Pergamon

Tetrahedron Letters 44 (2003) 4685–4688

TETRAHEDRON
LETTERS

A novel preparation of methyl ketones through one-carbon homologation of aldehydes

Lei Wang,[a,b,*] Pinhua Li,[a] Jincan Yan[a] and Zhongzhi Wu[c]

[a]*Department of Chemistry, Huaibei Coal Teachers College, Huaibei, Anhui 235000, PR China*
[b]*State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, PR China*
[c]*Department of Chemistry, The University of Tennessee, Knoxville, TN 37996-1600, USA*

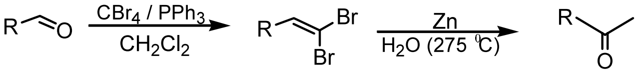
Received 7 March 2003; revised 15 April 2003; accepted 25 April 2003

Abstract—A novel two-step aldehyde homologation procedure for the preparation of methyl ketones has been developed, which involves the use of 1,1-dibromo-1-alkenes as precursors and zinc metal as mediator in near-critical water. © 2003 Elsevier Science Ltd. All rights reserved.

Conversion of aldehydes to the homologous methyl ketones is an important functional group transformation in organic synthesis and a variety of methods have been recommended for this purpose. The traditional synthetic method involves a Grignard or organolithium reagent addition to an aldehyde followed by oxidation of alcohol.[1] On the other hand, the direct insertion of an alkylidene unit from diazomethane to the aldehyde C–H bonds is also an effective approach.[2] Other methods, such as a hydride–methyl exchange reaction and Cr(II)-mediated homologation of aldehydes using Me_3SiCBr_3 have also been reported.[3] However, these methods suffer from either harsh reaction conditions that may not be compatible with many functional groups present in the molecules or moderate yields with a mixture of homologous ketones, oxiranes, higher homologs of starting aldehydes, or multi-homologation products along with waste handling problems.

Organic reactions carried out in water have received considerable attention in the last decade.[4] Unfortunately most organic compounds are poorly soluble in water at ambient temperature. Nonetheless, the unique properties of water near its critical point ($T_c = 374$°C, $P_c = 221$ bar) have prompted researchers to use it instead of organic solvents or ambient temperature water in organic synthesis.[5] Although much of supercritical water research has focused on the total oxidation of organic compounds and geochemical modeling,[6] there are increasing numbers of papers which suggest that near-critical water (250–325°C) can be an excellent solvent for organic reactions because reactions in near-critical water offer many advantages over those in traditional organic solvents. For example, it is environmentally benign and separation of products from the reaction mixture is simplified.[7]

1,1-Dibromo-1-alkenes, easily prepared from a simple reaction of an aldehyde with carbon tetrabromide and triphenylphosphine,[8] are important starting materials in organic synthesis. There are a few reports on the Pd-catalyzed cross coupling reactions of 1,1-dihalo-1-alkenes with boronic acids,[9] organostannanes,[10] alkynes and vinylalanes,[11] organozinc and Grignard reagents.[12] In addition, hydrogenolysis of 1,1-dibromo-1-alkenes with tributyltin hydride,[13] reduction with hydride anion,[14] reductive debromination with indium metal[15] and samarium diiodide,[16] and reaction with amine[17] have also been reported. However, to our knowledge, there is no report so far on the conversion of aldehydes to the homologous methyl ketones via 1,1-dibromo-1-alkene. Here, we wish to report a novel method for this conversion through the reaction of 1,1-dibromo-1-



Scheme 1.

Keywords: 1,1-dibromo-1-alkene; near-critical water; zinc metal; homologation; methyl ketone; aldehyde.

* Corresponding author. Tel.: +86-561-380-2069; fax: +86-561-309-0518; e-mail: leiwang@hbcnc.edu.cn

0040-4039/03/$ - see front matter © 2003 Elsevier Science Ltd. All rights reserved.
doi:10.1016/S0040-4039(03)01084-0

alkene (generated from aldehyde) with zinc metal in near-critical water (Scheme 1).

Our initial studies were directed towards exploring the reaction conditions for the reaction of 1,1-dibromo-1-alkenes with metallic zinc in hot water. The results are summarized in Table 1. 1,1-Dibromo-2-phenyl-1-ethene was chosen as a model compound for this investigation.

As can be seen from Table 1, the reaction temperature plays a very important role in the reduction of 1,1-dibromo-2-phenyl-1-ethene with metallic zinc in hot water. It is evident that 1,1-dibromo-2-phenyl-1-ethene cannot be converted to acetophenone with zinc metal in water at $T \leq 200°C$ without any additives[18] and only a small quantity of product was generated in the temperature range 200 to 250°C. When the reaction temperature was at 275°C, the yield of acetophenone was improved significantly. The ratio of zinc metal to 1,1-dibromo-2-phenyl-1-ethene was also examined. The results showed that when the ratio of zinc to 1,1-dibromo-2-phenyl-1-ethene was less than 2:1, the reduction was not complete (entries 7 and 8, Table 1) and while the ratio equals or was more than 3:1, satisfactory results were achieved (entries 5, 9 and 10, Table 1). We also investigated the effect of reaction time. The experimental data indicate that the reaction was not completed when the reaction time was less than 3 h (entries 11 and 12, Table 1). However, no increase in yield was observed when the reaction time was prolonged. The optimized conditions for the reaction of 1,1-dibromo-2-phenyl-1-ethene with zinc metal in water were found to be 1,1-dibromo-2-phenyl-1-ethene (1 mmol), Zn (3 mmol), H_2O (10 mL) at 275°C for 4 h.

A variety of 2-aryl-1,1-dibromo-1-alkenes were subjected the new reaction sequence. Essentially, all compounds were successfully converted to the corresponding aromatic methyl ketones in good to excellent yields (except for entry 8, Table 2). The reaction was carried out simply by stirring 2-aryl-1,1-dibromo-1-alkenes with commercially available zinc powder in water under nitrogen without any other organics or additives at 275°C. The results are listed in Table 2. As is evident from Table 2, electron-donating groups (such as CH_3O, CH_3) or electron-withdrawing groups (such as CO_2Et, F, Cl) and their location on the

Table 1. Optimization reaction conditions for the conversion of 1,1-dibromo-2-phenyl-1-ethene to acetophenone with zinc metal in water[a]

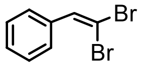
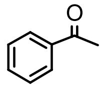
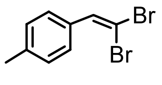
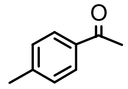
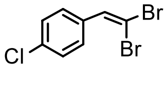
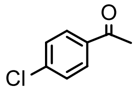
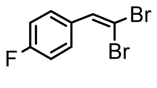
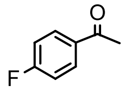
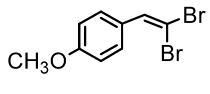
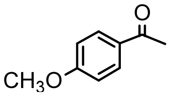
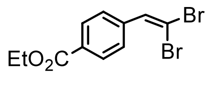
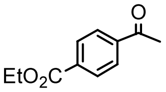
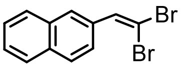
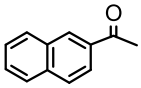
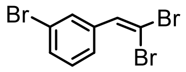
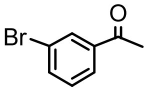
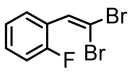
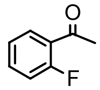
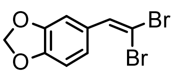
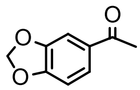
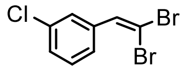
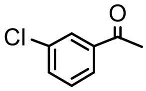
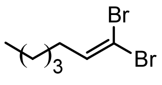
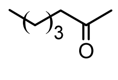
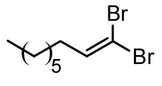
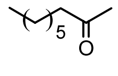
Entry	Zn:dibromide	Temp (°C)	Time (h)	Yield (%)[b]
1	3:1	175	4	0[c]
2	3:1	200	4	0
3	3:1	225	4	15
4	3:1	250	4	45
5	3:1	275	4	83
6	3:1	300	4	80
7	1:1	275	4	36
8	2:1	275	4	62
9	4:1	275	4	82
10	5:1	275	4	83
11	3:1	275	1	28
12	3:1	275	3	60
13	3:1	275	5	81
14	3:1	275	7	78

[a] Reaction conditions: 1,1-dibromo-2-phenyl-1-ethene (1.00 mmol), tap water (10 mL) in a high T/p batch reactor system.

[b] Isolated yields.

[c] Starting material 1,1-dibromo-2-phenyl-1-ethene (98%) was recovered.

Table 2. Conversion of 1,1-dibromo-1-alkenes to methyl ketones with zinc metal in near-critical water[a]

Entry	Dibromide	Ketone	Yield (%)[b]
1			82
2			84
3			78
4			75
5			68
6			70[c]
7			88
8			48[d]
9			79
10			66
11			81
12			76
13			80

[a] Reaction conditions: 1,1-dibromo-1-alkene (1.00 mmol), zinc metal (3.00 mmol), tap water (10 mL) in a high T/p batch reactor system at 275 °C for 4 h. [b] Isolated yields. [c] Ester hydrolysis product (11%) was isolated. [d] Along with 28% yield of debromination product.

aromatic ring had little effect on the reaction. However, a bromo group on the aromatic ring underwent reductive elimination in a competitive process, but a chloro group could tolerate the reaction conditions and remained unchanged. The reactivity of halogen atoms on the aromatic ring is Br>Cl, which is consistent with the expected reactivity and Poliakoff's experimental result.[19] Fortunately, 2-alkyl-1,1-dibromo-1-alkenes also react with zinc metal under reaction conditions to yield aliphatic methyl ketones (entries 11 and 12, Table 2). 1,1-Dichloro-1-alkenes were also examined, but they are far less reactive, probably due to the stronger carbon–chlorine bond.

Although a study of the detailed reaction mechanism has not been undertaken, the reaction presumably proceeds through the reduction of 1,1-dibromo-1-alkene by zinc to form the corresponding alkyne followed by hydration in the presence of $ZnBr_2$ formed in the reaction and under near-critical water reaction conditions to give the final methyl ketone.[20] In the case of phenylacetylene, an 89% yield of acetophenone was obtained from reactions with $ZnBr_2$ in near-critical water. Further investigation is currently underway.

General procedure for the reaction of 1,1-dibromo-1-alkenes with metallic zinc in near-critical water: 1,1-Dibromo-1-alkenes (1.00 mmol) and metallic zinc powder (196 mg, 3.00 mmol) were added to a high temperature and pressure stainless steel reactor charged with tap water (10 mL) under nitrogen with stirring. The reactor was heated at 275°C for 4 h. After cooling, ether (2×10 mL) was added to extract the products. The organic layer was dried with anhydrous sodium sulfate, the solvents were evaporated under reduced pressure, and the product was purified by flash chromatography to yield the methyl ketone.

CAUTION: This procedure involves a high temperature and pressure and must only be carried out in an apparatus with the appropriate pressure rating at the reaction temperature. The reaction should be performed in a safe place.

In conclusion, a novel, reliable, and practical two-step aldehyde homologation procedure for the preparation of methyl ketones has been developed, which involves the use of 1,1-dibromo-1-alkene as precursor and zinc metal as mediator in near-critical water. The method has the advantages of simple operation and the use of a cheap, nontoxic, nonflammable solvent.

Acknowledgements

We wish to thank the National Natural Science Foundation of China (No. 20172018), the Excellent Scientist Foundation of Anhui Province, China (No. 2001040), the Natural Science Foundation of the Education Department of Anhui Province, China (No. 2002kj254zd), the Scientific Research Foundation for the Returned Overseas Chinese Scholars, State Education Ministry, China (No. 2002247), and the Excellent Young Teachers Program of MOE, China (No. 2024) for financial support.

References

1. (a) Beugelmans, R.; Bois-Choussy, M.; Tang, Q. *J. Org. Chem.* **1987**, *52*, 3880–3883; (b) Summers, J. B.; Gunn, B. D.; Martin, J. G.; Martin, M. B.; Mazdiyashi, H.; Stewart, A. O.; Young, P. R.; Bouska, J. B.; Goetze, A. M.; Dyer, R. D.; Brooks, D. W.; Carter, G. W. *J. Med. Chem.* **1988**, *31*, 1960–1964; (c) Nakamura, S.; Oda, M.; Yasuda, H.; Toru, T. *Tetrahedron* **2001**, *57*, 8469–8480; (d) Baker, R. W.; Kyasnoor, R. V.; Sargent, M. V. *Tetrahedron Lett.* **1999**, *40*, 3475–3478; (e) Fleming, I.; Morgan, I. T.; Sarkar, A. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2749–2763.
2. (a) Gutsche, C. D. *Org. React.* **1954**, *8*, 364–429; (b) Cowell, G. W.; Ledwith, A. Q. *Q. Rev.* **1970**, *24*, 119–167; (c) Maruoka, K.; Concepcion, A. B.; Yamamoto, H. *Synlett* **1994**, 521–523.
3. (a) Hirao, T.; Misu, D.; Agawa, T. *J. Am. Chem. Soc.* **1985**, *107*, 7179–7181; (b) Hodgson, D. M.; Comina, P. J. *Synlett* **1994**, 663–664.
4. (a) Li, C. J. *Chem. Rev.* **1993**, *93*, 2023–2035; (b) Lubineau, A.; Auge, J.; Queneau, Y. *Synthesis* **1994**, 741–760; (c) Li, C. J. *Tetrahedron* **1996**, *52*, 5643–5668; (d) Li, C. J.; Chan, T. H. *Organic Reactions in Aqueous Media*; Wiley: New York, 1997; (e) Lindstrom, U. M. *Chem. Rev.* **2002**, *102*, 2751–2771.
5. (a) Franck, E. U. *J. Chem. Thermodyn.* **1987**, *19*, 225–242; (b) Marshall, W. L.; Franck, E. U. *J. Phys. Chem. Ref. Data* **1981**, *10*, 295–304; (c) Connolly, J. F. *J. Chem. Eng. Data* **1966**, *11*, 13–16.
6. (a) Siskin, M.; Katritzky, A. R. *Science* **1991**, *254*, 231–237; (b) Katritzky, A. R.; Allin, S. M. *Acc. Chem. Res.* **1996**, *29*, 399–406; (c) Siskin, M.; Katritzky, A. R. *Chem. Rev.* **2001**, *101*, 825–835; (d) Kuhlmann, B.; Arnett, E. M.; Siskin, M. *J. Org. Chem.* **1994**, *59*, 3098–3101; (e) Savage, P. E. *Chem. Rev.* **1999**, *99*, 603–621; (f) Akiya, N.; Savage, P. E. *Chem. Rev.* **2002**, *102*, 2725–2750.
7. (a) Boix, C.; Fuente, J. M.; Poliakoff, M. *New J. Chem.* **1999**, *23*, 641–643; (b) Boix, C.; Poliakoff, M. *Tetrahedron Lett.* **1999**, *40*, 4433–4436; (c) Lu, J.; Brown, J. S.; Liotta, C. L.; Eckert, C. A. *Chem. Commun.* **2001**, 665–666; (d) Katritzky, A. R.; Nichols, D. A.; Siskin, M.; Murugan, R.; Balasubramanian, M. *Chem. Rev.* **2001**, *101*, 837–892; (e) Zurer, P. *Chem. Eng. News* **2000**, *78*, 26–27.
8. (a) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, *13*, 3769–3772; (b) Ramirez, F.; Desai, N. B.; McKelvie, N. *J. Am. Chem. Soc.* **1962**, *84*, 1745–1747.
9. (a) Roush, W. R.; Koyama, K.; Curtin, M. L.; Moriarty, K. J. *J. Am. Chem. Soc.* **1996**, *118*, 7502–7512; (b) Roush, W. R.; Reilly, M. L.; Koyama, K.; Brown, B. B. *J. Org. Chem.* **1997**, *62*, 8708–8721.
10. (a) Shen, W.; Wang, L. *J. Org. Chem.* **1999**, *64*, 8873–8879; (b) Shen, W.; Wang, L. *Tetrahedron Lett.* **1998**, *39*, 7625–7628.
11. Ratovelomanana, V.; Hammoud, A.; Linstrumelle, G. *Tetrahedron Lett.* **1987**, *28*, 1649–1650.

12. (a) Minato, A.; Suzuki, K.; Tamao, K. *J. Am. Chem. Soc.* **1987**, *109*, 1257–1258; (b) Minato, A. *J. Org. Chem.* **1991**, *56*, 4052–4056.
13. (a) Uenishi, J.; Kawahama, R.; Yonemitsu, O.; Tsuji, J. *J. Org. Chem.* **1998**, *63*, 8965–8975; (b) Tietze, L. F.; Nöble, T.; Spescha, M. *J. Am. Chem. Soc.* **1998**, *120*, 8971–8977; (c) Uenishi, J.; Kawahama, R.; Yonemitsu, O.; Wada, A.; Ito, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 320–323.
14. McAlonan, H.; Montgomery, D.; Stevenson, P. *Tetrahedron Lett.* **1996**, *37*, 7151–7154.
15. Ranu, B. C.; Samanta, S.; Guchhait, S. K. *J. Org. Chem.* **2001**, *66*, 4102–4103.
16. Kunishima, M.; Hioki, K.; Ohara, T.; Tani, S. *J. Chem. Soc., Chem. Commun.* **1992**, 219–220.
17. Shen, W.; Kunzer, A. *Org. Lett.* **2002**, *4*, 1315–1317.
18. Hydrolyzation of 1,1-dibromo-1-alkenes to carboxylic acids with concentrated strong base (NaOH or KOH) at high temperature has been reported, see: Li, P.; Alper, H. *J. Org. Chem.* **1986**, *51*, 4354–4356.
19. Boix, C.; Poliakoff, M. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1487–1490.
20. Jerome, K. S.; Parsons, E. J. *Organometallics* **1993**, *12*, 2991–2993.