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# Stereoselective Synthesis of Dihydrofurans Under Phase-Transfer Catalyzed Conditions

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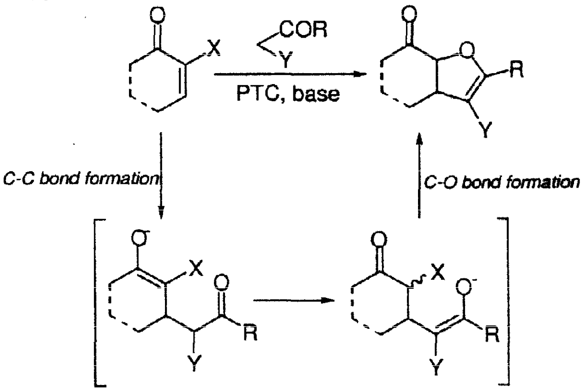
***Abstract*:** Treatment of cyclic or acyclic α-haloenones with various carbon nucleophiles involving active methylene functions afforded the corresponding dihydrofurans in a stereoselective manner with good to high yields. This reaction system can provide a general and practical methodology for the construction of dihydrofuran rings.

*Keyword*: Bicyclic heterocyclic compounds, Catalysts, Furans, Phase transfer

Quite recently, we reported the catalytic and highly stereoselective construction of a cyclopropane ring via successive processes of Michael addition, proton transfer, and intramolecular alkylation with various carbon nucleophiles under phase-transfer catalyzed (PTC) conditions[1] which allows it to be a practical method.[2] According to this reaction system, dihydrofurans can also be produced via both intermolecular C-C and intramolecular C-O bond formations utilizing the oxygen nucleophilicity of the enolate anions (Scheme 1). In this communication, we report our own results concerning the facile and efficient strategy for the synthesis of dihydrofurans under PTC conditions.[3]

Scheme 1



Initially, we attempted the catalytic cyclization reaction for the preparation of dihydrofurans using reactive cyclic enones such as α-chlorocyclohexenone **1a**.[4] The reaction of **1a** with α-sulfonylketone **2a** involving acidic protons was carried out in the presence of rubidium carbonate with a catalytic amount of commercially available quaternary ammonium salt as the PTC at room temperature. The reaction proceeded smoothly to give the desired product **3a** as the sole product in 81% yield under mild reaction conditions.[5] After screening of the PTC, tetrahexylammonium bromide (THAB) containing long hydrophobic chains gave the best result. On the other hand, the reaction in the absence of PTC was much slower than the PTC-promoted reaction systems and produced **3a** in lower yield. This result reveals that the PTC seems to act as an efficient catalyst for the dramatic enhancement of the reaction rate.

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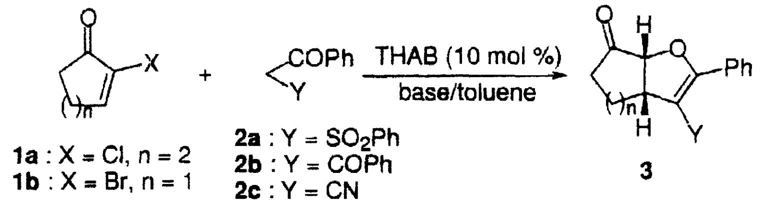


**1a** : X = Cl, n = 2
**1b** : X = Br, n = 1

**2a** : Y = $SO_2Ph$
**2b** : Y = COPh
**2c** : Y = CN

**3**

Table 1

| entry | enone | 2 | base (eq) | temp & time | yield of 3 (%) |
|---|---|---|---|---|---|
| 1 | **1a** | **2a** | $Rb_2CO_3$ (1.6) | rt, 37 h | **3a** : 81 |
| 2 | **1a** | **2b** | $Rb_2CO_3$ (1.6) | rt, 36 h | **3b** : 95 |
| 3 | **1a** | **2c** | $K_2CO_3$ (1.6) | -10°C, 22 h | **3c** : 90 |
| 4 | **1b** | **2a** | $K_2CO_3$ (2.0) | rt, 36 h | **3d** : 62 |
| 5 | **1b** | **2b** | $K_2CO_3$ (2.0) | 4°C, 46 h | **3e** : 82 |
| 6 | **1b** | **2c** | $K_2CO_3$ (2.0) | rt, 11 h | **3f** : 64 |

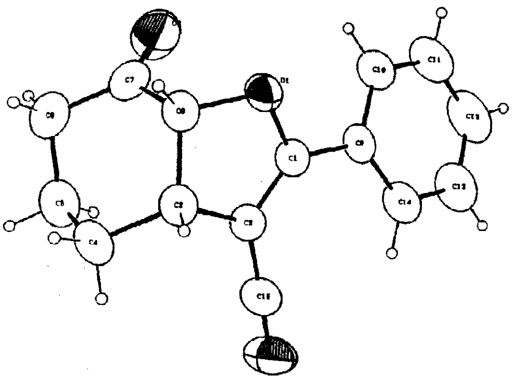


Figure 1. The ORTEP diagram of **3c**

As shown in Table 1, the treatment of **1a** with other types of carbon nucleophiles such as dibenzoylmethane **2b** and α-cyanoacetophenone **2c** also gave the corresponding bicyclic adducts **3b** and **3c** as the sole diastereomer under similar reaction conditions in 95 and 90% yields, respectively (entries 2 and 3).[6] Surprisingly, no cyclopropanated adducts were obtained in these reaction systems. As shown in Figure 1, the relative configuration of the obtained bicyclic compounds were determined to have a *cis* orientation by X-ray crystallographical analysis and by $^1H$ NMR analysis. In the case of the 5-membered ring compounds, α-bromocyclopentenone **1b** also afforded the cyclized products in good to high yield. Especially, the reaction of **1b** with **2b** under similar PTC conditions gave **3e** in 82% yield (entry 5). These systems also gave the desired products in lower yield in the absence of PTC. Thus, we have succeeded in the establishment of a PTC catalyzed efficient methodology for the synthesis of bicyclic dihydrofurans under mild reaction conditions.

Next, we utilized the (*E*)-acyclic α-chloroenones **4** as substrates under similar reaction conditions. Enone **4** also smoothly reacted with the carbon nucleophiles **2** to give the corresponding dihydrofurans. Especially, the reaction of the enone **4a** with **2c** smoothly proceeded with complete stereoselectivity to give the corresponding cycloadduct **5a** as the sole product in 67% yield. The $^1H$ NMR analysis revealed that the stereochemistry of **5a** was found to be the thermodynamically stable *trans* orientation.[7] On the other hand, both **5a** and the cyclopropanated product were obtained in the absence of PTC under similar reaction conditions in 14% and 52% yields, respectively. Thus, the addition of the quaternary salt as the PTC is essential for the promotion of the C-O bond formation to obtain the corresponding dihydrofuran in good yield. Other types of acyclic enones also reacted with **2b** and **2c** to give the *trans* dihydrofurans **5** as the major isomer in good yield. As illustrated in Figure 2, each stereochemistry of the obtained isomers was determined by NOE. Although the *cis* isomers were detected on TLC in these reaction systems, the obtained *cis* isomer was found to be easily transformed into the *trans* isomer in the presence of DBU in benzene. These results are summarized in Table 2 and Scheme 2.

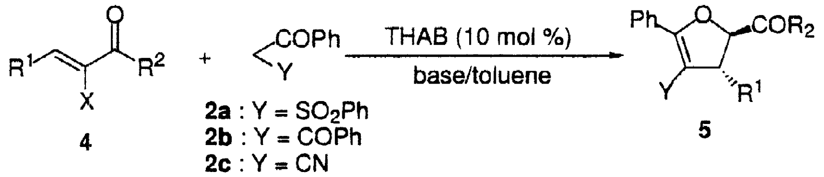


Table 2

| entry | enone | $R^1$ | $R^2$ | X | 2 | base (eq) | temp & time | yield of 5 (%) |
|---|---|---|---|---|---|---|---|---|
| 1 | **4a** | Ph | Ph | Cl | **2c** | $Rb_2CO_3$ (2.0) | rt-60°C, 87 h | **5a** : 67 |
| 2 | **4b** | Ph | Me | Br | **2b** | $K_2CO_3$ (2.0) | rt, 86 h | **5b** : 71[a] |
| 3 | **4b** | Ph | Me | Br | **2c** | $K_2CO_3$ (2.0) | 60°C, 23 h | **5c** : 60 |
| 4 | **4c** | 4-Br-$C_6H_4$ | Ph | Cl | **2c** | $Rb_2CO_3$ (2.0) | 60°C, 15 h | **5d** : 60[b] |

a) *cis*:*trans* = 1:1.6. b) The cyclopropanated compound was obtained as a by-product in 11% yield.

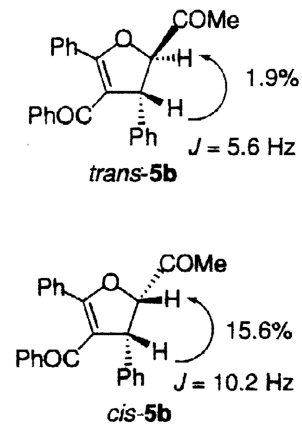
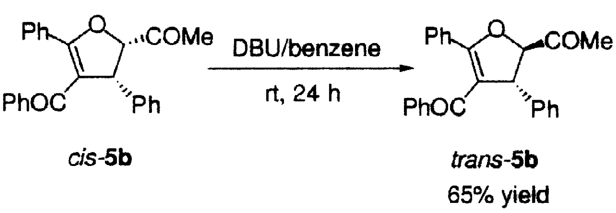


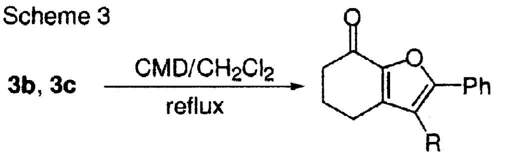
Figure 2. NOE effect of 5

Moreover, we attempted to transform the obtained dihydrofurans to the corresponding furans using mild oxidant, chemical manganese dioxide (CMD),[8] that has been found to be quite effective for chemically oxidizing unstable or reactive substrates under mild reaction conditions.[9] The reaction of **3b** and **3c** prceeded smoothly to give the corresponding furan **6a** and **6c** in 72 and 61% yields as the sole product, respectively (Scheme 3).

Scheme 2



Scheme 3



**6a** : R = COPh, 72%
**6c** : R = CN, 61%

In conclusion, we have found that catalytic stereoselective furan ring forming reactions proceed smoothly to give the desired products in good to high yields with excellent stereoselectivities under PTC-catalyzed conditions. This protocol can provide a novel and effective methodology for the preparation of dihydrofurans in a stereoselective fashion. Many applications of this novel reaction system for the synthesis of dihydrofurans are now under investigation.

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5. Treatment of the corresponding α-iodo or bromoenone under similar reaction conditions gave **3a** in low yields. Furthermore, the cyclic haloenones described in Table 1 were found to be unstable in basic media and lead to slow decomposition.
6. A typical procedure for the dihydrofuran ring forming reaction under phase-transfer catalyzed conditions is as follows: To a solution of α-chloroenone **1a** (65.0 mg, 0.5 mmol), dibenzoylmethane **2b** (168.0 mg, 0.75 mmol) and tetrahexylammonium bromide (21.8 mg, 0.05 mmol) in toluene (3.0 mL) was added rubidium carbonate (185.0 mg, 0.8 mmol) at room temperature and the reaction mixture was stirred at room temperature for 37 h. The mixture was quenched with 1*N* HCl (3.0 mL), extracted with diethyl ether (15 mL X 3), washed with brine, and dried over $Na_2SO_4$. Removal of the solvent followed by flash column chromatography (silica gel, hexane:diethyl ether = 1:2) gave the desired product **3b** (150.3 mg, 95%) as a pale yellow oil.
7. The stereochemistry of the monocyclic dihydrofurans were determined by comparison with the literature data, see (a) Alonso, M. E.; Morales, A.; Chitty, A. W. *J. Org. Chem.* **1982**, *47*, 3747-3754. (b) Alonso, M.E.; Jano, P.; Hernandez, M.; I.; Greenberg, R. S.; Wenkert, E. *J. Org. Chem.* **1983**, *48*, 3047-3050.
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