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Isochroman-3-ones via Site-Selective Ring Opening of Benzocyclobutenones Promoted by Lithium Tetramethylpiperidide and Reaction with Aromatic Aldehydes

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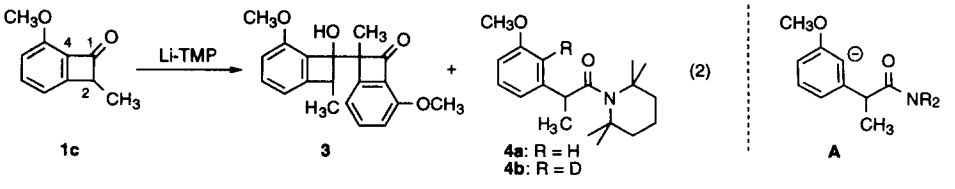
Abstract: In the presence of Li-TMP and an aromatic aldehyde, benzocyclobutenone undergoes an unusual heterolytic C(1)–C(4) bond fission, and subsequent reaction with the aldehyde gives, after acidic workup, isochroman-3-one in high yield. © 1997 Elsevier Science Ltd.

We report herein a new synthetic method of isochroman-3-ones based on the reaction of an aldehyde and a benzocyclobutenone promoted by lithium tetramethylpiperidide (Li-TMP) (eq. 1). The study stemmed from an accidental finding of a unique reactivity (vide infra), which was subjected to an optimization.

1 **2** (1)

Previously, we reported an access to various benzocyclobutenones via the [2+2] cycloaddition of benzyne and ketene silyl acetals.[1] In our subsequent study on the potential reactivities of such strained carbonyls, we were intrigued by its conversion to the enolate (an 8π system) or the α-keto carbanion. Various attempts along these lines, however, showed the extreme rapidity of the self aldol reaction: Treatment of **1c** with Li-TMP at –78 °C quickly gave **3**, suggesting the high reactivity of the derived enolate and also the high susceptibility of **1c** toward nucleophilic attack.[2]

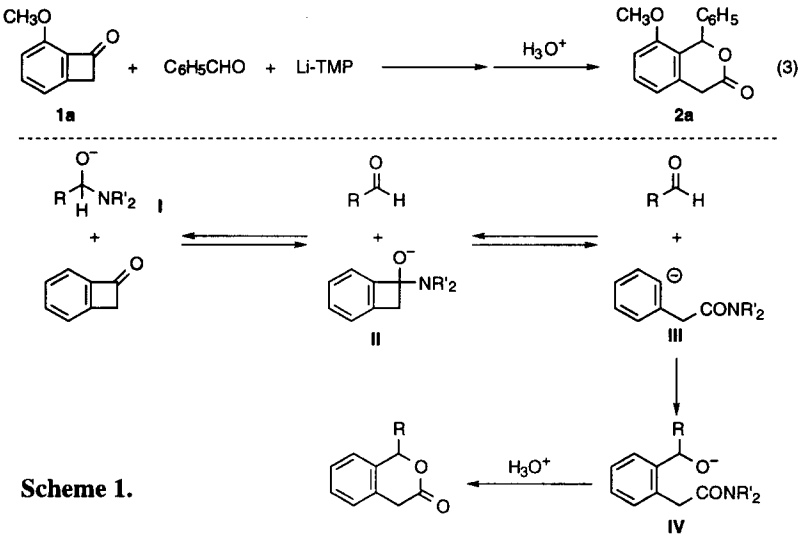


1c **3** **4a**: R = H **4b**: R = D **A**

During such attempts, we encountered a notable minor product **4a** among many unidentified products. Although obtained in a small, but varying amount, formation of **4a** suggested the possible heterolytic cleavage of the C(1)–C(4) bond in **1c** to generate an aryl anion **A**. Indeed, D_2O-quenching gave amide **4b** with a full

deuteration. Although such a mode of bond fission of benzocyclobutenone was invoked in its basic hydrolysis to give arylacetic acid,[3,4] trapping of the intermediary aryl anion by a carbon electrophile had not been reported, to which we focused our attention. After considerable experimentation, we found an effective protocol for the trapping by aldehydes under specified conditions.

The major difficulty was the extreme readiness of the self-aldolization (vide supra), which was only circumvented by a specific protocol that includes the prior mixing of the aldehyde and Li-TMP before the addition of benzocyclobutenone. To a solution of Li-TMP (2.5 equiv.) in THF at 0 °C was added benzaldehyde (3.4 equiv.) followed by benzocyclobutenone **1a** (1 equiv.), and the mixture was stirred for 10 min. Acidic workup (4 M HCl, 25 °C, 1 h) gave isochromanone **2a** in 70% yield (eq. 3; run 1 in Table 1).



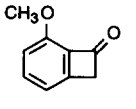
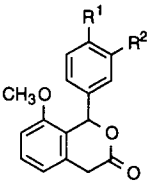
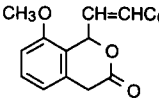
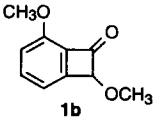
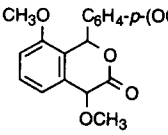
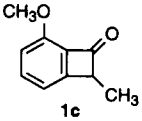
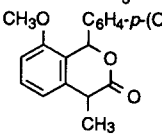
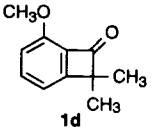
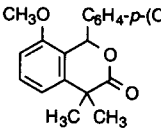
Scheme 1.

Our rationale is the following. Upon mixing, the aldehyde and the lithium amide form adduct **I**, which, although its exact nature or even stoichiometry is unknown,[5] masks the mutual reactivities of each components. In particular, the absence of the free Li-TMP, if any, serves to avoid the self aldol reaction. The adduct **I** in turn serves as a reservoir that slowly supplies the aldehyde and the amide.[5] Upon addition of benzocyclobutenone, an equilibrium generates, via an exchanged adduct **II**, the key aryl anion **III** that attacks the co-existing aldehyde to give the addition product **IV**. Final aqueous workup furnishes isochromanone.

The protocol was successfully applied to various substrate combinations (Table 1). Runs 1–6 show the reaction of **1a** with aromatic aldehydes as well as a vinylogue, cinnamaldehyde, that gave the corresponding isochroman-3-ones in high yields. Due to the highly basic reaction media, the reaction with aliphatic aldehydes gave, not surprisingly, an intractable mixture of many products. Runs 7 and 8 show the application to the benzocyclobutenones possessing a substituent at the α-position to the carbonyl to furnish α-alkoxy and α-alkyl isochroman-3-ones, **2g** and **2h**, which are not readily accessible due to the difficulty in the oxidation and the mono-alkylation of the parent compound, respectively.[6a,d] It should be noted that *gem*-dimethyl substrate **1d** also underwent the reaction to give **2i**, albeit in low yield, which ruled out the mechanisms that necessitate the presence of an α-proton (Fig. 1), such as (1) the aldehyde addition of ketene

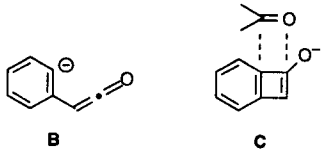
B or (2) the hetero Diels–Alder reaction of enolate **C** followed by fragmentation,[2] which are less likely, yet conceivable in a formal sense.

Table 1.

Run	Benzocyclobutenone	Aldehyde	Isochroman-3-one	Yield[a,b]
1	 **1a**	C_6H_5CHO		**2a** ($R^1 = R^2 = H$): 70%
2		4-$(CH_3O)C_6H_4CHO$		**2b** ($R^1 = CH_3O$, $R^2 = H$): 87%
3		4-$CH_3C_6H_4CHO$		**2c** ($R^1 = CH_3$, $R^2 = H$): 73%
4		4-ClC_6H_4CHO		**2d** ($R^1 = Cl$, $R^2 = H$): 64%
5		3,4-$(CH_3O)_2C_6H_3CHO$		**2e** ($R^1 = R^2 = CH_3O$): 78%
6		C_6H_5-CH=CHCHO		**2f**: 54%
7	 **1b**	*p*-$(CH_3O)C_6H_4CHO$		**2g**: 83%[c]
8	 **1c**	*p*-$(CH_3O)C_6H_4CHO$		**2h**: 81%[d]
9	 **1d**	*p*-$(CH_3O)C_6H_4CHO$		**2i**: 40%

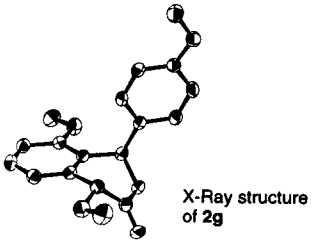
(a) Isolated yield. (b) In all cases, neither the self-aldol product nor the amide, corresponding to **3** and **4** in eq. 2, were not detected. (c) The stereoselectivity was 14/1. The major isomer was *trans* with respect to the C(1) and C(4) substituents, which was confirmed by X-ray analysis (Fig. 2). We thank Ms. Sachiyo Kubo for X-ray analyses. (d) The stereoselectivity was 3.4/1. The stereostructure was not determined.

Figure 1.



B **C**

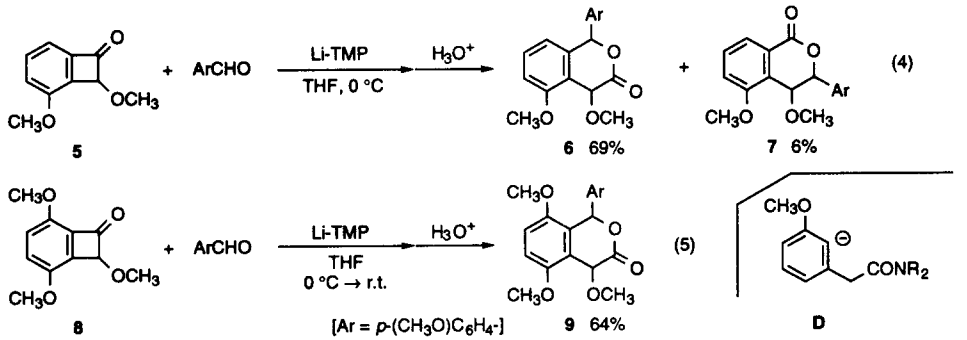
Figure 2.



X-Ray structure of **2g**

All the cases listed in Table 1 gave the isochroman-3-ones as the exclusive product, which is notable in light of the potential competing process of the C(1)–C(2) bond cleavage. As a control experiment, benzocyclobutenone **5**, isomeric to **1b** with respect to the position of the methoxy group on the aromatic ring,

was subjected to the same reaction conditions (eq. 4). It turned out that, though the C(1)–C(4) cleavage still prevailed, a small amount of isomeric product **7** was obtained that resulted from the C(1)–C(2) bond cleavage. Thus, the presence of the *o*-methoxy group is contributing (see **D**), at least partially, to the mode of the bond cleavage. As a further example, the reaction of bis-methoxy derivative **8** gave isochroman-3-one **9** as the sole product, and none of the isomeric product, corresponding to **7**, was detected.



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2. For previous attempts along these lines, see: Bertelli, D. J.; Crews, P. *J. Am. Chem. Soc.* **1968**, *90*, 3889–3990. All attempts at effecting the enolization of **1** failed: Slow addition of **1** to an excess of lithium amide brought about the self-aldol product. For a leading book dealing with the chemistry of benzocylobutadiene derivatives, see: Cava, M. P.; Mitchel M. J. *Cyclobutadiene and Related Compounds*; Academic: New York, 1967.
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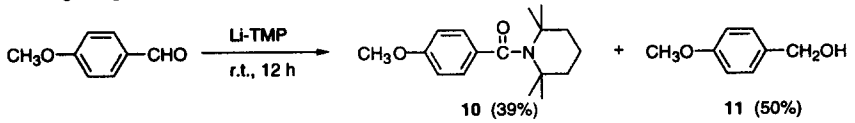
5. Although such a complex formed from an aldehyde and lithium dialkylamide has been used in organic synthesis, the exact structure or nature of the species involved has not been clarified. For example, Comins, D. L.; Brown, J. D. *J. Org. Chem.* **1984**, *49*, 1078–1083. We studied the mixture of 4-$(CH_3O)C_6H_4CDO$ and Li-TMP by ^{2}H-NMR spectroscopy. To a THF solution of Li-TMP in an NMR sample tube was added an equimolar amount of 4-$(CH_3O)C_6H_4CDO$. The ^{2}H spectrum showed the absence of the aldehyde peak, and such a situation persisted even after further addition of the aldehyde in small portions (up to 3 equiv. to Li-TMP), suggesting the adduct is never be of a simple 1:1 stoichiometry. Upon addition of water, the aldehyde signal appeared at the expected position. Prolonged exposure of the aldehyde with Li-TMP, in a separate run, brought about a Cannizzaro-type reaction, giving amide **10** and alcohol **11**.



6. Selected examples on the isochroman-3-one synthesis: (a) Oppolzer, W. *Heterocycles* **1980**, *14*, 1615–1630. (b) Shishido, K.; Shitara, E.; Fukumoto, K. *J. Am. Chem. Soc.* **1985**, *107*, 5810–5812. (c) Khanapure, S. P.; Biehl, E. R. *J. Org. Chem.* **1987**, *52*, 1333–1337. (d) Isobe, K.; Takeda, N.; Mohri, K.; Tsuda, Y. *Chem. Pharm. Bull.* **1989**, *37*, 3390–3392.

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