Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 8033–8036

TETRAHEDRON LETTERS

A convenient one-pot synthesis of homoallylic halides and 1,3-butadienes

Ken-Tsung Wong* and Ying-Yueh Hung

Department of Chemistry, National Taiwan University, Taipei 106, Taiwan, ROC

Received 11 April 2003; revised 2 July 2003; accepted 31 July 2003

Abstract—An efficient one-pot synthetic pathway for the preparation of homoallylic halides by in situ generated MgBrCl-promoted ring opening of cyclopropylcarbinyl acetates has been established. An easily accessible one-pot synthetic protocol of 1,3-butadienes by the elimination of hydrogen halides from the resulting homoallylic halides in the presence of an excess amount of strong base has also been developed.

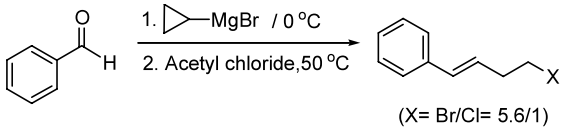
In modern molecular design and synthesis, 1,3-butadiene serves as a versatile building skeleton for the construction of complicated molecule via the famous Diels–Alder reaction.[1] A convenient synthetic protocol is highly desired for the quick access of this important precursor. A possible synthetic pathway towards the 1,3-butadiene is the direct elimination of hydrogen halides from homoallylic halides. However, the synthetic approaches of homoallylic halides to the best of our knowledge are very limited. One feasible way to homoallylic halides relies on the direct functional group transformation from homoallylic alcohols with suitable reagent such as PBr_3.[2] Another intriguing approach for the synthesis of homoallylic bromides is focused on the ring opening of cyclopropylcarbinols and their derivatives.[3] For example, treatment of the cyclopropylcarbinols with aqueous HBr or HCl stereoselectively afforded the *E*-homoallylic bromides or chlorides as the major products with reasonable yields respectively.[4] However, at lower reaction temperature, direct replacement of the hydroxy group by the Br group led to cyclopropylcarbinyl bromide as the major product.[5] Ring opening of the cyclopropylcarbinol promoted by PBr_3 has also been reported to afford the homoallylic bromide.[6] More recently, this transformation has been improved from the view point of chemical yields by treating the α-benzyl-substituted cyclopropylcarbinols with $PPh_3{\cdot}CBr_4$ complex in a mixed solvent of CH_2Cl_2 and acetonitrile.[5] Lewis acid such as $MgBr_2$ or MgI_2 has also been reported to mediate the ring opening of cyclopropylcarbinols to give the corresponding homoallylic halides. However, a mixture of *E*/*Z* alkenes was obtained upon using these conditions.[7] In addition, $ZnBr_2$-promoted ring opening of cyclopropylcarbinyl bromide has also been shown to furnish homoallylic bromide quantitatively.[5] The isolation of the starting compounds such as cyclopropylcarbinols or cyclopropylcarbinyl bromide is necessary in the above transformations. We report herein a convenient one-pot synthetic protocol for the stereospecific synthesis of homoallylic halides by in situ generated Lewis acid MgBrCl-promoted ring opening of cyclopropylcarbinyl acetate, without isolating the cyclopropylcarbinyl acetate. Further treatment of the resulting crude homoallylic halides with a strong base led to a convenient one-pot procedure for the synthesis of 1,3-butadiene. The easy access of the starting cyclopropylcarbinyl acetates renders this one-pot procedure more valuable for a quick preparation of homoallylic halides and 1,3-butadienes.

The addition of cyclopropylmagnesium bromide to benzaldehyde should give (cyclopropylphenylmethoxy) magnesium bromide, and subsequently quenching of this intermediate with acetyl chloride should provide the cyclopropylcarbinyl acetate as a single product. However, a slight change of the work-up procedure led to a different result. Instead of quenching the addition mixture with aqueous solution, the resulting reaction mixture was concentrated by rotary evaporation, and was followed by extracting with ether. It cleanly afforded a ring opening product, which was confirmed by ^1H NMR with the absence of the characteristic

Keywords: ring opening; homoallylic halide; 1,3-butadiene; cyclopropylcarbinyl acetate.
* Corresponding author. E-mail: kenwong@ccms.ntu.edu.tw

0040-4039/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2003.07.006

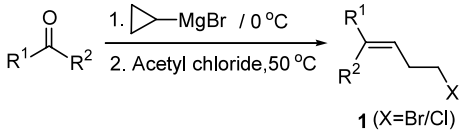
chemical shifts corresponding to cyclopropyl protons. After adding the acetyl chloride to the Grignard reagent adduct of benzaldehyde, the reaction mixture was heated up to 50°C to lead to the isolation of the same product (1).[8]



(1)

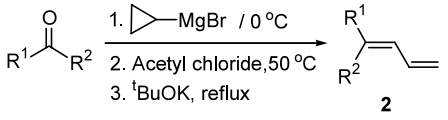
^{1}H NMR analysis of the resulting product indicates two quartets at 2.80 ppm (stronger intensity) and 2.71 ppm (weaker intensity), and two triplets at 3.50 ppm (stronger intensity) and 3.65 ppm (weaker intensity) with a ratio of 5.6 to 1. However only two types of olefinic protons with the same intensity were observed at 6.47 ppm (d, $J=16$ Hz) and 6.21 ppm (dt, $J=7.2$, 16 Hz), respectively. The large coupling constant of the olefinic protons indicates the formation of a *trans*-olefin exclusively. Careful analysis of the resulting products by GC–MS clearly indicated that the minor product contains a chlorine atom whereas the major product contains a bromine atom. According to the spectroscopic characterization, it is reasonable to assign the major product as a homoallylic bromide and the minor counterpart as a homoallylic chloride. The halides in the product can be assumed to come from the in situ generated magnesium salt, MgBrCl.

In order to explore the scope and limitation of this reaction, different carbonyl compounds, including aryl aldehydes (entries 2 and 3), cinnamaldehyde (entry 4), aliphatic aldehydes (entries 5 and 6), and arylketones (entries 7 and 8) were employed as substrates (Eq. (2)), the results are summarized in Table 1. In general, the isolated yields of the resulting homoallylic halides are better for activated carbonyl compounds. However, aryl ketones showed much lower reactivity towards this transformation as compared to that of aryl aldehydes. For example, starting from benzophenone, only 73% of the homoallylic halides were obtained with a Br/Cl ratio of 3.4 (entry 7). The homoallylic halides derivatized from aliphatic aldehydes by our one-pot synthesis only results in moderate yields (entries 5 and 6). Apparently, only *trans* isomer was formed that is opposed to the previous report[4] of HBr or $MgBr_2$-promoted ring opening of cyclopropylcarbinols, which led to a mixture of *cis*/*tans* isomers.



(2)

Initial attempts to eliminate the HX (X = Br or Cl) by treating the isolated homoallylic halides with KOH in the presence of 18-crown-6[9] only resulted in the recovery of the starting homoallylic compounds. Other organic bases such as Et_3N, DBU,[10] and $EtN(^iPr)_2$ have also been tested for the elimination of hydrogen halides from the in situ generated homoallylic halides. However, no evidence indicated the formation of the desired 1,3-butadienes. The desired 1,3-butadienes can be obtained by treating the homoallylic halides with a strong bulky base, *tert*-BuOK,[11] in reflux THF. Thus, combining the easy and convenient synthesis of homoallylic halides and the subsequent elimination of HX, a one-pot synthesis of 1,3-butadiene has been developed. The in situ generated cyclopropylcarbinyl acetates were heated to 50°C for 1 h, then an excess amount of *tert*-BuOK (3.5 equiv.) was added subsequently and the mixture was refluxed overnight to afford 1,3-butadienes in moderate yields (Eq. (3)).[8] The results are shown in Table 1.



(3)

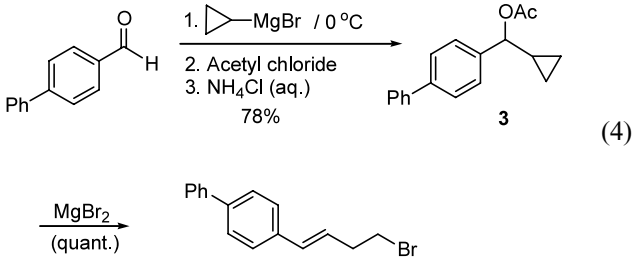
This one-pot synthetic protocol displays promising potential for the preparation of 1-aryl-1,3-butadienes (entries 1–3). 1-Phenyl-1,3,5-triene can also be isolated conveniently in 53% yield (entry 4). 1,1-Disubstituted-1,3-butadienes are also accessible by this method (entries 7 and 8). However, the product analyses of the 1,3-butadienes derivatized from the corresponding aliphatic homoallylic halides by ^{1}H NMR and GC–MS indicated that the product consists of a mixture of isomers with lower isolation yields (entries 5 and 6). The complicated product distribution may be attributed to the presence of allylic protons in the aliphatic butadienes, which isomerized through a deprotonation–protonation process under strong basic condition.

Table 1. The results of one-pot synthesis of homoallylic halides and 1,3-butadienes

Entry	R^1	R^2	Br/Cl	**1** Yield (%)[a]	**2** Yield (%)[a]
1	Ph	H	5.6	81	63
2	4-MeO-Ph	H	6.4	90	63
3	4-Ph-Ph	H	8.1	83	69
4	*trans*-$PhCH_2$=CH_2	H	4.1	85	53
5	$CH_3(CH_2)_8$-	H	10.4	40	33[b]
6	*c*-C_6H_{11}	H	8.8	50	23[b]
7	Ph	Ph	3.4	73	58
8	Ph	CH_3	8.0	70	56

[a] All yields are isolated yields.
[b] A mixture of isomers was detected by GC–MS analysis.

Mechanistic studies on the $MgBr_2$-promoted ring opening of cyclopropylcarbinols have suggested a mechanism involving rapid formation of an ion-pair intermediate, which successively undergoes ring opening to give homoallylic bromide.[7c] The coordination of the -OH group with Lewis acid is the pre-requirement for the activation of the C–O bond to form the ion-pair intermediate. In this present investigation, we believe that the homoallylic halides obtained by our one-pot synthesis come from the in situ generated Lewis acid (MgBrCl)-promoted ring opening of the cyclopropylcarbinyl acetates via the coordination of Lewis acid on the oxygen of the acetate. Subsequent attack of the resulting ion-pair intermediate by the corresponding halides (Br^- or Cl^-) led to the products as a mixture. In order to prove this assumption, the following two experiments have been performed. (1) Replacement of acetyl chloride by acetyl bromide could generate $MgBr_2$ in situ as the Lewis acid, which should subsequently promote the ring opening reaction of the resulting cyclopropylcarbinyl acetate and lead to the isolation of homoallylic bromide as the single product. Indeed, treatment of 4-biphenylcarboxaldehyde by our one-pot procedure using acetyl bromide as the acetylating agent only afforded the corresponding homoallylic bromide with an isolated yield of 82%. This observation depicts that the source of chloro substitutent found in the products is originated from the in stiu generated Lewis acid, MgBrCl. (2) α-Biphenyl cyclopropylcarbinyl acetate **3** was isolated in 78% by aqueous work-up, which afforded the homoallylic bromide quantitatively by its treatment with $MgBr_2$ in reflux THF (Eq. (4)). The result of this stepwise reaction clearly indicates that the cyclopropylcarbinyl acetate can serve as a starting material for the synthesis of homoallyic halides via ring opening transformation promoted by the in situ generated Lewis acid MgBrX.



(4)

In summary, by slightly modifying the reaction condition we have established an efficient one-pot synthetic pathway for the preparation of homoallylic halides by in situ generated MgBrCl-promoted ring opening of cyclopropylcarbinyl acetates. In the presence of an excess amount of a strong base, elimination of hydrogen halides from homoallylic halides gives 1,3-butadienes. An easily accessible one-pot synthetic protocol of the synthesis of 1,3-butadiene from in situ generated homoallylic halides has also been developed.

Acknowledgements

We thank the National Science Council of Taiwan for the financial support.

References

1. (a) Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 1668–1698; (b) Quinkert, G.; Del Grosso, M. *Stereosel. Synth.* **1993**, 109–134; (c) Brocksom, T. J.; Correa, A. G.; Naves, R. M.; Silva, F., Jr.; Catani, V.; Ceschi, M. A.; Zukerman-Schpector, J.; Toloi, A. P.; Ferreira, M. L.; Brocksom, U. *Org. Synth. Theory Applic.* **2001**, *5*, 39–87.
2. Glennon, R. A.; Salley, J. J. *J. Med. Chem.* **1981**, *24*, 678–683.
3. Sarel, S.; Yovell, J.; Imber, M. S. *Angew. Chem., Int. Ed. Engl.* **1968**, *8*, 577–588.
4. (a) Corey, E. J.; Hartmann, R.; Vatakencherry, P. A. *J. Am. Chem. Soc.* **1962**, *95*, 2611–2614; (b) Hanack, M.; Eggensperger, H. *Chem. Ber.* **1963**, *96*, 1259–1264; (c) Hanack, M.; Kang, S.; Häffner, J.; Görler, K. *Liebigs Ann. Chem.* **1965**, *690*, 98–114; (d) Liedtke, R. J.; Gerrard, A. F.; Diekman, J.; Djerassi, C. *J. Org. Chem.* **1972**, *37*, 776–789; (e) Julia, M.; Paris, J.-M. *Tetrahedron Lett.* **1974**, *38*, 3445–3446.
5. Matveeva, E. D.; Kvasha, M. P.; Kurts, A. L. *Russ. J. Org. Chem.* **1996**, *32*, 17–20.
6. (a) Maercker, A.; Roberts, J. D. *J. Am. Chem. Soc.* **1966**, *88*, 1742–1759; (b) Brady, S. F.; Ilton, M. J. A.; Johnson, W. S. *J. Am. Chem. Soc.* **1968**, *90*, 2882–2889; (c) Johnson, W. S.; Li, T.; Faulkner, D. J.; Campbell, S. F. *J. Am. Chem. Soc.* **1968**, *90*, 6225–6226.
7. (a) McCormick, J. P.; Barton, D. L. *J. Chem. Soc., Chem. Commun.* **1975**, 303–304; (b) McCormick, J. P.; Barton, D. L. *J. Org. Chem.* **1980**, *45*, 2566–2570; (c) McCormick, J. P.; Fitterman, A. S.; Barton, D. L. *J. Org. Chem.* **1981**, *46*, 4708–4712.
8. *Experimental procedure for the one-pot synthesis of homoallylic halides and 1,3-butadienes from the corresponding aldehyde and ketone*: Cyclopropylmagnesium bromine (1.0 M, 1.2 equiv.) was freshly prepared by treating cyclopropyl bromine with Mg turning in THF. To this Grignard solution, the corresponding aldehyde or ketone (1.0 equiv.) was added in one portion at 0°C. The resulting mixture was further added with acetyl chloride (1.2 equiv.) at room temp. and heated to 50°C for 1 h. The solvent was removed in vacuo, the crude product was extracted from the residue with Et_2O. Pure homoallyl product was purified by chromatography on SiO_2 with elution of EtOAc/hexanes (1/9, v/v).
   For 1,3-butadienes, the mixture after adding acetyl chloride was heated at 50°C for 1 h. Excess amount (3.5 equiv.) of KO^{t}Bu was added and the mixture was refluxed overnight. The crude 1,3-butadiene was isolated according to the general procedure and purified by chromatography on SiO_2 eluing with hexanes.

9. (a) Huang, W.; Pulaski, S. P.; Meinwald, J. *J. Org. Chem.* **1983**, *48*, 2270–2274; (b) Millar, J. G.; Underhill, E. W. *Can. J. Chem.* **1986**, *64*, 2427–2430; (c) Mori, K.; Takeuchi, T. *Liebigs Ann. Chem.* **1989**, 453–458.
10. Roversi, E.; Monnat, F.; Vogel, P.; Schenk, K.; Roversi, P. *Helv. Chim. Acta* **2002**, *85*, 733–760.
11. (a) Kataoka, F.; Shimizu, N.; Nishida, S. *J. Am. Chem. Soc.* **1980**, *102*, 711–716; (b) Kataoka, F.; Nishida, S.; Tsuji, T.; Murakami, M. *J. Am. Chem. Soc.* **1981**, *103*, 6878–6884; (c) Toth, M.; Szoecs, G.; van Nieukerken, E. J.; Philipp, P.; Schmidt, F.; Francke, W. *J. Chem. Ecol.* **1995**, *21*, 13–28.