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Synthesis of New Heterocycles through a Cation-Driven Tandem Ring-Enlargement–Annulation Reaction

Angela M. Bernard,* Enzo Cadoni, Angelo Frongia, Pier P. Piras,* and Francesco Secci

Dipartimento di Scienze Chimiche, Università degli studi di Cagliari, Cittadella Universitaria di Monserrato, S.S 554, Bivio per Sestu, I-09042 Monserrato (Cagliari), Italy

ppiras@unica.it

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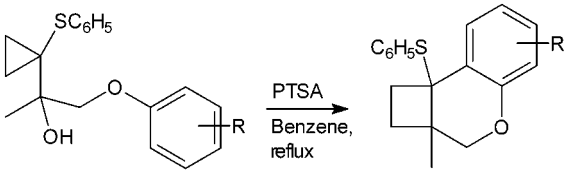
ABSTRACT



The thionium ion, generated through a cyclopropylcarbinyl-cyclobutyl ring expansion, is, for the first time, intramolecularly intercepted by activated aromatic rings to generate new versatile 2a-methyl-8b-(phenylsulfanyl-1,2a,3,8b-tetrahydro-*2H*-cyclobuta[c]chromenes.

Rearrangements involving the cyclopropyl group of properly substituted cyclopropanes are well-known in organic synthesis as they represent a practical access to ring-opened products or to carbo- and heterocyclic derivatives.[1] If the cyclopropanes bear an electron-donor substituent (O, S, N) and an electron-deficient center on the same atom, they undergo ring expansion to give cyclobutanones,[1−3] through a transformation closely related to the Wagner−Merwein rearrangement. Among the different ways of accomplishing this transformation, particularly important is the reaction with acids of the cyclopropylcarbinols obtained from the reaction of the metalated cyclopropyl phenyl sulfide with carbonyl partners.[3b,4,5]

The reaction is believed to proceed through a cyclobutyl α-thiocarbocation to give the cyclobutanone. The first and only example of intramolecular interception of the thionium

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(3) (a) Salaun, J. *Top. Curr. Chem.* **1988**, *144*, 1. (b) Trost, B. M. *Top. Curr. Chem.* **1986**, *133*, 3. (c) Nemoto, H.; Ishibashi, H.; Mori, M.; Fujita, S.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2835. (d) Nemoto, H.; Yamada, T.; Ishibashi, H.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1991**, 3149. (e) Nemoto, H.; Ishibashi, H.; Nagamochi, M.; Fukumoto, K. *J. Org. Chem.* **1992**, *57*, 1707. (f) Nemoto, H.; Yamada, T.; Ishibashi, H.; Takazawa, J.; Fukumoto, K. *Heterocycles* **1991**, *32*, 863. (g) Nemoto, H.; Tanabe, T.; Nagamochi, M.; Fukumoto, K. *Heterocycles* **1993**, *35*, 707. (h) Nemoto, H.; Shiraki, M.; Fukumoto, K. *Tetrahedron* **1994**, *50*, 10391. (i) Nemoto, H.; Miyata, J.; Hakamata, H.; Nagamochi, M.; Fukumoto, K. *Tetrahedron* **1995**, *51*, 5511. (j) Krief, A.; Ronvaux, A.; Tuch, A. *Bull. Soc. Chim. Belg.* **1997**, *106*, 699. (k) Diffendal, J. M.; Filan, J.; Spoors, P. G. *Tetrahedron Lett.* **1999**, *40*, 6137. (l) Chevtchouk, T.; Ollivier, J.; Salaun, J. *Tetrahedron: Asymmetry* **1997**, *8*, 1011. (m) Bernard, A. M.; Floris, C.; Frongia, A.; Piras, P. P. *Tetrahedron* **2000**, *56*, 4555. (n) Youn, J.-H.; Lee, J.; Cha, J. K. *Org. Lett.* **2001**, *3*, 2935.

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(5) A potential severe limitation of this approach is that the starting cyclopropylcarbinols are only available from cyclopropyl phenyl sulfide itself and its 2-hydroxymethyl derivative. The presence of other substituents on the cyclopropyl ring makes proton removal extremely difficult or impossible. The solution of this problem has been found by Cohen by producing 1-phenylthiocyclopropyl carbinols, containing several arrangements of substituents on the cyclopropyl ring, by reaction of 1-lithio-1-phenylthiocyclopropane generated by reductive lithiation of the corresponding 1,1-bis-phenylthiocyclopropane. Cohen, T.; Daniewski, W. M.; Weisenfeld, R. B. *Tetrahedron Lett.* **1978**, 4665. Cohen, T.; Weisenfeld, R. B.; Gapinski, R. E. *J. Org. Chem.* **1979**, *44*, 4744.

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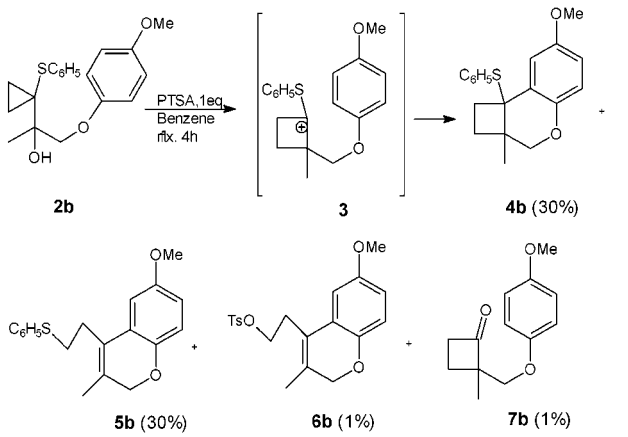
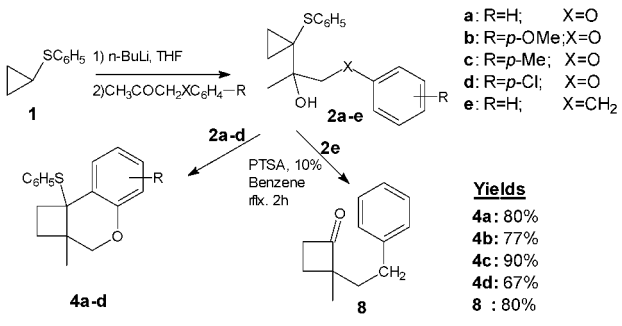
ion, generated through a cyclopropylcarbinyl-cyclobutyl ring expansion with an in situ-generated enol, was recently reported.[2] This reaction increases the potentialities of the Trost reaction, up to now limited to the synthesis of cyclobutanones, giving the possibility of preparing new polycyclic derivatives. We now report the results we found in the attempted synthesis of the cyclobutanone **7b** through ring expansion of the alcohol **2b** obtained by reaction of 1-(4-methoxyphenyl)acetone with the lithiated cyclopropyl phenyl sulfide, in the Trost conditions (PTSA, 1 equiv in wet benzene). As a matter of fact, the reaction mixture contained only traces of the expected cyclobutanone **7b** and the major components were the derivatives **4b** and **5b** (30:30) with small quantities of the tosylate **6b** (Scheme 1).[7] In search of

Scheme 1



conditions to optimize the yields of **4b**, we found that the use of 10% of PTSA in refluxing dry benzene, with azeotropic removal of water, for 2 h gave the best yields of **4b** with only traces of the starting material, the cyclobutanone, and the tosylate, easily separable by column chromatography. The reaction was also extended to the different alcohols reported in Scheme 2 and obtained in yields

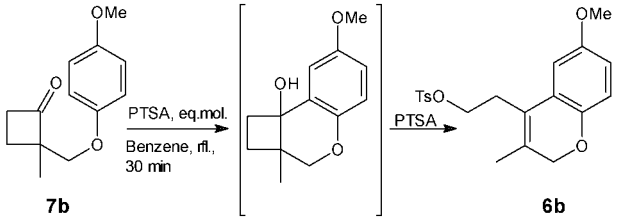
Scheme 2



ranging from 30 to 56%, with always variable amounts of unreacted cyclopropyl sulfide recovered from the reaction mixture. Good yields (67−90%) of derivatives **4a**−**d** were obtained with only negligible traces of the corresponding sulfides, tosylates, and cyclobutanones analogous to **5b**, **6b**, and **7b**, respectively. It was also discovered that activation of the aromatic ring was necessary for the reaction to occur, as demonstrated by the fact that the substrate **2e** does not give the expected carbocycle but the corresponding cyclobutanone **8**.

The presence of the sulfide **5b** and the tosylate **6b** in the reaction mixture can be rationalized in two ways. The first could involve the intermediacy of the cyclobutanone **7b**[8] that, as we have already reported,[9] can undergo a cascade ring closure ring fission in the presence of PTSA, with final formation of the tosylate **6b** that, by reaction with the thiophenol, produces the sulfide **5b**. Nevertheless, the compound **5b** was also obtained by reacting **4b** with 1 equiv of PTSA in refluxing benzene for 20 h, together with unreacted **4b** and the tosylate **6b**. Protonation of the sulfide sulfur is probably the first step of the reaction, with consequent cyclobutyl ring fission and formation of the tosylate **6b** as reported in Scheme 3. With regard to the

Scheme 3

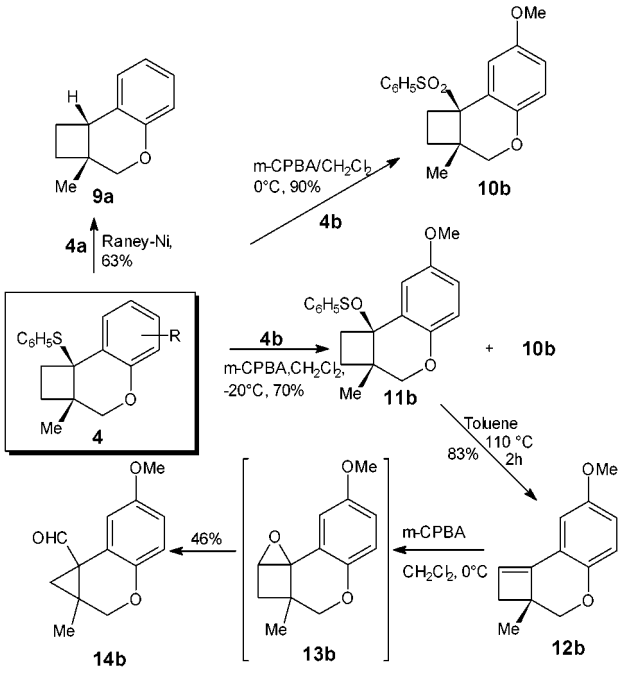


stereochemistry of derivatives **4**, we always found only a single diastereoisomer to which the cis geometry was tentatively assigned to the methyl and the phenylthio groups, as a consequence of the steric constraints in the cyclization step. In any case, we were not able to register any NOE effects between the protons of the phenylthio and the methyl group, but we recorded the presence of a NOE effect between the benzylic proton and the methyl group of the compound **9a** obtained by desulfuration of **4a** with Raney nickel (Scheme 4). Derivatives **4** are versatile compounds as demonstrated by the results reported in Scheme 4, where some synthetic possibilities are shown using **4a** and **4b** as starting materials.

Controlled oxidation at 0 °C with *m*-CPBA of **4b** led to the corresponding sulfone **10b**. Analogous oxidation of **4b** at −20 °C gave, with great stereoselectivity (90:10), the sulfoxide **11b** as a mixture of the two expected diastereoisomers easily separable by column chromatography. The reaction mixture contained also traces of the corresponding sulfone **10b** (Scheme 4). Heating the major diastereoisomer

(6) Witulski, B.; Bergstrasser, U.; Gossmann, M. *Tetrahedron* **2000**, *56*, 4747.
(7) Ratios were determined by ^{1}H NMR.
(8) Thiophenol is produced during the formation of the cyclobutanone.
(9) Bernard, A. M.; Floris, C.; Frongia, A.; Piras, P. P. *Synlett* **2002**, *5*, 796.

Scheme 4



of the sulfoxide **11b** in toluene for 2 h led, through a pyrolitic elimination, to the labile cyclobutene **12b** that was promptly epoxidized with *m*-CPBA to give the new cyclopropa[c]-chromene **14b**, probably through the intermediacy of the epoxycyclobutane[1a] **13b**. This constitutes a new approach to the synthesis of this relatively new class of compounds[10] whose carbon skeleton is found in the radulanins I−K,[11] isolated from the liverwort *Radula javanica*, and in some biologically active cyclopropyl analogues of precocene I.[12]

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Supporting Information Available: Detailed descriptions of experimental procedures and characterization of compounds **2a**−**e**, **4a**−**d**, **8**, **9a**, **10b**, **11b**, **12b**, and **14b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) For some examples of synthesis of these derivatives, see: (a) Sacquet, M.-C.; Graffe, B.; Maitte, P. *Bull. Soc. Chim. Fr.* **1971**, 2557. (b) Graffe, B.; Sacquet, M.-C.; Maitte, P. *Bull. Soc. Chim. Fr.* **1971**, 4016. (c) Padwa, A.; Carlsen, P. H. J.; Ku, A. *J. Am. Chem. Soc.* **1978**, *100*, 3494. (d) Carson, D.; Cass, M. W.; Crombie, L.; Holden, I.; Whiting, D. A. *J. Chem. Soc., Perkin Trans. 1* **1982**, 773. (e) Chatterjee, A.; Banerjee, D.; Banerjee, B.; Mallik, R. *Tetrahedron* **1983**, *39*, 2965. (f) Sasaki, M.; Collin, J.; Kagan, H. B. *Tetrahedron Lett.* **1988**, 6105. (g) Gotzhein, F.; Kirmse, W. *Tetrahedron Lett.* **1997**, 1373. (h) Gotzhein, F.; Kirmse, W. *Tetrahedron Lett.* **1997**, 1377. (i) Sun, B.; Adachi, K.; Noguchi, M. *Synthesis* **1997**, 53.

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