Organometallic Reactions in Aqueous Media. 2. Convenient Synthesis of Methylenetetrahydrofurans[1]

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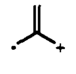
Summary: 2-(Chloromethyl)-3-iodo-1-propene (**5**) reacts with zinc and carbonyl compounds to give the alcohols **8**, which can be converted to methylenetetrahydrofurans (**7**) in high yield. The combination of **5**/Zn can be considered as the functional equivalent of trimethylenemethane **1**.

The 1,3-dipolar species trimethylenemethane (TMM, 1), which bears a nucleophilic and an electrophilic center, is quite useful in synthesis, since it can react with a carbonyl functionality (or its equivalents) in a 3 + 2 fashion to yield a five-membered-ring product. Methods developed for the generation of 1 include the use of precursors 2, where the nucleophilic component contains a stable organometalloid function rather than the more reactive conventional organometallic function.[2] Alternatively, for reagents containing the more nucleophilic organozinc[3] or organomagnesium[4] moiety, the electrophilic center tends to be the less reactive ether function (.e.g 3). Such a balance of reactivity of the two polar centers is necessary to prevent self-cyclization or di- and polymerization.



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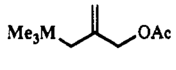
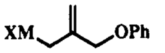
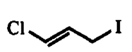


2 M=Si or Sn



3 MX=ZnBr or MgCl



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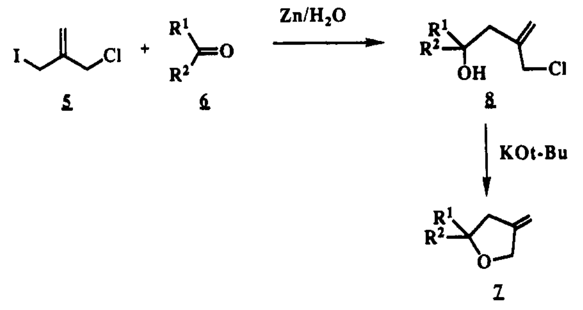
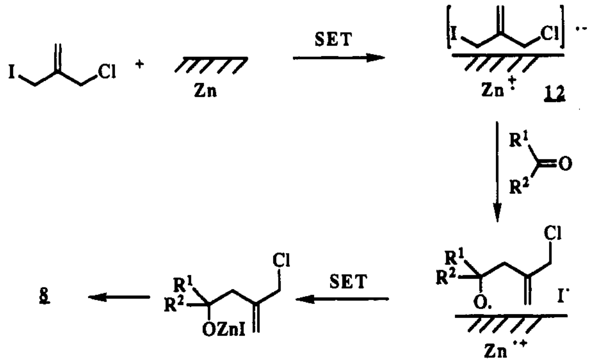
Recently, it has been demonstrated that organometallic-type reactions can be carried out in aqueous media, particularly in the reactions of allylic halides, metallic zinc, and carbonyl compounds, to give the corresponding homoallylic alcohols.[5] Even though there was no evidence to suggest that allylzinc halide was actually formed in these reactions, the overall transformation was equivalent to the reaction of allylzinc halide with carbonyl compounds. We recently demonstrated that the reactions can be extended to the synthesis of butadienes and vinyloxiranes by using the allylic 1,3-dihalides 4.[1] Other functionalized allylic halides should be amenable to the same type of reactions. We report here the reactions of 2-(chloromethyl)-3-iodo-1-propene (5) with carbonyl compounds (6) to give methylenetetrahydrofurans (7) via the intermediate alcohols 8 according to Scheme I.

Scheme I

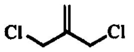


Scheme II[a]



[a] SET = single-electron transfer.

Compound 5 was prepared readily from 2-(chloromethyl)-3-chloro-1-propene (9) and 1 equiv of NaI in acetone and purified by vacuum distillation (bp 50–52 °C/1.1 mmHg). Its reaction with benzaldehyde was illustrative. A mixture of benzaldehyde (**6a**, 1 mmol), compound **5** (1.5 mmol), and zinc powder (1.5 mmol) in 10 mL of water was stirred vigorously at room temperature. Very often, 2–3 drops of saturated aqueous NH_4Cl solution or 48% hydrobromic acid was added to initiate the reaction. The mixture was stirred until the zinc almost disappeared (usually in 3–4 h). The reaction mixture was then extracted with ether to give **8a** in good yield. With or without purification, **8a** was converted to **7a** by treatment by KO-*t*-Bu/2-propanol (3 mmol/20 mL) or KO-*t*-Bu/hexane (2 mmol/20 mL).



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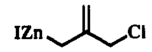

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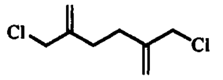

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The presence of water is critical to the success of the coupling step for the formation of **8a**. When the reaction of benzaldehyde with **5** was carried out in diethyl ether or tetrahydrofuran, there was no or little formation of **8a**. Addition of water (0.5 mL) to the organic solvent led to the formation of **8a** accompanied by the reduction product benzyl alcohol.

Other carbonyl compounds reacted similarly with **5** to give the coupled products and subsequently the methylenetetrahydrofurans in good yields (Table I). It is in-

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[1] For previous papers in this series, see: Chan, T. H.; Li, C. J. *Organometallics* **1990**, *9*, 2649.

[2] Trost, B. M.; King, S. A. *J. Am. Chem. Soc.* **1990**, *112*, 408 and references cited therein.

[3] van der Louw, J.; van der Baan, J. L.; Stichter, H.; Out, C. J. J.; Bickelhaupt, F.; Klump, G. W. *Tetrahedron Lett.* **1988**, *29*, 3579.

[4] van der Louw, J.; Out, C. J. J.; van der Baan, J. L.; de Kanter, F. J. J.; Bickelhaupt, F.; Klump, G. W. *Tetrahedron Lett.* **1989**, *3*, 4863.

[5] Uneyama, K.; Kamaki, N.; Moriya, A.; Torii, S. *J. Org. Chem.* **1985**, *50*, 5396. Petrier, C.; Einhorn, J.; Luche, J. L. *Tetrahedron Lett.* **1985**, *26*, 1449. Petrier, C.; Luche, J. L. *J. Org. Chem.* **1985**, *50*, 910. Einhorn, C.; Luche, J. L. *J. Organomet. Chem.* **1987**, *322*, 177. Petrier, C.; Depuy, C.; Luche, J. L. *Tetrahedron Lett.* **1986**, *27*, 3149. Luche, J. L.; Allavena, C. *Tetrahedron Lett.* **1988**, *29*, 5369. Luche, J. L.; Petrier, C.; Depuy, C. *Tetrahedron Lett.* **1988**, *29*, 5373. Wilson, S. R.; Guazzaroni, M. E. *J. Org. Chem.* **1989**, *54*, 3087.

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Table I. Synthesis of Methylenetetrahydrofurans from R^1COR^2 According to Scheme I

entry no.	carbonyl compd 6	reacn medium	initiator[a]	yield of 8, %	cyclization condition[b]	overall yield of 7, %
1	**6a**, $R^1 = C_6H_5-$, $R^2 = H$	H_2O	A	**8a**, 92	C	**7a**, 92
2		ether		0		
3		THF		0		
4		H_2O/ether (1:20)		**8a**, 65 +$PhCH_2OH$, <5		
5		H_2O/THF (1:20)		**8a**, 40 +$PhCH_2OH$, 30		
6	**6a** + **6k**, $R^1 = R^2 = n\text{-}C_4H_9$	H_2O	A	**8a**, 90 **8k**, 0		
7	**6b**, $R^1 = p\text{-}ClC_6H_4-$, $R^2 = H$	H_2O	A	**8b**, 93	C	**7b**, 92
8	**6c**, $R^1 = p\text{-}CH_3C_6H_4-$, $R^2 = H$	H_2O	A	**8c**, 85	C	**7c**, 85
9	**6d**, $R^1 = CH_3(CH_2)_8-$, $R^2 = H$	H_2O	A + B	**8d**, 92	C	**7d**, 90
10	**6e**, R^1 = cyclohexyl, $R^2 = H$	H_2O	A + B	**8e**, 88	D	**7e**, 88
11	**6f**, $R^1 = C_6H_5CH{=}CH-$, $R^2 = H$	H_2O	A	**8f**, 95	C	**7f**, 95
12	**6g**, cyclohexanone	H_2O	A + B	**8g**, 88	D	**7g**, 88
13	**6h**, $R^1 = C_6H_5-$, R^2 = Me	H_2O	A + B	**8h**, 65	D	**7h**, 65
14	**6i**, 2-cyclohexenone	satd aq NH_4Cl		**8i**, 45	D	**7i**, 42
15	**6j**, $R^1 = C_6H_5CH(CH_3)-$, $R^2 = H$	H_2O	A	**8j**, 85	D	**7j**, 82[c]

[a] Legend: A, 2–3 drops of saturated NH_4Cl water solution was added; B, 2–3 drops of 48% was added. [b] Legend: C, Ko-*t*-Bu/2-propanol; D, KO-*t*-Bu/hexane. [c] syn:anti = 2:1 by ^1H NMR spectroscopy.

teresting to note that the chloro group in **6b** (entry 7) was not affected. Ketones were converted to **8** as well as aldehydes. Conjugated carbonyl compounds reacted in a 1,2-fashion as demonstrated by cinnamaldehyde (entry 11) and cyclohexenone (entry 14). In a competitive experiment between benzaldehyde and 5-nonanone, benzaldehyde was found to react selectively (entry 6). With α-phenylpropanal as the typical α-chiral aldehyde, the reaction gave two diastereomeric products (syn/anti) in a ratio of 2:1 (entry 15), in agreement with Cram's rule or Felkin's model.[6]

In light of the known reactivity of organozinc compounds with water, it is unlikely that the organozinc intermediate **10** was actually generated in solution in the present reaction. On the other hand, when **5** was allowed to reacted with zinc under identical conditions in the absence of carbonyl compound **6**, the dimer **11** was obtained as the product. A possible reaction mechanism, invoking the intermediary of the radical anionic species **12**, is outlined in Scheme II. The critical carbon–carbon bond formation occurs prior to the formation of the free organozinc compound **10**. A similar single-electron-transfer process on metallic zinc has recently been invoked by us to account for crossed-aldol-type condensation reactions in aqueous media.[7]

Acknowledgment. We thank the NSERC and FCAR for financial support of this research.

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(7) Chan, T. H.; Li, C. J.; Wei, Z. Y. *J. Chem. Soc., Chem. Commun.* **1990**, 505.