Synlett, 2009(10), 1346-1350

A Mild and Efficient Bis-aldolization of Ketones and its Application towards Spirocyclic 1,3–Dioxanes and Novel 1,3,5–Trioxocanes.

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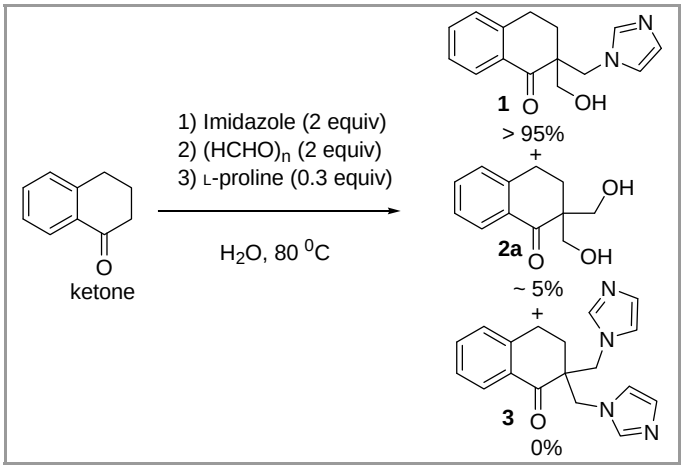
CDRI communication number; 7674.

Abstract: Bis-aldolization of aryl alkyl ketones as well as cyclic ketones with paraformaldehyde in the presence of catalytic amount L-proline and low concentration of aqueous sodium hydroxide has been developed in excellent yields. Further, these bis-aldols (1a–8a) are elaborated to corresponding spirocyclic dioxanes (9–16a) and novel spirocyclic trioxocanes (10b–16b) in the presence of p-toluene sulfonic acid. The structure and preferred conformation of these eight membered spirocyclic 1,3,5–trioxocanes is discussed.

Key words: aqueous media, bis-aldol, Mannich adduct, Mannich-aldol, L-proline, spirocylic dioxane, trioxocane.Bis-aldol (1,3-diol) units are frequently found in complex polyol architectures (which are raw material for lubricants, surface coatings, and synthetic resins) of natural products and have attracted a great deal of attention from synthetic organic chemists.[1] Mostly 1,3-diol units are the key substrates for the synthesis of dendrimers (drug carriers) and crown-ethers.[2] The traditional production methods of these bis-aldols use strong alkali and several anion-exchange resin catalysts.[3] These methods create mixtures of products (aldol, cross-aldol and acroleins) along with the required product.[4]

Cordova and co-workers have demonstrated the L-proline catalyzed direct stereo selective aldol reaction between ketone and formaldehyde, which have triggered a broad interest in organocatalysis.[5] However there is no report of bis-aldolization under similar reaction conditions. Ibrahem et.al, have introduced the first enantioselective three-component Mannich reaction of ketone, formaldehyde and amine using L-proline as catalyst.[6] Later, Erkkila et.al. and Wei Wang and co-workers used similar type of strategy for synthesis of α,β–unsaturated aldehydes and ketones respectively.[7] Based on this, for the first time we have reported the Mannich–adducts and Mannich–aldol products of unsubstituted azoles using L-proline as a catalyst.[8]

In connection with this study and our continued interest on azole based compounds,[9] we conducted an initial reaction of ketone (1.0 equiv), paraformaldehyde (2.0 equiv) and L-proline (0.3 equiv) with excess of imidazole (2.0 equiv). The reaction proceeded smoothly to furnish the Mannich-aldol type compound 1 (~ 93–95 %) along with small amount of bis-aldol product **2a**, but no bis-Mannich adduct **3** was observed (Scheme 1). This observation is consistent with the previous report that the unsubtituted azoles cannot form iminium ions with aldehydes,[10] so the Mannich-adduct of imidazole such as compound **1** (Scheme 1) is likely to form by a



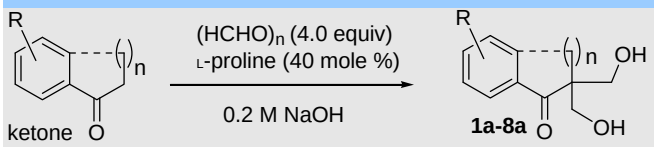
Scheme 1 Mannich adducts of azoles with excess of imidazole.

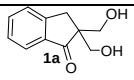
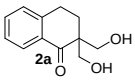
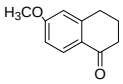
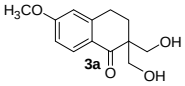
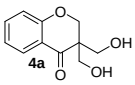
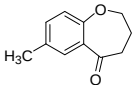
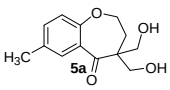
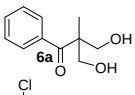
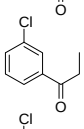
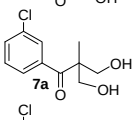
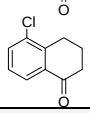
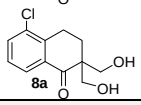
mechanism that proceeds first through aldol reaction with paraformaldehyde, then elimination to generate exo-enone and subsequent conjugate addition of the azole.

Herein, we report a very efficient L-proline and aq. NaOH catalyzed bis-aldol reaction of aryl alkyl and cyclic ketones in water,[11] the use of water making it an easy handling and attractive alternative for large scale production of bis-aldols. We also report elaboration of these bis-aldols into corresponding spirocyclic 1,3–dioxanes (**9–16a**) and novel spirocyclic 1,3,5–trioxocanes (**10b–16b**).

We next performed the above reaction (scheme 1) using more than 2.0 equiv of imidazole and observed that, the bis-aldol product (**2a**) also increased up to certain extent (5–7%). From this we anticipated that, bis-aldol formation is favored by increasing basicity of the reaction medium. This presumption was confirmed by carrying out the reaction of tetralone (1.0 equiv), paraformaldehyde (4.0 equiv) and L-proline (40.0 mole %) in aqueous 0.2 M NaOH (instead of imidazole) at ambient temperature to furnish exclusively the bis-aldol product in excellent yields (Table 1, **2a**). Consequently, on increasing the molar ratio of aqueous NaOH (> 0.2 M), several products were found in the reaction mixture (from TLC observation). However, in the absence of L-proline the ketone was not consumed and formation of bis-aldol adduct was not observed.

Table 1 L-Proline and aq. NaOH promoted bis-aldol reaction of ketones with paraformaldehyde.[a]



Entry	Ketone	Product[b]	Time (hrs)	Yield (%)[c]	m.p. (°C)
1			5	88	83
2			4	96	98
3			4.5	95	106
4			4	97	78
5			4	98	84
6			6.5	87	Oil
7			6	89	90
8			3.5	89	93

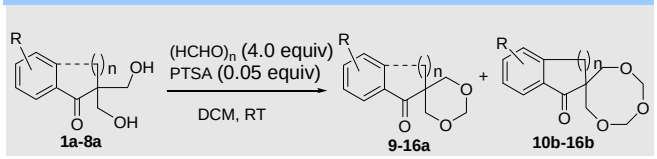
[a] For general synthetic procedure see Reference and notes section.
[b] Products identified by ^{1}H and ^{13}C NMR.
[c] Isolated yields.

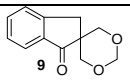
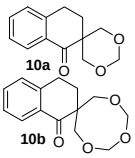
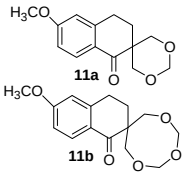
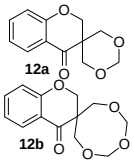
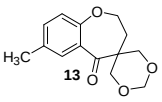
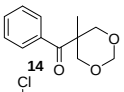
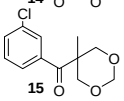
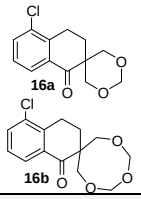
Encouraged by the results obtained in the above reaction, and in order to show the generality and scope of this new protocol, a wide variety of cyclic and aryl alkyl ketones were evaluated and the results are summarized in **Table 1**. These ketones reacted efficiently with paraformaldehyde to afford the desired products in high yields (**1a**–**8a**).

Further, instead of L-proline different amines were also examined in bis-aldolization under above reaction conditions. However, in the presence of secondary amines like pyrrolidine or morpholine the Mannich product of these amines were obtained in major amount (total amine involved in the reaction)[12] with only traces of the desired bis-aldol product. Thus the best results for bis aldolization were obtained with L-proline as catalyst.

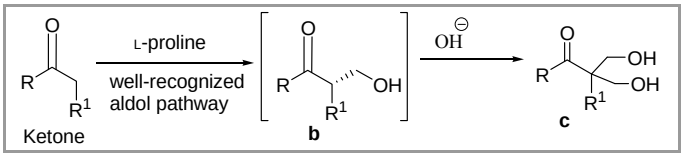
We speculate that the above reaction proceeds through an L-proline catalyzed aldol formation[13] and subsequent generation of enol in the presence of alkali followed by conjugate addition of formaldehyde to furnish the bis-aldol. To confirm this, we performed the reaction of a ketone with paraformaldehyde and L-proline in the absence of NaOH. The only product isolated was the mono-aldol **b**. On addition of 0.2 M aq. NaOH, the reaction proceeded very fast to completion and furnished the desired bis-aldol **c** (Scheme 2).

Table 2 Transformation of Bis-aldols to corresponding spirocyclic compounds.[a]



Entry	Product[b]	Time (hrs)	m.p. (°C)	Yield (%)[c, d]
1		12	82	99
2		11	47 Oil	100 (45 : 55)
3		11.5	101 Oil	100 (35 : 65)
4		12	Oil 62	97 (46 : 51)
5		9	88	100
6		8	102	98
7		8.5	128	96
8		10.5	Oil 134	100 (44: 56)

[a] For general synthetic procedure see Reference and notes section.
[b] Corresponding bis-aldols are the starting materials.
[c] Isolated yields.
[d] Both spirocyclic 1, 3–dioxane and 1, 3, 5–trioxocanes mentioned in specified ratios.



Scheme 2

We further, elaborated these bis-aldols in to spirocyclic ring systems. Thus a reaction between bis-aldol **2a** with paraformaldehyde and catalytic amount of PTSA[14] in DCM at room temperature, resulted in to the expected six membered spirocyclic 1,3–dioxane **10a** along with unexpected eight membered spirocyclic 1,3,5–trioxocane **10b** in almost equal amounts. Bis-aldols **1a–8a** were used to furnish the corresponding spirocyclic compounds **9–16b** and the results are summarized in Table 2. It can be seen from the table that all the bis-aldols **1a–8a** reacted to provide corresponding 1,3–dioxanes **9–16a**. Interestingly, it can also be seen that only chromanone and tetralone derived bis-aldols **2a**, **3a**, **4a** and **8a** reacted to provide corresponding 1,3,5–trioxocanes **10b**, **11b**, **12b** and **16b** respectively.

To the best of our knowledge, no report concerning spirocyclic 1,3,5–trioxocanes exist. However, limited number of literature is available regarding 1,2,4–, 1,3,5– and 1,3,6–trioxocanes.[15] Based on earlier reports we hypothesized that, the large molecules like the spiro-trioxocanes are unstable under extreme (high temperature, pressure and microwave assisted) conditions.[16] However, the reactions performed at ambient temperature and mild conditions have permitted us, the isolation and characterization of these novel compounds.

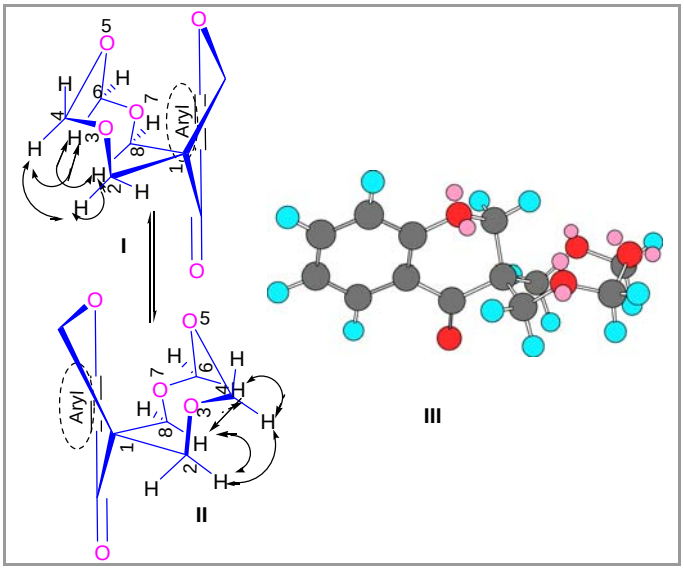


Figure 1 Characteristic NOEs and energy-minimized structure of **12b** was optimized from MM and MD simulations.

The structure and conformation of spiro cyclic trioxocanes was deduced from the ^{1}H, ^{13}C and 2D NMR data. The conformational flexibility could lead to two conformers **I** and **II** in which eight-member trioxocane ring is stable in crown-shape (figure 1), this was confirmed by 2D NOESY cross peaks between H-2 / H-8 and H-2 / H-4 of all same pole protons (like H-2, the H-4, H-6, and H-8 are also correlating). The energy-minimized structure **III** also supported the same fact.

In summary, we have developed a very efficient and mild reaction for synthesizing bis-aldols from cyclic and aryl alkyl ketones and converted them into spiro-cyclic 1,3–dioxanes and novel spiro-cyclic 1,3,5–trioxocanes. Further elaboration of this transformation and its synthetic applications are ongoing in our laboratory.

Supporting Information Experimental procedures, characterization data and 1D, 2D NMR spectra are available as supplementary data.

Acknowledgement

The authors are grateful to SAIF for analytical data and Anoop Srivastava for technical assistance. N.S.V and VKM are thankful to the UGC and CSIR, New Delhi, India for financial support.

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(17) **General procedure for the preparation of bis-aldols 1a-8a** (**for example 2a**). A solution of α–tetralone (1.0 mmol), paraformaldehyde (4.0 mmol) and L-proline (40 mole %) in water (0.5 mL) was stirred at room temperature for 3–4 hours. To this added 0.53 M NaOH (0.3 mL) solution slowly. After completion of the reaction (monitored by TLC) the reaction mixture was extracted with ethyl acetate (3 x 4 mL). The combined organic extracts were washed with distilled water (5 x 3 mL), dried over Na_2SO_4 and removal of the solvent under reduced pressure furnished the crude product, which was filtered through silica gel column (ethyl acetate/hexane = 1/2, v/v) to give (96 %) **2a** as a white solid; Mp 98–99 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.98 (t, *J* = 6.4 Hz, 2H), 3.01 (t, *J* = 6.4 Hz, 2H), 3.62 (bs, 2H), 3.71–3.95 (dd, *J* = 11.3 Hz, 4H), 6.69 (m, 2H), 6.84 (d, *J* = 8.8 Hz, 1H), 7.97 (d, *J* = 8.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.9, 26.4, 51.2, 64 (2C), 126.8, 127.6, 128.9, 131.6, 134.1, 143.8, 203.1; MS (ESI): m/z (%): 207 (100) $[M+1]^+$.

(18) **General procedure for preparation of 9–16b** (**for example 10a, 10b**). A mixture of 2,2-bis-hydroxymethyl-3,4-dihydro-2H-naphthalen-1-one **2a** (1.0 mmol), paraformaldehyde (4.0 mmol), and catalytic amount of para toluene sulphonic acid (0.05 equiv) in DCM (6 mL) was stirred at ambient temperature for 11 h. After completion of reaction (from TLC), the reaction mixture was filtered through sintered funnel. The filtrate was washed with 1% aq. sodium bicarbonate solution (2 x 2 mL), followed by water (3 x 2 mL), dried over anhydrous Na_2SO_4. Removal of the solvent under vacuum afforded the crude mixture of corresponding spirocyclic 1, 3–dioxane **10a** and 1, 3, 5–trioxocane **10b** in quantitative amount. The above mixture was subjected to florisil column (ethyl acetate / hexane = 1/20, v/v) to give pure products (**10a** & **10b**) (in 45:55 ratio). For **10a** Mp 46–47 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.92 (t, *J* = 6.9 Hz, 2H), 3.66 (d, *J* = 11.6 Hz, 2H), 3.98–4.07 (dd, *J* = 11.6 Hz, 2H), 4.69 (d, *J* = 5.8 Hz, 2H), 5.24 (d, *J* = 5.8Hz, 2H), 7.18 (m, 1H), 7.31 (m, 2H), 7.63 (d, *J* = 6.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.8, 27.5, 45.9, 70.6 (2C), 94.3, 126.8, 127.7, 128.9, 131.7, 133.9, 143.2, 198.1; IR (KBr, cm^{-1}) 3222, 2361, 1708, 1221, 1165, 762, 667; MS (ESI): m/z (%): 219 (77) $[M+1]^+$. for **10b** Oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.26 (t, *J* = 6.4 Hz, 2H), 3.04 (t, *J* = 6.4 Hz, 2H), 3.82–4.21 (dd, *J* = 12Hz, 4H), 4.8 (d, *J* = 6.7 Hz, 2H), 4.96 (d, *J* = 6.4 Hz, 2H), 7.34 (m, 2H), 7.52 (m, 1H), 8.03 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.8 (2C), 28.7, 29.6, 49.6, 69.9, 95.9, 126.7, 127.8, 128.7, 131.4, 133.5, 143.2, 199.4; IR (Neat, cm^{-1}) 3027, 2367, 1709, 1217, 1161, 767; MS (ESI): m/z (%): 249 (100) $[M+1]^+$.