A SOLVENT EFFECT IN THE REACTION OF DIAZOMETHANE WITH NORBORNANE-2,3-DIONE 3-HEMIKETALS

G. Hari Mangeswara Rao¹ and Faiz Ahmed Khan²
¹Department of Chemistry, RGU IIIT Nuzvid, Nuzvid, India
²Department of Chemistry, Indian Institute of Technology Hyderabad, Hyderabad, India

GRAPHICAL ABSTRACT

Abstract A solvent effect in the reaction of diazomethane with norbornane-2,3-dione 3-hemiketal in various aprotic solvents such as ether, dichloromethane, tetrahydrofuran (THF), dioxane, and chloroform is reported. Unlike in methanol, preparatively useful quantities of oxetane derivatives were obtained along with a novel hexahydro-1H-cyclopenta[c]furan-1-one in these aprotic solvents. Dichloromethane and THF gave optimal yields of the two products. In some cases, α-ketoketals were formed as minor products along with the aforementioned products. Interestingly, TMSCHN₂ furnished hexahydro-1H-cyclopenta[c]furan-1-one as the predominant product.

Keywords Diazomethane; hexahydro-1H-cyclopenta[c]furan-1-one; norbornane-2,3-dione 3-hemiketal; oxetane derivative; rearranged bicyclic product

INTRODUCTION

Diazomethane is a versatile one-carbon reagent for homologation or ring expansion of carbonyl compounds¹ and for methylation of functional groups possessing an acidic hydrogen such as the carboxylic group, phenols, enols, etc.² Diazomethane is commonly used in 1,3-dipolar cycloaddition reactions, in the preparation of α-diazoketones, and in transition-metal-catalyzed cyclopropanation of alkenes.³

Received March 7, 2014.
Address correspondence to G. Hari Mangeswara Rao, Department of Chemistry, RGU IIIT Nuzvid, Nuzvid 521201, India. E-mail: gmangeshiiit@rgukt.in

Color versions of one or more of the figures in the article can be found online at www.tandfonline.com/lsyc.
In 2001, Antkowiak and Sobczak reported a study of solvent effects on the reactivity of 1,10-phenanthroline-5,6-dione toward diazomethane. It was observed that 5,6-methylenedioxy-1,10-phenanthroline was formed as the sole product when aprotic solvents such as tetrahydrofuran (THF) or diethyl ether were used. On the other hand, protic solvents such as 2-propanol or ethanol resulted in the formation of the corresponding dispiro-epoxide as the main product. Surprisingly, when MeOH was used as a solvent, dimethyl 2,2-bipyridine-3,3'-dicarboxylate was obtained resulting from the cleavage of the C₅-C₆ bond as the only observable product, although in a very poor (10%) yield. In contrast to this, Klein reported a solvent effect on the reactivity of aromatic homocyclic analog of phenanthrenequinone, which gave an oxirane in dioxane solution of diazomethane. When the solvent was changed to MeOH, unlike the previous case, it was transformed to an epoxide with the central ring enlarged to a seven-membered one. Further, when the reaction of diazomethane was carried out in THF in the presence of LiCl, a bisoxirane was observed as the sole product.

We have reported earlier that the reaction of diazomethane with norbornane-2,3-diones 1 in protic solvent (MeOH) leads regioselectively to 3,3-dimethoxy-norbornan-2-ones 2. Interestingly, when internal hemiketals 3 derived from α-diketone 1 (when R=CH₂OH) were treated with diazomethane under similar conditions, a totally unexpected result was obtained as depicted in Scheme 1. The major product, an unexpected bicyclic derivative 4, was formed via an interesting molecular rearrangement involving a series of events including migration of one of the γ-methoxy groups. Another novel unanticipated product that was formed was identified as the oxetane derivative 5. The α-ketoketal 6, which was actually the expected product in this reaction, and the corresponding epoxyketone 7 were also formed depending upon the reaction conditions. It was demonstrated that 4 and 7 were formed via the intermediacy of the α-ketoketal 6. We thought of probing whether solvents play a role and alter the outcome of this interesting reaction.

Scheme 1. Reaction of α-diketones 1 and α-keto-hemiketals 3 with diazomethane.
RESULTS AND DISCUSSION

In this article, we have presented our results on the reactivity of diazomethane towards norbornane-2,3-dione 3-hemiketal 3 in aprotic solvents such as ether, dichloromethane, THF, dioxane, and chloroform. The results indeed demonstrate that the solvents play a significant role in this transformation by influencing the balance among various products formed and also furnish yet another new compound through a less common pathway.

When the dichloro compound 3a was dissolved in ether and treated with diazomethane at \(-10^\circ C\) for 3 h, the outcome of the reaction was different compared to the reaction performed in MeOH as solvent. The oxetane derivative 5a was formed as the major product in 54\% yield along with a novel product, hexahydro-1H-cyclopenta[c]furan-1-one 8a in 21\% yield (entry 1, Table 1). In \(^1\)H NMR spectrum, 8a showed a peak at 2.55 ppm for a methyl group attached to a keto group (\(\text{H}_2\text{C} = \text{C} = \text{O}\)). In \(^{13}\)C NMR spectrum appearance of a peak at 171.2 ppm for a \(\gamma\)-lactone carbonyl further supported the structural assignment of 8a. Surprisingly, the bicyclic derivative 4, which was the major product of reaction in solvent MeOH, epoxy ketal 7, and \(\alpha\)-ketoketal 6, were not detected. The oxetane derivatives 5 are important synthetic intermediates for the preparation of cyclobutane derivatives via base-induced ring-opening reactions. Similarly, bromo \(\alpha\)-ketohemiketal 3b in ether upon treatment with diazomethane under similar conditions produced oxetane derivative 5b and hexahydro-1H-cyclopenta[c]furan-1-one 8b in 46 and 24\% yields, respectively. In this case, \(\alpha\)-ketoketal 6b was obtained in 9\% yield as depicted in

| Entry | Solvent          | Substrate | Isolated yield(%) |
|-------|------------------|-----------|-------------------|
|       |                  | 5         | 8                 | 6     |
| 1     | Ether            | 3a        | 5a, 54            | 8a, 21| 6a, – |
| 2     | 3b               | 3a        | 5a, 63            | 8a, 26| 6a, – |
| 3     | 3b               | 3a        | 5a, 63            | 8a, 26| 6a, – |
| 4     | 3b               | 3a        | 5a, 63            | 8a, 26| 6a, – |
| 5     | 3b               | 3a        | 5a, 63            | 8a, 26| 6a, – |
| 6     | 3b               | 3a        | 5a, 63            | 8a, 26| 6a, – |
| 7     | 3b               | 3a        | 5a, 63            | 8a, 26| 6a, – |
| 8     | 3b               | 3a        | 5a, 63            | 8a, 26| 6a, – |
| 9     | 3b               | 3a        | 5a, 63            | 8a, 26| 6a, – |
| 10    | 3b               | 3a        | 5a, 63            | 8a, 26| 6a, – |
| 11    | Ether : MeOH (9:1)| 3a       | 5a, 54            | 8a, 21| 6a, 12|
| 12    | 3b               | 3a        | 5a, 54            | 8a, 21| 6a, 15|
When the solvent was changed to dichloromethane, the yields of oxetane derivatives (5a, 5b) were enhanced to 63 and 55%, whereas hexahydro-1H-cyclopenta[c]furan-1-ones (8a, 8b) were formed in 26 and 34% yields, respectively (entries 3 and 4, Table 1). The hemiketals 3a and 3b gave similar results with diazomethane in THF, dioxane, and chloroform (entries 5–10, Table 1), except that α-ketoketals 6 were observed in case of dioxane (entries 7 and 8) in 9% and 7% yields, respectively. Finally, we thought of probing the reaction of the substrates 3a and 3b in the commonly used mixed solvent system, ether/MeOH (9:1). The oxetane derivatives (5a and 5b) and hexahydro-1H-cyclopenta[c]furan-1-ones (8a and 8b) were formed in good yields along with the α-ketoketals (6a and 6b) in this case as depicted in Table 1 (entries 11 and 12).

A plausible mechanism for the formation of hexahydro-1H-cyclopenta[c]furan-1-one 8 is depicted in Scheme 2. A regio- and stereoselective addition of diazomethane to the keto form 9 of hemiketal 3 from the exo-face would give intermediate 10. This intermediate is well poised to form the hemiketal and upon proton shift gives 11. The tetraheiral intermediate 11 collapses with the breaking of the original C2-C3 σ bond and concomitant extrusion of nitrogen to give enol 12, which tautomerises to lactone 8.

We had described a plausible mechanism for the formation of products 4–7 in our previous publication.[7]

(Trimethylsilyl)diazomethane is a convenient, commercially available equivalent of diazomethane. We were curious to examine the reactivity of this reagent toward norbornane-2,3-dione 3-hemiketal 3a. Accordingly, a solution of 3a in dichloromethane was treated with (trimethylsilyl)diazomethane in the presence of

Scheme 3. Reaction of 3a with TMSCHN₂.
BF$_3$·OEt$_2$. The outcome of this reaction is depicted in Scheme 3. Interestingly, a complete reversal in the product distribution was observed. Hexahydro-1H-cyclopenta[c]furan-1-one $8a$ was formed as predominant product in 45% yield along with the oxetane derivative $5a$ in 31% yield. Unlike in protic medium, rearranged bicyclic product 4 was not detected (Scheme 3).

CONCLUSION

We have observed a significant effect of aprotic solvents such as ether, THF, dioxane, dichloromethane, and chloroform on the reaction of diazomethane with norbornane-2,3-dione 3-hemiketal. In contrast to the protic reaction medium, oxetane derivatives were formed as the major products along with a novel hexahydro-1H-cyclopenta[c]furan-1-one arising from an uncommon pathway. A reversal in the product distribution was observed when (trimethylsilyl)diazomethane was used.

EXPERIMENTAL

**General Procedure for the Addition of Diazomethane**

Distilled ethereal solution of diazomethane (excess) was added to a solution of norbornane-2,3-dione 3-hemiketal 3 (0.42 mmol) in distilled aprotic solvent (2 ml) at $-10^\circ$C and allowed to stand at $-10^\circ$C. After 3 h, the excess diazomethane was quenched with 2–3 drops of acetic acid. Solvent was evaporated by rota-evaporator and the crude reaction mixture was purified on silica-gel column chromatography using 5–7% EtoAc/hexane to afford the products as depicted in Table 1.

**General Procedure for the Addition of (Trimethylsilyl)diazomethane**

BF$_3$·OEt$_2$ (0.211 mmol) and TMSCHN$_2$ (0.211 mmol) were slowly added dropwise to a solution of norbornane-2,3-dione 3-hemiketal $3a$ (0.141 mmol) in dry dichloromethane (1 mL) under argon at $-5^\circ$C. The reaction mixture was stirred at room temperature under an argon atmosphere for 9 h until disappearance of the starting material as monitored by thin-layer chromatography (TLC). The reaction was diluted with water (4 mL) and the organic layer was extracted three times with EtOAc (3 × 3 mL). The combined organic layers were washed with brine solution (2 mL) and dried over anhydrous Na$_2$SO$_4$. The solvent was removed in vacuo to furnish a residue, which was purified by silica-gel column chromatography using 5–7% EtoAc/hexane afforded hexahydro-1H-cyclopenta[c]furan-1-one $8a$ and oxetane derivative $5a$ in 45% and 31% yields, respectively.

**5-Acetyl-5,6a-dichloro-6,6-dimethoxy-hexahydro-1H-cyclopenta[c]furan-1-one ($8a$).** Colorless solid, mp 121–123 $^\circ$C; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 4.59 (t, 1H, $J = 9.0$ Hz), 4.10 (dd, 1H, $J = 9.0, 4.1$ Hz), 3.76 (s, 3H), 3.43 (m, 1H), 3.20 (s, 3H), 2.79 (dd, 1H, $J = 14.6, 9.0$ Hz), 2.55 (s, 3H), 2.41 (dd, 1H, $J = 14.6, 9.0$ Hz); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 200.6, 171.2, 110.1, 80.7, 74.2, 71.1, 54.3, 51.8, 46.0, 40.5, 27.3; IR (KBr): 2900, 1740, 1720, 1420, 1160 cm$^{-1}$. EI-HRMS: $m/z$ calcd. for C$_{11}$H$_{14}$O$_3$Cl$_2$ [M]$^+$: 296.0218; found 296.0218.
5-Acetyl-5,6a-dibromo-6,6-dimethoxy-hexahydro-1H-cyclopenta[c]furan-1-one (8b). Colorless solid, mp 116–117 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 4.58\) (t, 1H, \(J = 9.0\) Hz), 4.12 (m, 1H), 3.77 (s, 3H), 3.57 (m, 1H), 3.22 (s, 3H), 2.80 (m, 1H), 2.64 (s, 3H), 2.49 (m, 1H); \(^1\)\(^3\)C NMR (100 MHz, CDCl\(_3\)): \(\delta = 199.8, 171.8, 109.2, 73.9, 70.4, 63.7, 54.5, 52.3, 47.1, 41.9, 27.7\); IR (KBr): 2900, 1760, 1700, 1420, 1040 cm\(^{-1}\). EI-HRMS: \(m/z\) calcd. for C\(_{11}\)H\(_{14}\)O\(_5\)Br\(_2\) [M]: 383.9208; found: 383.9204.

ACKNOWLEDGMENTS

This work is part of G. H. Mangeswara Rao’s Ph.D. thesis, and we thank the Indian Institute of Technology Kanpur (IITK) for Ph.D. registration and for providing the facility to carry out this work.

FUNDING

We thank the Department of Science (DST), New Delhi, for financial assistance.

SUPPORTING INFORMATION

Supplemental data for this article can be accessed at the publisher’s website.

REFERENCES

1. Sammakia, T. In Handbook of Reagents for Organic Synthesis: Reagents, Auxiliaries, and Catalysts for C-C Bonds; R. M. Coates and S. E. Denmark (Eds.); John Wiley & Sons: Chichester, UK, 1999.
2. (a) Krow, G. R. Tetrahedron 1987, 43, 3–38; (b) Black, T. H. Aldrichim. Acta 1983, 16, 3–10.
3. (a) Kottwitz, J.; Vorbrüggen, H. Synthesis 1975, 636–637; (b) Lautens, M.; Klute, W. Chem. Rev. 1996, 96, 49–92.
4. Antkowiak, W. Z.; Sobczak, A. Tetrahedron 2001, 57, 2799–2805.
5. Eistert, B.; Wollheim, R.; Fink, G.; Minas, H.; Klein, L. Chem. Ber. 1968, 101, 84.
6. Khan, F. A.; Satapathy, R.; Sudheer, Ch.; Rao, Ch. N. Tetrahedron Lett. 2005, 46, 7193–7196.
7. Khan, F. A.; Rao, G. H. M.; Satapathy, R.; Parasuraman, K. Org. Lett. 2007, 9, 1581–1584.
8. Rao, G. H. M.; Khan, F. A. J. Org. Chem. 2013, 78, 11092–11095.