Tetrahedron Letters,Vol.28,No.29,pp 3299-3302,1987 0040-4039/87 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

A GENERAL METHOD FOR THE REDUCTIVE DECHLORINATION OF 4,4-DICHLOROCYCLOBUTENONES

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Summary: Exposure of 4,4-dichlorocyclobutenones to the action of zinc dust in ethanol containing 5 equiv each of AcOH and TMEDA results in smooth reductive dechlorination producing simple cyclobutenones.

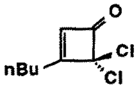
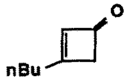
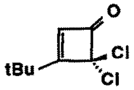
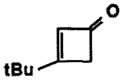
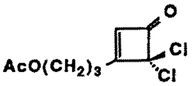
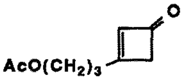
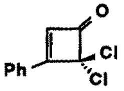
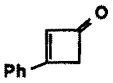
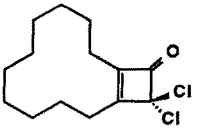
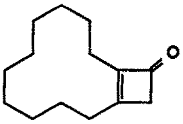
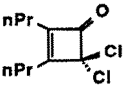
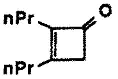
The development of efficient synthetic routes to cyclobutenones is a problem of considerable current interest, as these compounds can serve as versatile intermediates for the preparation of α,β-butenolides,[1] cyclopentenones,[1] and a variety of substituted cyclobutane derivatives. Recently we have shown that cyclobutenones also function as four-carbon annulation components in new routes to eight-membered carbocycles[2] and highly substituted aromatic compounds.[3,4] In connection with these annulation studies we required convenient access to simple 3-alkyl and 2,3-dialkylcyclobutenone derivatives. In principle, a variety of cyclobutenones should be available via the direct [2+2] cycloaddition of ketenes to alkynes, but unfortunately the negligible ketenophilicity of unactivated acetylenes renders this simple approach impractical,[5] with the exception of reactions employing highly reactive ketenes such as chlorocyanoketene[4a] and dichloroketene.[6] Till now non-halogenated cyclobutenones consequently have been prepared by indirect routes, involving for example the addition of $H_2C=C=O$ to highly ketenophilic heterosubstituted olefins or acetylenes, followed by subsequent functional group manipulations to convert the resulting cycloadducts to the desired cyclobutenone derivatives.

An alternative and much more attractive approach to simple cyclobutenones can be envisioned which would proceed via readily available 4,4-dichlorocyclobutenone derivatives. Unfortunately, previous studies by Hassner and Dillon[6b] imply that this route should not be feasible. Although it is well established that both zinc metal and tri-*n*-butyltin hydride can effect the smooth dechlorination of 4,4-dichlorocyclobutanones, these reagents were found to be ineffective for the reduction of the corresponding unsaturated compounds. Hassner and Dillon have attributed this reluctance of dichlorocyclobutenones to undergo reduction to the difficulty associated with generating oxyanion or radical intermediates that possess cyclobutadienoid antiaromatic character.

We have now found that under carefully controlled conditions the reductive dechlorination of 4,4-dichlorocyclobutenones is in fact a feasible and efficient process. In combination with the [2+2] cycloaddition of alkynes with dichloroketene,[6] this new procedure provides a general two-step protocol for the preparation of a variety of cyclobutenones. Table I summarizes our results.

The requisite dichloroketene cycloadditions generally proceed smoothly employing the standard procedure of Hassner and Dillon.[6] However, we have observed that reactions

Table I. Synthesis of Cyclobutenones from Alkynes

Case	Alkyne	Cyclobutenones		Isolated Yield[a]		
				Dichloroketene Addition[b]	Reductive Dechlorination[c]	Overall Yield
1	nBu-C≡CH	 1	 2	65-77	84	55-65
2	tBu-C≡CH	 3	 4[d]	80	68	54
3	$AcO(CH_2)_3$·C≡CH	 5	 6	80	70	56
4	Ph-C≡CH	 7	 8[e]	75-87	88	66-77
5	Cyclododecyne[f]	 9	 10			75
6	nPr-C≡C-nPr	 11[g]	 12			73

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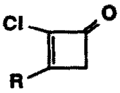
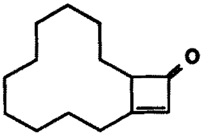
[a] Isolated yields of products purified (>95%) by distillation or chromatography. Infrared, ^1H NMR, ^{13}C NMR, and mass spectra were fully consistent with the assigned structures. [b] Dichloroketene additions[6] were carried out by slowly adding 2-3 equiv of CCl_3COCl and 1-4 equiv of $POCl_3$ to a mixture of alkyne and 3-6 equiv of Zn(Cu) in Et_2O over 2-11 h and then stirring the resulting mixtures for 2-15 h further at 10° (cases 5 and 6), 25° (cases 2 and 3), or 50° (cases 1 and 4). [c] Reductive dechlorinations were accomplished by stirring the dichlorocyclobutenones with 20 equiv of zinc dust (Zn-Ag in case 4) in EtOH containing 5 equiv each of TMEDA and AcOH at 25° for 1-5 h. [d] For a previous synthesis, see ref. 1. [e] For a previous synthesis, see ref. 6b. [f] Nozaki, H.; Noyori, R. J. Org. Chem. 1965, 30, 1652. [g] For the previous synthesis of this compound by a different route, see Breslow, R.; Altman, L. J.; Krebs, A.; Mohacsi, E.; Murata, I.; Peterson, R. A.; Posner, J. J. Am. Chem. Soc. 1965, 87, 1326.

involving *disubstituted* acetylenes lead to the desired 4,4-dichlorocyclobutenones (e.g. 9 and 11) contaminated with varying amounts of isomeric 2,4-dichloro derivatives, apparently generated via cine rearrangement[7] of the initial ketene adducts. Fortunately we found that the formation of these byproducts can be suppressed (to <10%) simply by carrying out the cycloaddition at temperatures between 10 and 15°C.

The reduction of dichlorocyclobutenones obtained from monosubstituted acetylenes was examined first. Under conventional reductive dechlorination conditions (20 equiv of zinc dust, AcOH, 25 or 50°C) the desired products were obtained contaminated with significant quantities of 2-chloro-3-alkylcyclobutenones. For example, reductive dechlorination of 1 using the standard procedure produced the desired enone 2 (48%) as well as the α-chloro derivative 13 (29% yield); no reduction of 13 was detected upon further treatment with excess zinc dust in AcOH at 50°C. In other cases examined the conventional reductive dechlorination procedure also furnished the desired cyclobutenones in low (35-41%) yield contaminated with significant amounts of partially reduced byproducts.



13 R = nBu
14 R = tBu



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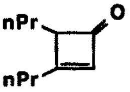
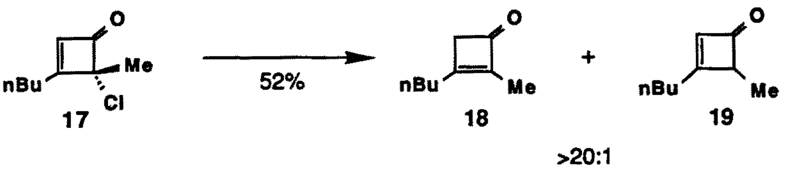


16

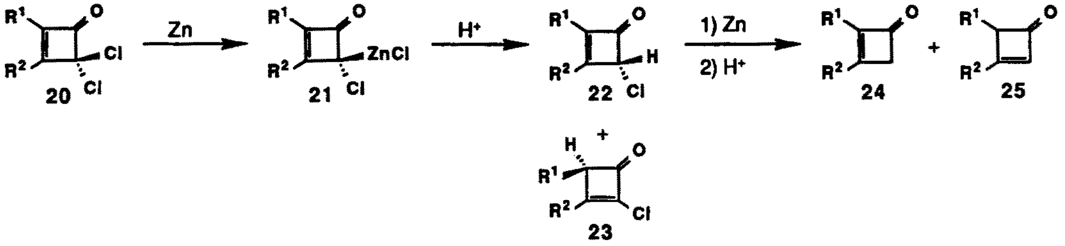
A systematic investigation of conditions for effecting the reductive dechlorination reaction revealed that the desired transformation can be accomplished cleanly provided that the reduction is carried out at room temperature in alcoholic solvents (preferably EtOH) in the presence of 5 equiv of AcOH and 5 equiv of a tertiary amine (preferably TMEDA). Using this procedure 1 could be reduced to 2 in 84% yield, and none of the α-chloro enone 13 was observed to form under these conditions. Reduction of the *t*-butyl derivative 3 was also accomplished smoothly (68% yield; only 35% using Zn-AcOH), although in this case the α-chloro side product 14 was also obtained in 11% yield (vide infra).

The reductive dechlorination of dichloroketene adducts generated from disubstituted acetylenes was performed without purification of the intermediate 4,4-dichlorocyclobutenones because of the sensitivity of these compounds to cine rearrangement. Reduction of 9 and 11 using our new procedure generated the desired cyclobutenones cleanly in excellent overall yield. In contrast to these results, reductive dechlorination under "classic" conditions led to the formation of 1:1 mixtures of the desired cyclobutenones and the α,β-enone isomers 15 and 16. It is significant to note that stirring 15 in ethanol containing AcOH and TMEDA resulted in isomerization to the more substituted isomer 10, but no rearrangement was observed to take place in acetic acid solution alone.

Preliminary studies indicate that 4-alkyl-4-chlorocyclobutenones also undergo reductive dechlorination smoothly using our procedure. Thus, exposure of 17[8] to the action of Zn-AcOH-TMEDA in EtOH at 25°C for 8 h produced the cyclobutenones 18 and 19 (>20:1) in 52% yield after purification by chromatography.



Although at this time the detailed course of the reductive dechlorination reaction is a matter for conjecture, the following scheme offers one reasonable mechanistic hypothesis.



Oxidative addition of **20** to Zn could generate the organozinc derivative **21** without proceeding through a high-energy antiaromatic intermediate. Rapid S_E2 or S_E2' protonolysis would then provide the monochloro derivatives **22** and **23**, of which only **22** can apparently undergo further direct reduction. In the presence of a tertiary amine, however, interconversion of **22** and **23** takes place, either via isomerization to the deconjugated β,γ-isomer, or alternatively, by addition-elimination of the TMEDA. This rearrangement is not possible when $R^2 = t$-butyl, thus accounting for the isolation of the byproduct 14 in case 2. Finally, we note that the absence of α-chloro side products (23) in the reduction of dialkyl-substituted cyclobutenones can be explained if protonolysis in these cases occurs predominantly via the S_E2 pathway due to steric factors.

Acknowledgment. We thank the National Institutes of Health for generous financial support.

References and Notes

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2. Danheiser, R.L.; Gee, S.K.; Sard, H. *J. Am. Chem. Soc*. 1982, *104*, 7670.
3. (a) Danheiser, R.L.; Gee, S.K. *J. Org. Chem*. 1984, *49*, 1672; (b) Danheiser, R.L.; Gee, S.K.; Perez, J.J. *J. Am. Chem. Soc*. 1986, *108*, 806; and references cited therein.
4. See also: (a) Fishbein, P.L.; Moore, H.W. *J. Org. Chem*. 1985, *50*, 3226; (b) Liebeskind, L.S.; Iyer, S.; Jewell, C.F. *Ibid*. 1986, *51*, 3065; (c) Perri, S.T.; Foland, L.D.; Decker, O.H.W.; Moore, H.W. *Ibid*. 1986, *51*, 3068; (d) Moore, H.W.; Decker, O.H.W. *Chem. Rev*. 1986, *86*, 821.
5. Ghosez and coworkers have reported that several cyclobutenones can be prepared via the addition of keteniminium salts to alkynes (followed by hydrolysis).[1] However, all of our attempts to accomplish the addition of keteniminium salts to monoalkyl and dialkyl acetylenes according to this procedure have thus far been unsuccessful.
6. (a) Hassner, A.; Dillon, J. *Synthesis*, 1979, 689; (b) Hassner, A.; Dillon, J.L. *J. Org. Chem*. 1983, *48*, 3382; (c) Danheiser, R.L.; Sard, H. *Tetrahedron Lett*. 1983, *24*,
7. For examples of related cine rearrangements, see: Roberts, J.D.; Kline, E.B.; Simmons, H.E. *J. Am. Chem. Soc*. 1953, *75*, 4765. Caserio, M.C.; Simmons, H.E.; Johnson, A.E.; Roberts, J.D. *J. Am. Chem. Soc*. 1960, *82*, 3102.
8. Cyclobutenone 15 was prepared by addition of Me(Cl)C=C=O (from 2-chloropropionyl chloride and Et_3N) to ethoxyacetylene (68% yield), followed by treatment with n-BuLi (Et_2O, -78°) and hydrolysis (1N HCl, 25°C, 1 h; 93% yield). We thank Dr. Kollol Pal for carrying out these experiments.

Note added in proof: For a closely related study, see Ammann, A.A.; Rey, M.; Dreiding, A.S. *Helv. Chim. Acta* 1987, *70*, 321.

(Received in USA 16 April 1987)