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Elimination versus Ring Opening: A Convergent Route to Alkylidene-Cyclobutanes

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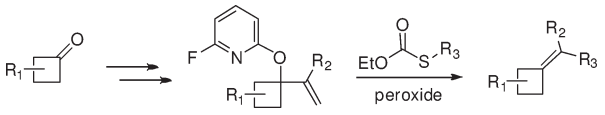
ABSTRACT



Functionalized alkylidene-cyclobutanes have been prepared from 2-fluoropyridinyl-6-oxy precursors derived from vinyl cyclobutanols by a radical addition−elimination process. A wide range of functional groups is tolerated, and the alkylidene-cyclobutanes can be further elaborated into cyclopentanones. The limitation of this approach resides in the competition with opening of the cyclobutane ring.

Alkylidene-cyclobutanes are strained structures that exhibit enhanced reactivity and a strong propensity for undergoing various rearrangements.[1] Yet, as a class, they have not attracted the attention they deserve, and their use in synthetic planning has been relatively limited. One likely reason is the dearth of convenient methods for their synthesis. [2 + 2]-Cycloadditions of allenes,[2] Wittig and related reactions on cyclobutanones,[3] and a few specialized transition metal catalyzed transformations[4] represent the main routes to these structures. In view of the considerable but still latent synthetic potential of alkylidene-cyclobutanes, we report herein an alternative approach which complements existing routes, and which offers some advantages in terms of convergence and functional group tolerance.

As a part of our ongoing exploration of the degenerative radical addition of xanthates,[5] we recently described the use of 2-fluoropyridine derivatives to convert alcohols into leaving groups in a radical sense.[6a−c] This approach was

(1) (a) Boontanonda, P.; Grigg, R. *J. Chem. Soc., Chem. Commun.* **1977**, 583. (b) Jiang, M.; Shi, M. *Org. Lett.* **2008**, *10*, 2239. (c) Crépin, D.; Dawick, J; Aïssa, C. *Angew. Chem., Int. Ed.* **2010**, *49*, 620. (d) Sun, K.; Liu, S.; Bec, P. M.; Driver, T. G. *Angew. Chem., Int. Ed.* **2011**, *50*, 1702.

(2) Recent examples of thermal [2 + 2]-cycloaddition of allenes: (a) Ohno, H.; Mizutani, T.; Kadoh, Y.; Miyamura, K.; Tanaka, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 5113. (b) Ohno, H.; Mizutani, T.; Kadoh, Y.; Aso, A.; Miyamura, K.; Fujii, N.; Tanaka, T. *J. Org. Chem.* **2007**, *72*, 4378.

(3) For recent exemple of synthesis of alkylidene-cyclobutanes from cyclobutanones using Wittig and related approaches, see: (a) Pearson, W. H.; Fang, W.-K. *J. Org. Chem.* **2000**, *65*, 7158. (b) Choi, S.-Y.; Horner, J. H.; Newcomb, M. *J. Org. Chem.* **2000**, *65*, 4447. (c) Clayden, J.; Johnson, P.; Pink, J. H. *J. Chem. Soc., Perkin Trans. 1* **2001**, 371. (d) Binot, G.; Zard, S. Z. *Tetrahedron Lett.* **2003**, *44*, 7703. (e) Danappe, S.; Pal, A.; Alexandre, C.; Aubertin, A.-M.; Bourgougnon, N.; Huet, F. *Tetrahedron* **2005**, *61*, 5782. (f) Suhrada, C. P.; Selcuki, C.; Nendel, M.; Cannizzaro, C.; Houk, K. N.; Rissing, P.-J.; Baumann, D.; Hasselmann, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 3548. (g) Kawashima, T.; Kashima, H.; Wakasugi, D.; Satoh, T. *Tetrahedron Lett.* **2005**, *46*, 3767. (h) Bernard, A. M.; Frongia, A.; Ollivier, J.; Piras, P. P.; Secci, F.; Spiga, M. *Tetrahedron* **2007**, *63*, 4968. (i) Reisman, S. E.; Ready, J. M.; Weiss, M. M.; Hasuoka, A.; Hirata, M.; Tamaki, K.; Ovaska, T. V.; Smith, C. J.; Wood, J. L. *J. Am. Chem. Soc.* **2008**, *130*, 2087. (j) Yu, W.; Williams, L.; Malveaux, E.; Camp, V. M.; Olson, J. J.; Goodman, M. M. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1264. (k) Jai, W. S.; Hee, J. K.; Byoung, S. L.; Katzenellenbogen, J. A.; Dae, Y. C. *J. Org. Chem.* **2008**, *73*, 715. (l) Satoh, T.; Awata, Y.; Ogata, S.; Sugiyama, S.; Tanaka, M.; Tori, M. *Tetrahedron Lett.* **2009**, *50*, 1961. (m) Felluga, F.; Pitacco, G.; Valentin, E.; Venneri, C. D.; Ghelfi, F.; Roncaglia, F. *Tetrahedron: Asymmetry* **2010**, *21*, 2183. (n) Patel, R. M.; Argade, N. P. *Synthesis* **2010**, 1188. (o) Zhou, Q.; Snider, B. B. *Org. Lett.* **2011**, *13*, 526.

(4) (a) González, A. Z.; Benitez, D.; Tkatchouk, E.; Goddard, W. A., III; Toste, F. D. *J. Am. Chem. Soc.* **2011**, *133*, 5500. (b) Gulías, M.; Collado, A.; Trillo, B.; López, F.; Oñate, E.; Esteruelas, M. A.; Mascareñas, J. L. *J. Am. Chem. Soc.* **2011**, *133*, 7660. (c) Rao, W.; Susanti, D.; Chan, P. W. H. *J. Am. Chem. Soc.* **2011**, *133*, 15248.

(5) For general review on xanthate, see: (a) Zard, S. Z. *Angew. Chem., Int. Ed.* **1997**, *36*, 672. (b) Zard, S. Z. In *Radical in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, 2001; Vol. 1, p 90. (c) Quiclet-Sire, B.; Zard, S. Z. *Chem.—Eur. J.* **2006**, *12*, 602. (d) Quiclet-Sire, B.; Zard, S. Z. *Top. Curr. Chem.* **2006**, *264*, 201. (e) Zard, S. Z. *Aust. J. Chem.* **2006**, *59*, 663. (f) Zard, S. Z. *Org. Biomol. Chem.* **2007**, *5*, 205. (f) Quiclet-Sire, B.; Zard, S. Z. *Pure Appl. Chem.* **2011**, *83*, 519.

(6) (a) Charrier, N.; Quiclet-Sire, B.; Zard, S. Z. *J. Am. Chem. Soc.* **2008**, *130*, 8898. (b) Debien, L.; Quiclet-Sire, B.; Zard, S. Z. *Org. Lett.* **2011**, *13*, 5676. (c) Braun, M.-G.; Quiclet-Sire, B.; Zard, S. Z. *J. Am. Chem. Soc.* **2011**, *133*, 15954.

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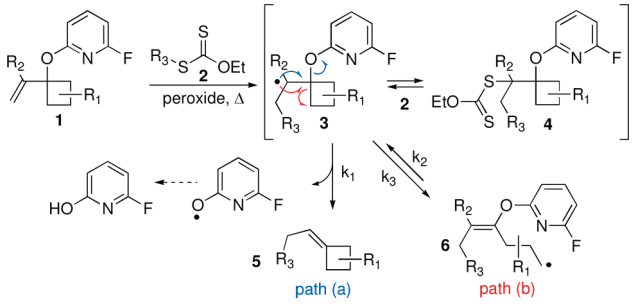
exploited in a convenient access to alkenes,[6a] enols ethers,[6b] and vinyl sulfones.[6c] We envisaged applying the same strategy to prepare alkylidene-cyclobutanes, as outlined in Scheme 1 (path a). However, such an approach raises one major problem, namely the competing ring-opening of the cyclobutane ring from cyclobutylcarbinyl radical intermediate **3** (path b), which was not an issue in the previous studies.

Scheme 1. Addition–Elimination Radical Strategy to Alk ylidene-Cyclobutanes

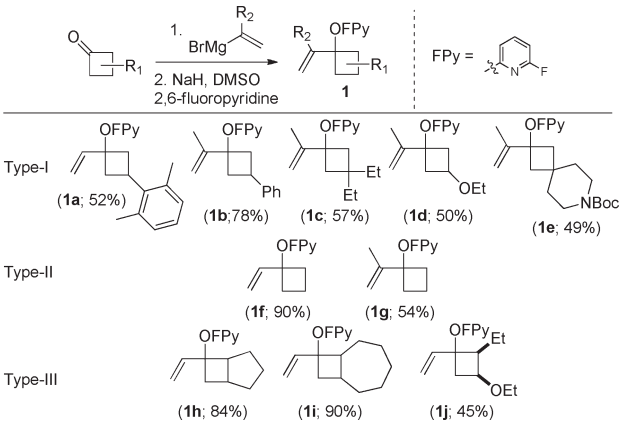


The homolytic elimination of the 2-fluoro-6-pyridinyloxy radical is, on the time scale of radical reactions, a relatively slow process. Indeed, in some instances, intermediates corresponding to **3** could be captured by a xanthate transfer, giving adducts of type **4** *before the elimination of the pyridinyloxy radical could occur*. Since the xanthate transfer is reversible, this was of no practical consequence. Indeed, advantage was taken of the slow fragmentation to produce vinylsulfones in a highly stereoselective manner, and these could be further converted at will into (*E*)- or (*Z*)-alkenes using stereoselective desulfonylation reactions developed by Julia.[6c] In the present case, the sluggishness of the homolytic scission becomes a handicap, in a sense that it gives the competing ring-opening process more time to occur. Even if, as shown in Scheme 1, the ring opening is in principle reversible, the 4-*exo* ring closure is expected to be too slow to allow the establishment of a useful equilibrium.[7] Nevertheless, it was worthwhile undertaking this study since, whatever the outcome, an approximate idea of the rate of the fragmentation of the fluoropyridinyloxy group could perhaps be obtained. Such information would be useful in planning future applications.

For our study, three types of precursors, with various substitution patterns, were prepared in a two-step procedure from a number of cyclobutanones (Scheme 2). Specifically, addition of a vinyl Grignard reagent, followed by nucleophilic aromatic substitution of 2,6-fluoropyridine, furnished the desired products in moderate to good yield over two steps.

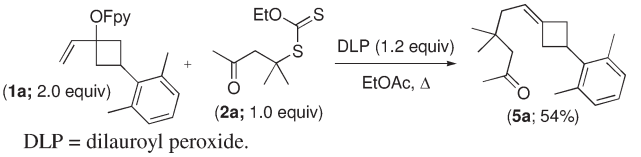
(7) For kinetic studies of ring opening of cyclobutylcarbinyl radical systems, see: (a) Beckwith, A. L. J.; Moad, G. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1083. (b) Ingold, K. U.; Maillard, B.; Walton, J. C. *J. Chem. Soc., Perkin Trans. 1* **1981**, 970.

Scheme 2. Synthesis of Olefinic Precursors



With the different precursors in hand, we could explore the scope of the reaction. The radical addition–elimination sequence was examined in a preliminary experiment with precursor **1a** and xanthate **2a**. Under typical conditions, the desired alkylidene-cyclobutane **5a** was isolated in good yield (Scheme 3). All type-I olefins displayed in Scheme 2 were found to undergo addition–elimination with various xanthates (Table 1). The desired products were isolated in moderate to good yields. In addition, it was found that the ratio of olefin to xanthate could be reversed without affecting the yield of the transformation.

Scheme 3. Preliminary Results



DLP = dilauroyl peroxide.

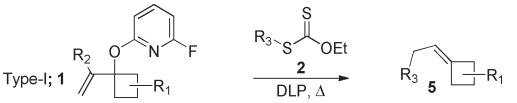
We then examined the behavior of type-II precursors with no substituents on the cyclobutane (Scheme 4). In a preliminary test, precursor **1f** (1.0 equiv) and xanthate **2b** (2.0 equiv) were submitted to our previous conditions. Surprisingly, in this case, only the product resulting from simple xanthate addition to the olefin was observed in the NMR spectrum of the crude mixture. This observation led us to perform the addition–fragmentation in a sequential manner. Thus, the first addition–xanthate transfer step was carried out in ethyl acetate.

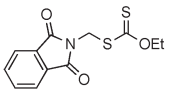
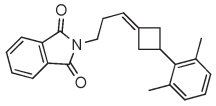
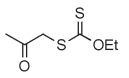
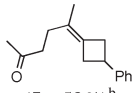
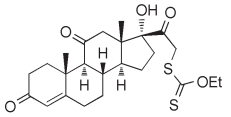
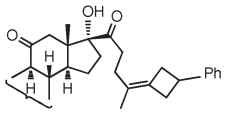
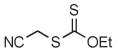
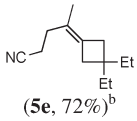
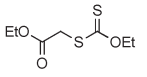
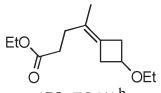
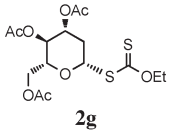
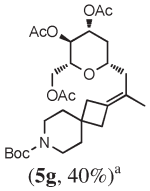
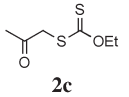
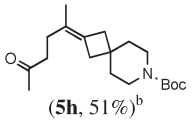
The corresponding adducts **7** and **8** were obtained in good yield from precursors **1f** and xanthates **2b** and **2h** respectively. Subsequent addition of stoichiometric amounts of dilauroyl peroxide[8] or di-*tert*-butyl peroxide in refluxing chlorobenzene promoted the desired

(8) Dilauroyl peroxide (DLP) is often sold under the name lauroyl peroxide.

elimination to furnish alkylidene-cyclobutanes **5i** and **5j**. The reaction could also be performed directly in refluxing chlorobenzene as illustrated by the synthesis of **5k** in comparable yield.

Table 1. Scope of the Reaction with Type-I Precursors



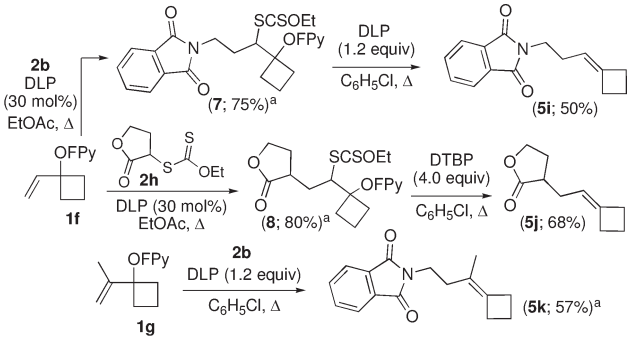
entry	olefin	xanthate	product
1	**1a**	 **2b**	 (**5b**; 64%)[a]
2	**1b**	 **2c**	 (**5c**, 52%)[b]
3	**1b**	 **2d**	 (**5d**, 60%)[a]
4	**1c**	 **2e**	 (**5e**, 72%)[b]
5	**1d**	 **2f**	 (**5f**, 70%)[b]
6	**1e**	 **2g**	 (**5g**, 40%)[a]
7	**1e**	 **2c**	 (**5h**, 51%)[b]

[a] Precursor (2.0 equiv), xanthate (1.0 equiv). [b] Precursor (1.0 equiv), xanthate (2.0 equiv).

To complete the delineation of the scope of the process, we attempted the addition−fragmentation on vinyl cyclobutanol derivatives of type-III (Scheme 5). In contrast to the previous cases examined so far, these substrates bear a substituent adjacent to the vinyl group and are expected to undergo a more facile ring-opening of the cyclobutane, as fragmentation would lead to the formation of a more stable secondary radical.

In the event, the addition−fragmentation in refluxing ethyl acetate with precursor **1h** (1.0 equiv) and xanthate **2d** (2.0 equiv) under the initial conditions furnished a rather complex mixture containing little if any of the

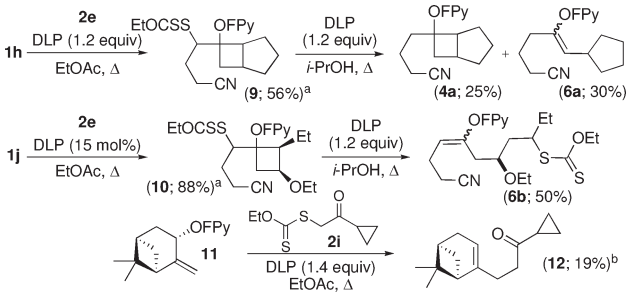
Scheme 4. Scope of the Reaction with Type-II Precursors



[a] Precursor (1.0 equiv), xanthate (2.0 equiv). DTBP = di-*tert*-butyl peroxide.

addition−elimination desired product from which adduct **9** was isolated in moderate yield. However, it was possible by using a substoichiometric amount of DLP to isolate the simple adducts **10** in a respectable yield from precursor **1j** (1.0 equiv) and xanthate **2d** (2.0 equiv). To simplify the analysis of the addition−elimination reaction mixture previously observed, we submitted the various adducts to reductive dexanthylation in isopropanol. Exposure to a stoichiometric amount of DLP in refluxing isopropanol furnished the prematurely reduced product **4a** (25%) and the reduced ring-opened product **6a** (30%).[9] In the case of adduct **10**, the ring-opened product **6b** was isolated in 50% yield.

Scheme 5. Limitation of the Reaction with Type-III Precursors



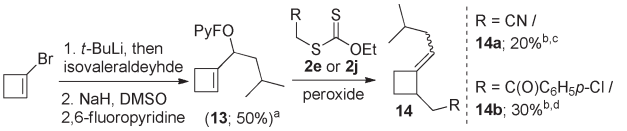
[a] Precursor (2.0 equiv), xanthate (1.0 equiv).

These experiments confirmed that the ring-opening was faster than the desired elimination of the fluoropyridyloxy group with precursors of type-III. It is interesting, in this respect, to note that the reaction of β-pinene derived precursor **11** with xanthate **2l** gave the addition−elimination product **12** in a small yield (19%), even if the ring opening of the cyclobutane ring would have produced a tertiary radical. This observation appears to indicate that

(9) (a) Isopropanol is a convenient hydrogen-atom donor in dexanthylation reactions; see: Liard, A.; Quiclet-Sire, B.; Zard, S. Z. *Tetrahedron Lett.* **1996**, *37*, 5877. (b) The xanthate transfer−reductive dexanthylation sequence performed with **1i** and **2d** gave similar results to those observed with **1h**; see Supporting Information.

the β-elimination represented in the passage from **3** to **5** (Scheme 1) and leading to a strained alkylidene-cyclobutane is significantly more difficult (*i.e.*, slower) than β-elimination in nonstrained structures. This is not unexpected but would indicate that the rate of the β-elimination in unstrained substrates is comparable to the rate of ring opening of a substituted cyclobutylmethyl radical, and therefore of the order of 10^3–10^4 s^{-1}.

Scheme 6. Route to 2-Substituted Alkylidene-Cyclobutanes

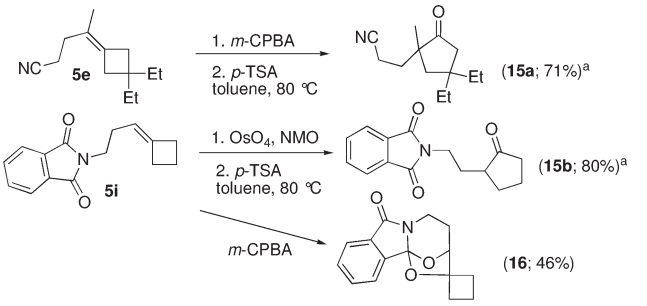


[a] Yield over two steps. [b] Stereoselectivity determined by ^{1}H NMR spectrocopy of isolated compound. [c] E/Z = 10:1. [d] E/Z = 4:1.

While these last results expose the limitations of the present olefination process as far as alkylidene-cyclobutane derivatives having substituents in the 2-position are concerned, valuable information on the ease of homolytic β-scission of the fluoropyridyloxy group was nevertheless obtained. From a synthetic perspective, an alternative route to 2-substituted alkylidene-cyclobutane derivatives consists in starting with cyclobutene carbinols as shown in Scheme 6. Indeed, the use of such strained olefins allows both addition of the xanthate and elimination without forming the cyclobutylcarbinyl radical.[10] Precursor **13** was prepared in a two-step procedure in moderate overall yield. The radical addition–elimination with xantahtes **2e** and **2j** proceeded as expected to give the respective product **14a** and **14b**. The yields are modest, but such compounds would be very tedious to make by more conventional routes. Finally, as an illustration of the utility of the alkylidene-cyclobutanes, we briefly investigated the ring expansion to cyclopentanone derivatives (Scheme 7).[11]

Epoxidation of **5e** under standard conditions and subsequent epoxide rearrangement under Brønsted acidic conditions gave the desired cyclopentanone **15a** in good yield. It is worth pointing out that treatment of crude epoxide with various Lewis acids (e.g., LiI, $TiCl_4$, Et_2AlCl) did not furnish the ring expanded product. In the case of **5i**, the epoxidation with *m*-CPBA did not furnish the desired epoxide but, rather unexpectedly, amido-orthoformate 16.[12] In contrast, dihydroxylation of **5i** followed by an acidic treatment of the crude diol with *p*-TSA gave the expected cyclopentanone **15b** in good yield.

Scheme 7. Synthetic Application of Alkylidene-Cyclobutanes



[a] Yield over two steps.

To the best of our knowledge, this is the first time alkylidene-cyclobutanes have been prepared by a radical addition–fragmentation process. The present reaction tolerates a wide range of functional groups, and the alkylidene-cyclobutanes may be readily transformed into cyclopentatones. This study also furnished a rough idea of the rate of the homolytic O–C cleavage, which appears to proceed at about an order of magnitude faster than the rate of an unsubtituted cyclobutylmethyl radical. The rate is perhaps a further order of magnitude faster in the case of unstrained structures.

Acknowledgment. J.B. and M.M. thank the ANR and l'Oréal respectively for a scholarship. This paper is dedicated with respect and admiration to Professor Léon Ghosez (IECB, Bordeaux).

Supporting Information Available. Experimental procedures, full spectroscopic data, and copies of ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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