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An expedient synthesis of *cis/trans*-1,3-disubstituted cyclobutanols

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ABSTRACT

A two-step procedure is described to access 3-alkoxycyclobutanones from chloroacetyl chloride utilizing a step-wise [2+2] ketene cycloaddition followed by catalytic hydrogenation to reduce the α-chlorine in a single reaction sequence. The resulting cyclobutanones can be readily converted into a variety of *cis* or *trans*-1,3-disubstituted aminocyclobutanols and cyclobutanediols.

The cyclobutanone and corresponding cyclobutanol rings are important constituents in many natural products, often possessing novel and/or important bioactivities.[1] As such, the synthesis of these highly strained compounds has been a focus of the synthetic community for many years. Numerous methods for the construction of the cyclobutanone framework have been developed over the years[2] including but not limited to: photolytic[3] and thermolytic[4] [2+2] cycloaddition processes, ring contraction reactions,[5] ring expansion of cyclopropanes,[6] and radical processes.[7]

During work on a drug development project we required a rapid and cost effective means of accessing *N*-Boc-protected *trans*-3-aminocyclobutanol **1a** (Fig. 1). Previous work relied on a cyclodialkylation of tosylmethyl isocyanide (TOSMIC) with epichlorohydrin to assemble the cyclobutane framework. Unfortunately several issues including overall length, intermediate stability, and cost of goods made the route untenable.

A survey of the literature, taking into account overall route efficiency/simplicity and material costs, led us to investigate the thermal [2+2] cycloaddition with chloroketene.[8] A [2+2] cycloaddition of chloroketene and electron-rich olefins would assemble the cyclobutanone scaffold **5** rapidly and efficiently, while also providing functional group handles for further manipulation (Scheme 1). Our strategy was to convert the carbonyl of cyclobutanone **5a–i** into either the amine or alcohol of **1** and, therefore, the X-substituent could be either the alcohol or amine. Despite the disjointed and

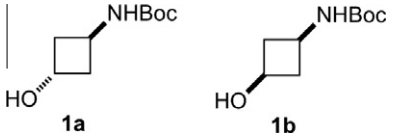

Figure 1.

sometimes conflicting reports in the literature as to the reactivity of ketenophiles with chloroketene, we undertook a systematic screen to better map out their reactivity profile (Scheme 1). Entries a–d were the most appealing substrates as either the alcohol (entries a and b) or amine (entries c and d) functionality could be installed directly during the cycloaddition and the reagents were cheap, easily handled materials. Unfortunately, the lower reactivity of the vinyl ester compounds failed to give any reaction at all (entries a, b),[9] and the vinyl amides provided only the acyclic acylated products **4c/d** (entries c and d).[10] Benzyl vinyl ether (entry e) was also an attractive substrate due to the mild conditions needed to reveal the alcohol functionality, but it provided poor isolated yields and a messy reaction profile. The reaction of chloroketene with the extremely reactive dimethyl ketene acetal provided only the product of C-acylation (entry f). Finally, despite the anticipated difficulty in the cleavage of alkyl ethers, cycloadditions with commercially available alkyl vinyl ethers (entries g–i) were studied and the use of *i*-butyl or *t*-butyl vinyl ether (*i*-BVE and *t*-BVE, respectively) were found to be more successful than *n*-butyl vinyl ether (entry g vs h and i). The greater selectivity and higher yields

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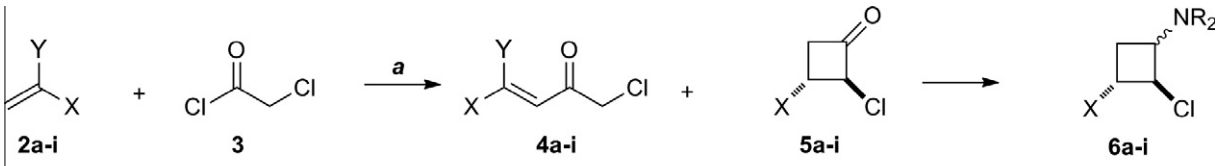


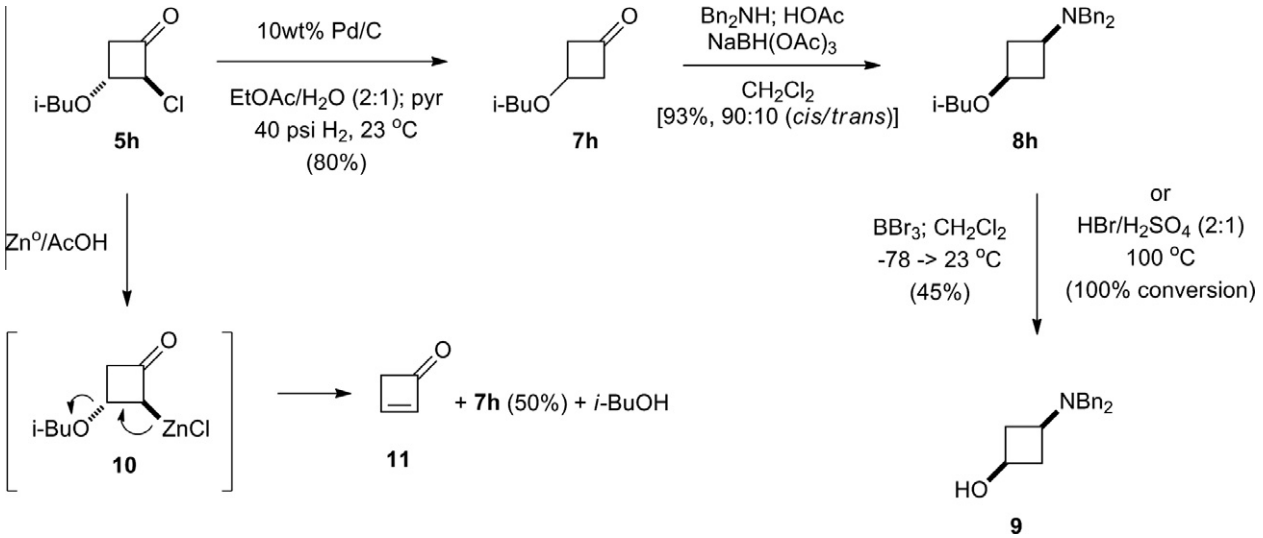
Entry	X	Y	Yields[b]	Ratio(4:5)
a	AcO	H	0	0
b	PhC(O)O	H	0	0
c	NMeAc[c]	H	n.d.	1:0
d	N(CHO)Boc	H	n.d.	1:0
e	BnO	H	46%	1:>20
f	OMe	OMe	n.d.	1:0
g	*n*-BuO	H	50-60%[d]	1:2
h	*i*-BuO	H	60-70%	1:8-10
i	*t*-BuO	H	80-90%	1:>20

Scheme 1. Ketenophile screen of the 2+2 cycloaddition. [a]Typical conditions: NMM (1.5 eq) added via syringe pump over 30 min to a solution of enol ether/enamide (1 eq) and chloroacetyl chloride (1.05 eq) in TBME (7 vol) at 50 °c. [b]Yield referes to the desired cyclobutanone. [c]Reaction performed under "typical condition" as well as inverse addition in which a solution of chloroacetyl chloride in TBME was added to a solution of enamide and NMM giving identical results. [d]Reaction performed under inverse addition of chloroacetyl chloride to a solution of enol ether and NMM. Under "typical conditions" acylation of the enol ether by the acid chloride was observed.

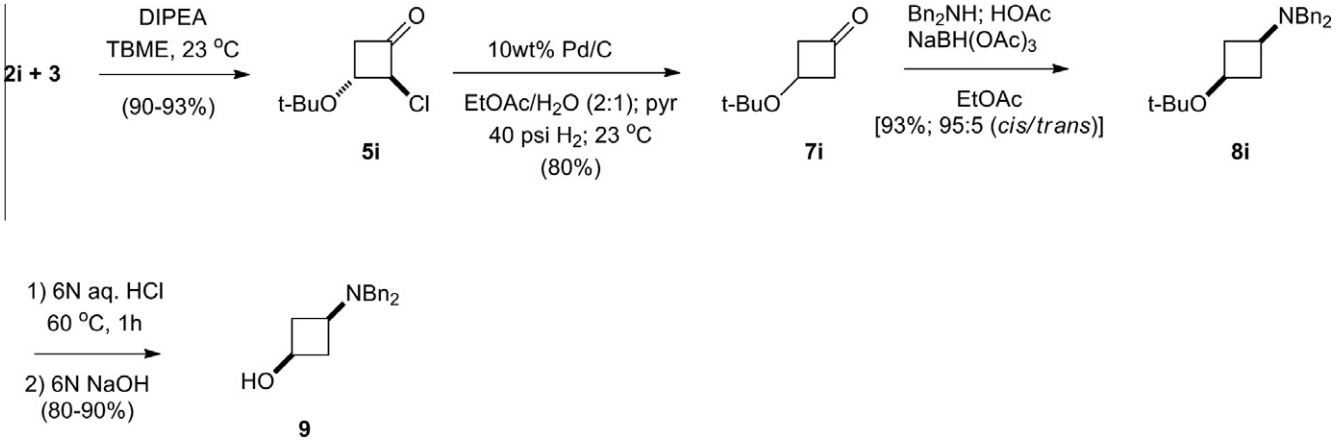
(of **5** vs **4**) observed with increased steric bulk on the vinyl ethers may be rationalized by the greater cation stability (via an enhancement in oxonium stability through hyperconjugation) in going from a 1° to 3° alkyl ether.[11] In general, the crude cycloadducts (**5g–i**), formed as predominantly the *trans* isomer,[11,12] and could be carried on without further purification.[13] However, in order for the [2+2] strategy to remain a viable route, two challenges remained: an efficient means of chlorine removal and the ability to cleave the alkyl ether selectively.

Removal of the C2-chlorine of cylcobutanone **5g–i** became our first of the challenges. Dechlorination of 2-chlorocyclobutanones possessing a C3-leaving group with Zn°/AcOH has been reported, however, mediocre yields are typically obtained.[14] The poor yields most likely arise from the competing Boord reaction,[15] resulting in formation of the volatile and unstable cyclobutenone **11**. Additionally, the use of stoichiometric Zn° made this process less desirable on scale. In our hands, treatment of **5h** with Zn°/AcOH provided only a ~50% yield of desired cyclobutanone **7h** with large amounts of *i*-butanol observed by GC (Scheme 2). Instead, attention was turned to catalytic hydrogenolysis of **5h**.[16] A preliminary solvent and base screen was performed and the optimal conditions ($EtOAc/H_2O$ (2:1, 20 vol), 3 equiv pyridine, 10 wt % Pd/C at 40 psi H_2) provided an 80% yield of cyclobutanone **7h** on 30 g scale (Scheme 2). Pyridine and its derivatives provided the best yields and conversion rates, while inorganic bases, triethylamine, and other basic 3° alkyl amines provided inferior results. Other solvents gave poor to moderate conversions. The need for water in the mixture is unclear at this point.

With conditions for effecting the removal of the chlorine in hand, we focused next on the alkyl ether cleavage. A variety of classical ether cleavage conditions[17] were examined, but a complete lack of regioselectivity (cyclobutane C–O bond vs *i*-butyl C–O bond cleavage) plagued both compounds **5h** and **7h**. The desired *i*-butyl ether C–O cleavage was eventually realized by treating *N,N*-



Scheme 2. Catalytic hydrogenolysis and acid promoted ether cleavage.



Scheme 3. Synthesis of cyclobutylamine **9** from *t*-BVE.

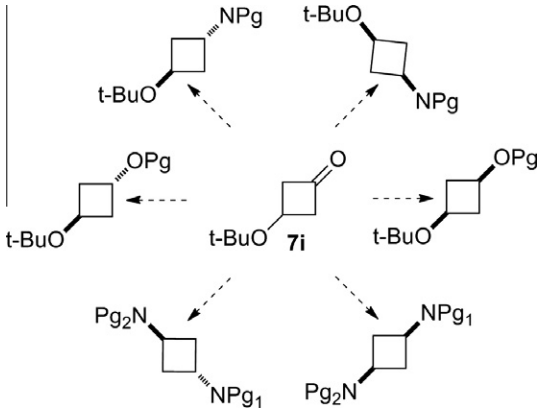


Figure 2. Functional group elaboration of cyclobutanone **7i**.

dibenzylamine **8h**, formed by reductive amination of **7h** with dibenzylamine, with strongly Lewis acidic reagents to give amino cyclobutanol **9** with no decrease in the *cis*/*trans* ratio (Scheme 2).

Despite the success utilizing *i*-BVE, the cleaner and higher yielding reaction profile for the cycloaddition of *t*-BVE (Scheme 1) and the more easily cleaved *t*-butyl group led us to pursue its use instead. Although the original patent literature[8b] claimed a need for slow addition of NMM at 50 °C over 2 h, followed by a 4 h hold, in situ monitoring with ReactIR showed that the [2+2] cycloaddition between **2i** and **3** was reagent addition controlled and upon complete addition of the NMM the reaction was complete.[18] Ultimately, it was found that the addition time of base could be shortened to 0.5 h without detriment to yield. Additionally, the patent claimed[8b] that the amine base must have a pK_a = 6–8 (NMM has a pK_a = 7.4), but a base screen was undertaken that ultimately showed *i*-Pr$_2$NEt (pK_a = 10.5) gave **5i** in yields as good if not better than NMM (typically 90–93% crude yield with 95% purity) (Scheme 3).[19] Preliminary scoping studies using Design of Experiment also found that elevated temperatures are not required for high yields. In fact, the reaction could be run at 0 °C with no decrease in yield.[20] Following the cycloaddition, **5i** was subjected to the hydrogenation conditions developed for cyclobutanone **5h** and provided the *des*-chloro **7i** in 80–85% overall yield from *t*-BVE (Scheme 3). Conversion of **7i** into the *N,N*-dibenzylcyclobutylamine **8i** via reductive amination followed by treatment with 6 N aq HCl efficiently led to the isolation of the 3-*N,N*-dibenzylaminocyclobutanol **9** in excellent yields (Scheme 3).

At this point, a four-step sequence in which all of the route could be telescoped and/or utilize crude material had been developed to deliver a suitably protected *cis*-3-aminocyclobutanol in high yields. The intermediates could be readily transformed into the desired *trans*-**1a** through inversion with KOAc/DMF/130 °C, debenzylation, and Boc protection. In addition, cyclobutanone **7i** serves as an excellent starting point for elaboration into a variety of 1,3-disubstituted cyclobutanol structures which find use throughout natural product synthesis and pharmaceutical development (Fig. 2).

In summary, 3-*t*-butoxycyclobutanone **7i** can be obtained in high yields and purity from *t*-butyl vinyl ether and chloroacetyl chloride in a one-pot, two step sequence which is amenable to further manipulation to access the *trans*-**1a** isomer as well. The cyclobutanone core with all the necessary heteratoms present for further elaboration into *cis*/*trans*-3-aminocyclobutanols as well as a variety of other 1,3-disubstituted cyclobutanes is readily available on gram to kilogram scale from inexpensive starting materials.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.06.027.

References and notes

1. (a) Thomas, A. F.; Bassiere, Y. In *The Total Synthesis of Natural Products*; ApSimon, J. W., Ed.; Wiley: New York, 1988; Vol. 7, pp 275–454; (b) Devon, T. K.; Scott, A. I. In *Handbook of Naturally Occurring Compounds Terpenes*; Academic Press: New York, 1972; Vol. 2,
2. (a) Salaün, J. *Sci. Synth.* **2005**, *26*, 557–606; (b) Trost, B. M. In *Strain and Reactivity: Partner for Selective Synthesis in Small Ring Compounds in Organic Synthesis I*; de Meijere, A., Ed.; Springer: Berlin, 1986; pp 3–82.
3. For examples see: (a) Eaton, P. E. *J. Am. Chem. Soc.* **1962**, *84*, 2454–2455; (b) Corey, E. J.; Bass, J. D.; LeMahieu, R.; Mitra, R. B. *J. Am. Chem. Soc.* **1964**, *86*, 5570–5583; (c) Corey, E. J.; Mitra, R. B.; Uda, H. *J. Am. Chem. Soc.* **1964**, *86*, 485–492; (d) Alibés, R.; Bourdelande, J. L.; Font, J.; Gregori, A.; Parella, T. *Tetrahedron* **1996**, *52*, 1267–1278; (e) Wagner, P. J.; McMahon, K. *J. Am. Chem. Soc.* **1994**, *116*, 10827–10828; (f) Tanaka, K.; Toda, F. *J. Chem. Soc., Perkin Trans. I* **1992**, 943–944.
4. For examples with ketene, see: (a) Danheiser, R. L.; Casebier, D. S.; Loebach, J. L. *Tetrahedron Lett.* **1992**, *33*, 1149–1152; (b) Pittol, C. A.; Roberts, S. M.; Sutton, P. W.; Williams, J. O. *J. Chem. Soc., Chem. Commun.* **1994**, 803–804; (c) Ganz, I.; Kunz, H. *Synthesis* **1994**, 1353–1358; (d) de Azevedo, M. B. M.; Greene, A. E. *J. Org. Chem.* **1995**, *60*, 4940–4942; For cycloadditions promoted with Lewis acids, see: (e) Ahmad, S. *Tetrahedron Lett.* **1991**, *32*, 6997–7000; (f) Narasaka, K.; Hayashi, Y.; Shimadzu, H.; Niihata, S. *J. Am. Chem. Soc.* **1992**, *114*, 8869–8885; (g) Narasaka, K.; Hayashi, K.; Hayashi, Y. *Tetrahedron* **1994**, *50*, 4529–4542; (h) Seebach, D.; Dahinden, R.; Marti, R. E.; Beck, A. K.; Plattner, D. A.; Kühnle, F. N. M. *J. Org. Chem.* **1995**, *60*, 1788–1799; For examples with keteniminium ions, see: (i) O'Brien, J. M.; Kingsbury, J. S. *J. Org. Chem.* **2011**, *76*, 1662–1672; (j) Marchand-Brynaert, J.; Ghosez, L. *J. Am. Chem. Soc.* **1972**, *94*, 2870–2872; For a review on keteniminium 2+2 reactions see: (k) Snider, B. B. *Chem. Rev.* **1988**, *88*, 793–811.

5. (a) Malanga, C.; Menicagli, R.; Pecunioso, A.; Lardicci, L. *Gazz. Chim. Ital.* **1991**, *121*, 17–20; (b) Ito, H.; Taguchi, T.; Hanzawa, Y. *Tetrahedron Lett.* **1993**, *34*, 7639–7640.
6. Nemoto, H.; Fukumoto, K. *Synlett* **1997**, 863–875.
7. (a) Paquette, L. A.; Sugimura, T. *J. Am. Chem. Soc.* **1986**, *108*, 3841–3842; (b) Kocovsky, P.; Srogl, J. *J. Org. Chem.* **1992**, *57*, 4565–4567; (c) Weignes, K.; Schmidbauer, S. B.; Schick, H. *Chem. Ber.* **1994**, *127*, 1305–1309; (d) Kocozsky, P.; Srogl, J.; Pour, M.; Gogoll, A. *J. Am. Chem. Soc.* **1994**, *116*, 186–197.
8. (a) Tidwell, T. T. *Eur. J. Org. Chem.* **2006**, 563–576. and references cited therein; (b) Matsushita, S.; Shimizu, I.; Toyoda, H.; Tanaka, A. US Patent No. US6331653 B1, 2001.
9. The successful use of vinyl acetate in the [2+2] cycloaddition with trichloroacetyl chloride and Zn°/Cu°-couple has previously been demonstrated, see: Danheiser, R. L.; Savariar, S.; Cha, D. *Org. Synth.* **1993**, *Coll. Vol. 8*, 82–87. however the large amounts of Zn° required for the cycloaddition and concomitant dechlorination reactions in addition to very low yields for the dechlorination made this route undesirable.
10. The β-keto *N*-acyliminium intermediates formed in entries c and d rapidly deprotonate to give acylated products **4c/d**. These results coupled with the results from entries e–i, Table 1 indicate that a step-wise mechanism is most likely operative. Separate experiments in which isolated **5** was resubjected to the reaction conditions failed to provide any of the acyclic acylated material **4**.
11. Sieja, J. B. *J. Am. Chem. Soc.* **1971**, *93*, 130–136.
12. Stirring the reaction mixture with a slight excess of base leads to complete epimerization to the trans isomer in <1 h; storing the cycloadducts neat leads to complete epimerization over time (~1 week).
13. Acyclic enone **4e–g** was purged following chlorine removal (vida infra) by washing with 3 N HCl.
14. For examples of 2,2-dichlorocyclobutanones with no C3 leaving group see: (a) Baldwin, J.; Leber, P. A.; Powers, D. C. *J. Am. Chem. Soc.* **2006**, *128*, 10020–10021; (b) Wrobleski, M. L.; Reichard, G. A.; Paliwal, S.; Shah, S.; Tsui, H.-D.; Duffy, R. A.; Lachowicz, J. E.; Morgan, C. A.; Varty, G. B.; Shih, N.-Y. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3859–3863; (c) Trost, B. M.; Xie, J. *J. Am. Chem. Soc.* **2006**, *128*, 6044–6045; (d) Verniest, G.; Colpaert, J.; Toernroos, K. W.; De Kimpe, N. *J. Org. Chem.* **2005**, *70*, 4549–4552; (e) Neudeck, H.; Brinker, U. H. *Tetrahedron Lett.* **2005**, *46*, 1893–1895; For examples of dechlorination with cyclobutanones possessing a C3 leaving group providing high yields see: (f) Darses, B.; Greene, A. E.; Coote, S. C.; Poisson, J.-F. *Org. Lett.* **2008**, *10*, 821–824; (g) Ferguson, A. C.; Adlington, R. M.; Martyres, D. H.; Rutledge, P. J.; Cowley, A.; Baldwin, J. E. *Tetrahedron* **2003**, *59*, 8233–8243; (h) Ambrosio, J. C. L.; Santos, R. H. De A.; Correia, C. R. D. *J. Braz. Chem. Soc.* **2003**, *14*, 27–38; For examples of low yielding dechlorination of cyclobutanones possessing a C3 leaving group see: (i) Wang, C.; Zhen, Z.; Zhao, J.; Dowd, P. *Synth. Commun.* **1999**, *29*, 631–643; (j) Dehmlow, E. V.; Bueker, S. *Chem. Ber.* **1993**, *126*, 2759–2763; (k) Redlich, H.; Lenfers, J. B.; Kopf, J. *Angew. Chem.* **1989**, *101*, 764–765.
15. Swallen, L. C.; Boord, C. E. *J. Am. Chem. Soc.* **1930**, *52*, 651–660.
16. See for example: Takuma, Y.; Kasuga, Y.; Watanabe, Naoyuki; Lin, Shu-Su (Mitsubishi Chemical Corp., Japan) Jpn. Patent JP 2002249454 A, 2002.
17. (a) Bhar, S.; Ranu, B. C. *Org. Prep. Proced. Int.* **1996**, *28*, 371–409; (b) Harada, T.; Kita, K.; Oku, A. *Tetrahedron Lett.* **1982**, *23*, 681–684; (c) Ganem, B.; Small, V. R., Jr. *J. Org. Chem.* **1974**, *39*, 3728–3730; (d) Bhar, S.; Ranu, B. C. *J. Org. Chem.* **1995**, *60*, 745–747; (e) Gupta, M. K.; Reddy, B. V. S.; Reddy, K.; Yadav, J. S. *Tetrahedron Lett.* **2005**, *46*, 8493–8495.
18. Results were general for any reaction utilizing chloroacetyl chloride, an amine base, and an alkyl vinyl ether.
19. Yields based on solution assays. Reaction profile by GC and ^{1}H NMR showed slightly higher impurity profiles compared to reactions using NMM as the base. Other bases screened include Et_3N, *N*,*N*,*N*′,*N*′-tetramethyl-1,3-propanediamine, pyridine, Et_3N/pyridine, DABCO, (−)-Sparteine, and DBU.
20. Yields were found to be comparable, but the cis/trans ratio favored the kinetic product by ~60:40. See Ref. 4.