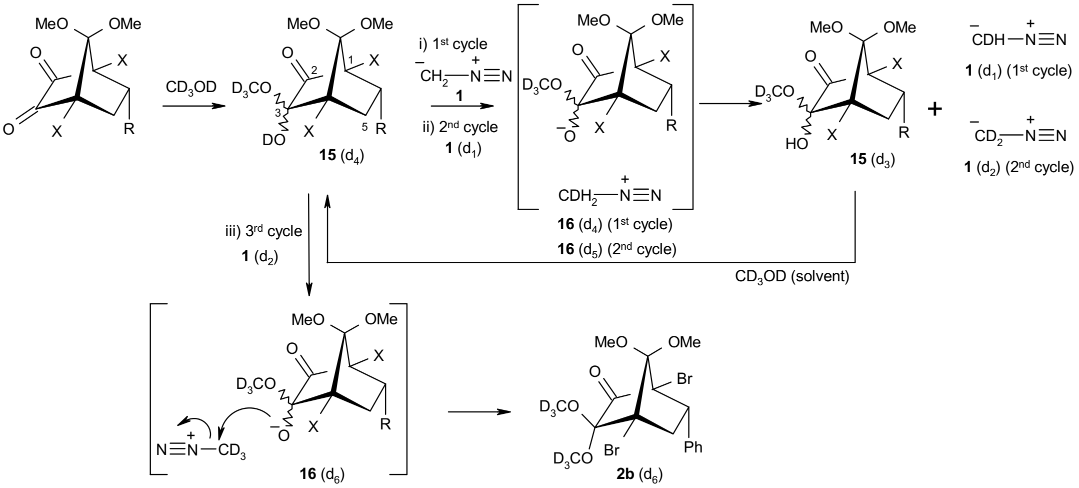
Scheme 2. Reactions of **2a** and **12a** in EtOH as solvent.

from the *exo*-face, as evident from the exclusive formation of epoxides **2**–**14c**. Our earlier observations on allylindium addition to monosubstituted norbornyl α-diketones also substantiated this fact.[11] Hence, initial attack of EtOH from the *endo*-face leading eventually to **b2** is surely ruled out. A plausible mechanism is depicted in Scheme 3. While both diazomethane **1** and alcohol R^1OH compete as nucleophiles for the addition at the electrophilic carbonyl carbon, the latter predominates when pre-dissolved in alcohol R^1OH ($R^1 = Me$ or Et) leading to the intermediate hemiketal **15**. Abstraction of an acidic proton by **1** would lead to the ion pair **16** which upon nucleophilic displacement by alkoxide furnished the diastereomer **b1**. On the other hand, the negative charge on the alkoxide oxygen may be delocalized onto the carbonyl oxygen via *endo*-oxirane intermediate **17**. The *endo*-oxirane **17** is capable of reorganizing itself to the *exo*-oxirane **18** by an intramolecular nucleophilic attack on the adjacent carbon, thereby inverting the OR^1 group to the *endo*-position leading to ion pair **19** and finally to diastereomer **b2** (the cationic part for ion pairs **17** and **18** is not shown for clarity). The regio- and stereo-selective formation of spiro-epoxides **2**–**14c**, in the absence of the alcohol R^1OH, proceeds via the tetrahedral betaine intermediate **20**.

As far as deuteration of the diazomethane-derived OMe group of the newly formed ketal in **2b** and **12b** is concerned, we believe that sequential deuterium exchange from the initially formed d_4-**15** gives rise to d_3-**15** and



Scheme 3. A plausible mechanism for the formation of diastereomeric **b1** and **b2**.



Scheme 4. A plausible mechanism for the deuterium exchange.

d_1-**1** via d_4-**16** in the first cycle. Similarly, d_3-**15** and d_2-**1** are formed from d_4-**15** and d_1-**1** via d_5-**16** in the second cycle (Scheme 4). Finally, the ion pair d_6-**16**, formed in the third cycle leads to **2b** (or **12b**). The unambiguous evidence for the formation of diastereomers of d_4-**15** came from ^{1}H and ^{13}C NMR spectra of diketone **2a** in d_4-MeOH. A pair of singlets for the OMe groups of each diastereomer of d_4-**15** and a diagnostic influence of the *endo*-oxygen substituent on the C-5 methylene protons which now appear in the 2.83–2.72 ppm range,[12] closely matching ketal **2b**, were observed in ^{1}H NMR.[13] In ^{13}C NMR, the two carbonyl signals at 188.3 and 187.1 ppm observed in CDCl$_3$ for the diketone moiety in **2a** completely vanished in d_4-MeOH to give two close pairs at 198.9, 198.5 and 97.5, 97.1 for the C-2 carbonyl and C-3 hemiketal carbons for each diastereomer of d_4-**15**, respectively.[13]

In conclusion, we have observed a novel reaction of diazomethane with norbornyl α-diketones which gave ketals regioselectively as the major products when methanol was used as the solvent. Changing the solvent to ether provided a regio- and stereo-selective entry to spiro-epoxides. A mechanism is proposed to account for the formation of the unusual diastereomer as well as deuterium exchange in the diazomethane-derived OMe group of the newly formed ketal. The finding that diazomethane can be used to prepare ketals under neutral conditions adds yet another, hitherto unknown, dimension to the versatility of this century old one-carbon reagent and may be used in sophisticated applications.

Acknowledgements

This work was supported by the Department of Science and Technology (DST), New Delhi. F.A.K. acknowledges the DST for a Swarnajayanti Fellowship. R.S., C.S. and C.N.R. thank CSIR/UGC for fellowships.

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