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Efficient Synthesis of Enantiomerically Pure α-Alkyl Cyclopropanecarbonitrile Derivatives from Pyrazolines†

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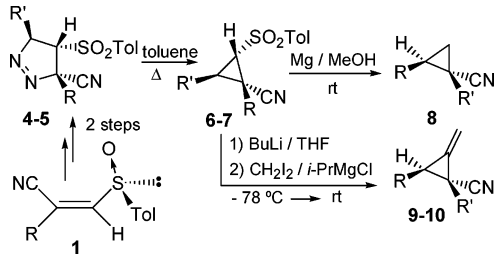
ABSTRACT



Thermolysis of enantiopure sulfonyl pyrazolines 4 and 5, easily obtained from (*Z*)-3-*p*-tolylsulfinylacrylonitriles (1), afforded sulfonyl cyclopropanes (6, 7) in a completely stereoselective manner in almost quantitative yields. Both cyclopropanes and alkylidenecyclopropanes, containing one or two chiral carbon atoms, one of them being quaternary, were obtained by hydrogenolysis of the C–S bonding and under the conditions reported by Julia, respectively. The highly stereoselective extrusion of nitrogen suggests a concerted mechanism.

The wide occurrence of cyclopropane rings in naturally occurring and biologically active compounds has stimulated the development of many methods and strategies for cyclopropanation.[1] One of the most powerful and efficient methods for obtaining cyclopropanes involves the enantioselective cycloaddition of different metal carbenes, generated by catalytic decomposition of diazocompounds, to alkenes.[2] However, its use in an enantioselective manner is restricted to electron-rich olefins and its efficiency sharply decreases when the steric hindrance becomes larger. The Michael addition-ring closure of special nucleophiles, like sulfur ylides, to electron-deficient alkenes appears as a complementary cyclopropanation procedure, but the reported stereoselectivities are usually moderate.[3]

Decomposition of pyrazolines has proved to be an excellent method for the preparation of cyclopropanes.[4] Photochemically induced processes are usually more important for this purpose, in comparison with the thermal ones, because of their higher stereoselectivity and usually larger proportion of cyclopropanes.[5] Although the thermal extrusion of nitrogen

† This paper is dedicated to the memory of Professor Jesús H. Rodríguez Ramos.

(1) (a) *Small Ring Compounds* in *Organic Synthesis VI*; de Meijere, A., Ed.; Springer: Berlin, 2000. (b) *Houben-Weyl: Methods of Organic Chemistry*; de Meijere, A., Schaumann, A., Eds.; Thieme Verlag: Stuttgart, 1997; Vol. E17. (c) Lebel, H.; Marcoux, J.; Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 977. (d) Donaldson, W. A. *Tetrahedron* **2001**, *57*, 8589.

(2) (a) See Pfaltz, A.; Lydon, K. M.; McKervey, M. A. In *Comprehensive Asymmetric Catalysis II*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999. (b) Doyle, M. P.; Hu, W.; Weathers, T. M., Jr. *Chirality* **2003**, *15*, 369 and references therein.

(3) (a) García Ruano, J. L.; Fajardo C.; Martín, R.; Midura, W. H.; Mikolajczyk, M. *Tetrahedron: Asymmetry* **2004**, *15*, 2475. (b) Midura, W. H.; Krysiak, J. A.; Mikolajczyk, M. *Tetrahedron: Asymmetry* **2003**, *14*, 1245. (c) Takagi, R.; Nakamura, M.; Kojima, S.; Ohkata, K. *Tetrahedron Lett.* **2001**, *42*, 5891.

(4) (a) Engel, P. S. *Chem. Rev.* **1980**, *80*, 99 and references therein. (b) Martín-Vilà, M.; Hanafi, N.; Jiménez, J. M.; Álvarez-Larena, A.; Piniella, J. F.; Branchadell, V.; Oliva, A.; Ortuño, R. M. *J. Org. Chem.* **1998**, *63*, 3581.

(5) (a) Otto, A.; Ziemer, B.; Liebscher, J. *Synthesis* **1999**, 965. (b) Bartels, A.; Jones, P. G.; Liebscher, J. *Synthesis* **1998**, 1645. (c) De Lange, B.; Feringa, B. L. *Tetrahedron Lett.* **1988**, *29*, 5317.

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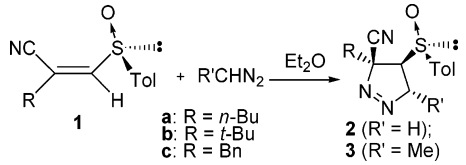
from pyrazolines mainly gives olefins, there are also known examples yielding cyclopropanes as the main products.[6] The use of these processes in asymmetric synthesis has been only occasionally exploited because of their usually low stereoselectivity. Additionally, the low number of general and efficient methods for preparing optically pure Δ^1-pyrazolines[7,8] could be another important reason accounting for this absence.

Recent efforts in our laboratory have focused on the use of vinyl sulfoxides as chiral dipolarophiles in reactions with different dipoles.[9] They have been shown to be excellent precursors for the synthesis of pyrazolines.[9a] Namely, reactions of optically pure (*Z*)-3-*p*-tolylsylfinylacrylonitriles with diazoalkanes afforded differently substituted Δ^1-pyrazolines (**2** and **3**) in high yields and with a complete control of the regioselectivity and the *endo/exo* and π-facial selectivities[10] (Scheme 1). The easy availability of the starting sulfinyl

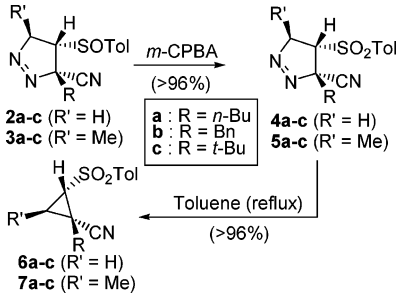
Scheme 1



nitriles **1**[11] (two steps from commercial alkynes) conferred this procedure a wide scope in the synthesis of optically pure sulfinyl pyrazolines. Consequently, we decided to evaluate the efficiency of these compounds as the starting materials for the preparation of optically pure cyclopropanes. The results obtained in this study are reported herein.

Compounds **2a**−**c** and **3a**−**c** (Scheme 1) were prepared according to the previously reported procedure[10] and subsequently used as starting materials. Initially, we studied the behavior of these substrates under thermal conditions (refluxing toluene). However, all attempts failed, giving rise to complex reaction mixtures. To avoid pyrolytic desulfinylation, able to promote decomposition of these compounds, we decided to oxidize the sulfinyl group into a sulfonyl group prior to treatment of pyrazolines under conditions of thermal decomposition. Sulfonyl pyrazolines **4** and **5** were readily obtained in quantitative yields by oxidation with *m*-CPBA (Scheme 2).

Scheme 2



Compounds **4a**−**c** and **5a**−**c** proved to be excellent starting materials for the synthesis of the sulfonyl cyclopropanenitriles **6a**−**c** and **7a**−**c**. Thus, after stirring for 7−9 h in refluxing toluene, cyclopropanes were obtained in almost quantitative yields (>96%) in all cases. This is one of the most efficient reactions reported to date affording cyclopropanes by thermal decomposition of pyrazolines. The formation of the corresponding olefins was not detected in any experience. However, even more interesting is the exclusive formation of one cyclopropane, **6** or **7**, exhibiting a cis arrangement between the alkyl groups R and R′, even in the case of the *t*-butyl derivative. This result demonstrates that these reactions take place in a completely stereoselective way (de > 98%), as it was determined by integration of well-separated signals of the ^{1}H NMR of their crude mixtures.

The absolute configuration at the stereogenic center of cyclopropanes **6** and **7** bearing the sulfonyl group was assigned as *S* by assuming that it was maintained unaltered in the extrusion step (it had been unequivocally assigned for the starting sulfinyl pyrazolines **2** and **3**[10]). The cis relationship existing between the R groups and the proton at sulfonylated carbon in compounds **6** and **7** as well as between R and Me groups in compounds **7** could be deduced from the ^{1}H NMR parameters (values of NOEs). In Figure 1 are indicated the most significant values observed for **7b**.[12] This assignment indicates that the extrusion of nitrogen has taken place with retention of the configuration at the three chiral

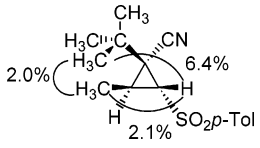


Figure 1. NOE values for **7b**.

(6) (a) Vasquez, P. C.; Bennett, D. C.; Tows, K. K.; Kennedy, G. D.; Baumstark, A. L. *Heteroatom Chem.* **2000**, *11*, 299. (b) Begley, M. J. *Chem. Commun.* **1978**, 461.

(7) See, for example: Kanemasa, S.; Kanai, T. *J. Am. Chem. Soc*. **2000**, *122*, 10710.

(8) There are several efficient methods for preparing optically pure Δ^2-pyrazolines (see: (a) Barluenga, J.; Fernandez-Marti, F.; Aguilar E.; Viado, A. L.; Olano, B.; García Granda, S.; Moya-Rubiera, C. *Chem. Eur. J.* **1999**, *5*, 883 and references therein. (b) Mish, M. R.; Guerra, F. M.; Carreira, E. M. *J. Am. Chem. Soc*. **1997**, *119*, 8379. (c) Guerra, F. M.; Mish, M. R.; Carreira, E. M. *Org. Lett*. **2000**, *2*, 4265. (d) Sasaki, H.; Carreira, E. M. *Synthesis* **2000**, 135), but they are not the most convenient substrates for the preparation of cyclopropanes.

(9) (a) **Diazoalkanes**: García Ruano, J. L.; Fraile, A.; Gonzalez, G.; Martín, M. R.; Clemente, F. R.; Gordillo, R. *J. Org. Chem.* **2003**, *68*, 6522 and references therein. (b) **Nitrile oxides**: García Ruano, J. L.; Bercial, F.; Fraile, A.; Martín, M. R. *Synlett* **2002**, 73 and references therein. (c) **Nitrones**: García Ruano, J. L.; Andrés Gil, J. I.; Fraile, A.; Martín Castro, A. M.; Martín, M. R. *Tetrahedron Lett*. **2004**, *45*, 4653. (d) **Azomethine ylides**: García Ruano, J. L.; Peromingo, M. Tito, A. *J. Org. Chem*, **2003**, *68*, 10013 and references therein.

(10) García Ruano, J. L.; Alonso de Diego, S. A.; Blanco, D.; Martín Castro, A. M.; Martín, M. R.; Rodríguez Ramos, J. H. *Org. Lett.* **2001**, *3*, 3173.

(11) García Ruano, J. L.; Esteban Gamboa, A.; Martín Castro, A. M.; Rodríguez, J. H.; López-Solera, M. I. *J. Org. Chem.* **1998**, *63*, 3324.

centers of the starting pyrazoline. To our knowledge, this is one of the few examples of extrusion of nitrogen from pyrazolines under thermal conditions giving rise to optically pure cyclopropanes with complete control of the stereoselectivity.

Whereas a diradical mechanistic pathway has been proposed by several groups[13] to explain the highly stereoselective evolution of pyrazolines under photolytic conditions, the course of the thermal decomposition of pyrazolines into cyclopropanes still remains controversial. Indeed, the hitherto reported stereochemical results from thermal decomposition of 1-pyrazolines are quite divergent and strongly dependent on the nature of the substituents at the ring. Ionic[14] or diradical[15] mechanisms have been postulated to explain the most usual pyrolytic processes proceeding without stereoselectivity, although there is a report that assumes a diradical mechanism to explain some stereoselective transformations.[16]

Many years ago,[17] a concerted mechanism was invoked to account for the retention of configuration observed in some cyclopropanes resulting from extrusion of nitrogen of pyrazolines. Bearing in mind the electron-withdrawing groups existing at the pyrazoline rings reported herein, our stereochemical results are consistent with the concerted thermal decomposition proposed by McGreer[17a,b] of a series of 4- and 5-alkyl-substituted 3-methyl-3-methoxycarbonyl-Δ^1-pyrazolines, which afford cyclopropanes by extrusion of nitrogen through a polar transition state, where the degree of bond breaking of the C(3)−N bond is advanced over the bond breaking of the C(5)−N bond (Figure 2). The common

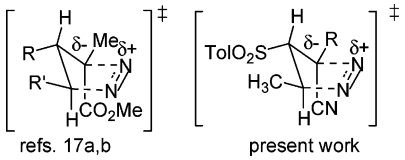


Figure 2. Proposed transition states for the concerted nitrogen extrusion under thermal conditions.

feature of compounds **4** and **5** with those studied by McGreer[17a,b] is the existence of a quaternary carbon at C-3 of the pyrazoline ring, supporting an electron-withdrawing group able to stabilize the negative charge.[18]

Due to the potential interest of the availability of a cyclopropane moiety in organic structures, as a consequence of its presence in building blocks of naturally occurring compounds[19] or to its effectiveness in restricting the conformational mobility of biologically active compounds,[20] we embarked on the task of transforming our previously synthesized enantiopure sulfonyl cyanocyclopropanes (**6** and **7**) into other cyclopropane derivatives.[21]

Reductive desulfonylation of compounds **7a** (R = *n*-Bu) and **7b** (R = *t*-Bu) proved to be a difficult task in the synthesis of other sulfinyl cyclopropanes.[3] In our case, we used different systems to get the hydrogenolysis of the C−S bond such as Li^+Naft^-,[22] [Al(Hg)],[23] [Na(Hg)],[24] Ni(Raney), $Li/EtNH_2$,[25] but the results obtained were not satisfactory in any case. Finally, it was accomplished by treatment of **7a** and **7b** with magnesium in methanol following previously reported procedures,[20a,26] which were slightly modified.[27] After 1−3 days at room temperature, we obtained the expected compounds (Scheme 3) in ca. 80% yield of the crude reaction (chemically pure by NMR). Distillation of the crude mixture afforded **8a** and **8b** in 60 and 56% yields, respectively.[28] The four-step procedure described herein for preparing enantiomerically pure cyclopropanes containing two chiral centers (one of them quaternary) from sulfinyl

(12) Double Pulsed Field Gradient Echo-DPFGS (Bruker DRX-500).

(13) (a) Muray, E.; Illa, O.; Castillo, J. A.; Alvarez-Larena, A.; Bourdelande, J. L.; Branchadell, V.; Ortuño, R. M. *J. Org. Chem.* **2003**, *68*, 4906 and references therein. (b) Karatsu, T.; Itoh, H.; Kikunaga, T.; Ebashi, Y.; Hotta, H.; Kitamura, A. *J. Org. Chem.* **1995**, *60*, 8270. (c) White, D. H.; Condit, P. B.; Bergman, R. G. *J. Am. Chem. Soc.* **1972**, *94*, 1348.

(14) (a) Tabushi, I.; Takagi, K.; Okano, M.; Oda, R. *Tetrahedron* **1967**, *23*, 2621. (b) Van Auken, T. V.; Rinehart, K. L., Jr. *J. Am. Chem. Soc.* **1962**, *84*, 3736.

(15) (a) Padwa, A.; Meske, M.; Rodríguez, A. *Heterocycles* **1995**, *40*, 191. (b) Reedich, D. E.; Sheridan, R. S. *J. Am. Chem. Soc.* **1988**, *110*, 3697. (c) Crawford, R. J.; Erickson, G. L. *J. Am. Chem. Soc.* **1967**, *89*, 3907. (d) Crawford, R. J.; Ali, L. H. *J. Am. Chem. Soc.* **1967**, *89*, 3908.

(16) Nakano, Y.; Hamaguchi, M.; Nagai, T. *J. Org. Chem.* **1989**, *54*, 1135.

(17) (a) McGreer, D. E.; Chiu, W. K.; Vinge, M. G.; Wong, K. C. K. *Can. J. Chem.* **1965**, *43*, 1407. (b) McGreer, D. E.; Masters, I. M. E.; Liu, M. T. H. *J. Chem. Soc., Perkin Trans. 2* **1975**, 1791. (c) Deleux, J. P.; Leroy, G.; Weiler, J. *Tetrahedron* **1973**, *29*, 1135. (d) Eberhard, P.; Huisgen, R. *J. Am. Chem. Soc.* **1972**, *94*, 1345.

(18) Stereoselective formation of alkylidenecyclopropanes by thermal nitrogen extrusion from alkylidenepyrazolines has been recently published (Hamaguchi, M.; Nakaishi, M.; Nagai, T.; Tamura, H. *J. Org. Chem.* **2003**, *68*, 9711). The mechanistic model proposed in that paper by the authors is not significantly different from that proposed by McGreer in refs 16a and 16b. Alkylidenepyrazolines described therein also contain electron-withdrawing groups (apparently very important in the course of the reaction) and quaternary centers.

(19) See, for example, Hirohara, H.; Mitsuda, S.; Audo, E.; Komaki, R. In *Biocatalysts in Organic Synthesis*; Tramper, J., Van der Plas, H. C., Linko, P., Eds.; Elsevier: Amsterdam, 1985; p 119. See also Johnson, C. R.; Barbachyn, M. *J. Am. Chem. Soc.* **1982**, *104*, 4290. Greuter, H.; Dingwall, J.; Martin, P.; Bellus, D. *Helv. Chim. Acta* **1981**, *64*, 2812. Kim, G.; Chu-Moyer, M. Y.; Danishefsky, S. J.; Schulte, G. K. *J. Am. Chem. Soc.* **1993**, *115*, 30. Salaün, J. *Top. Curr. Chem.* **2000**, *207*, 1. Pietruszka, J. *Chem. Rev.* **2003**, *103*, 1051. Wessjohann, L. A.; Brandt, W.; Thiemann, T. *Chem. Rev.* **2003**, *103*, 1625.

(20) (a) Kazuta, Y.; Matsuda, A.; Shuto, S. *J. Org. Chem.* **2002**, *67*, 1669. (b) Díaz, M.; Ortuño, R. M. *Tetrahedron: Asymmetry* **1996**, *7*, 3465.

(21) The low stability of the benzyl derivatives **2c** and **3c** − they decomposed upon standing at room temperature for several hours − justified that their use in further transformations was discarded.

(22) (a) Ager, D. J. *J. Chem. Soc., Chem. Commun*. **1984**, 486. (b) Ager, D. J. *J. Org. Chem.* **1984**, *49*, 168.

(23) De Lucchi, O.; Lucchini, V.; Marchioro, C.; Valle, G.; Modena, G. *J. Org. Chem*. **1986**, *51*, 1457.

(24) Trost, B. M.; Seoane, P.; Mignani, S.; Acemoglu, M. *J. Am. Chem. Soc.* **1989**, *111*, 7487.

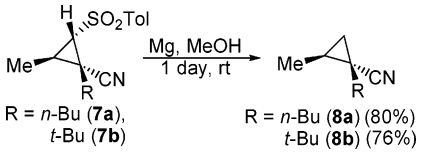
(25) Solladiè, G.; Demailly, G.; Greck, C. *J. Org. Chem*. **1985**, *50*, 1552.

(26) Benedetti, F.; Berti, F.; Risaliti, A. *Tetrahedron Lett.* **1993**, *34*, 6443. Brown, A. C.; Carpino, L. A. *J. Org. Chem.* **1985**, *50*, 1749.

(27) Reported procedure did not yield the expected cyclopropanes. Therefore, it was modified as follows: To a flask containing 15 mL of anhydrous methanol were added Mg turnings (10 equiv), and the mixture was heated (55 °C) under argon. A solution of sulfonyl cyclopropane (1 equiv) in 3 mL of anhydrous methanol was cannulated under positive argon pressure, and the resulting mixture was vigorously stirred at room temperature. Two additional portions of Mg (2 × 10 equiv) were added at regular intervals (every 2 h). Upon completion, the reaction was quenched by dilution with CH_2Cl_2 (10 mL) and further addition of $Na_2SO_4 \cdot 10H_2O$ (200 mg). The mixture was stirred overnight, filtered through a Celite pad, and concentrated under reduced pressure.

(28) All the tested chromatographic attempts to purify compounds **8a** and **8b** were unsuccessful.

Scheme 3



acrylonitriles (six steps from commercial terminal alkynes) is one of the shortest and most efficient methods so far reported.

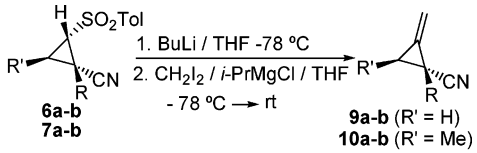
We have also taken advantage of the presence of the SO_2-Tol moiety in the cyclopropanenitriles **6** and **7** to incorporate other functionality into the molecule during the elimination step of the sulfonyl group. Thus, we have used them to prepare optically pure alkylidenecyclopropanes, interesting substrates in the synthesis of heterocyclic compounds,[29] as well as for the preparation of other cyclopropane derivates.[30] In our case, compounds **9a**,**b** and **10a**,**b** were obtained from **6a**,**b** and **7a**,**b**, respectively, under the conditions reported by Julia[31] (Scheme 4). Yields were almost quantitative as determined by NMR, only small amounts of the unaltered substrates having been detected in the reaction crudes. However, optically pure **9a**,**b** and **10a**,**b** could be isolated only in moderate to high yields by distillation from the reaction crudes.[32]

(29) Brandy, A.; Cicchi, S.; Cordero, F. M.; Goti, A. *Chem. Rev.* **2003**, *103*, 1213. For recent papers, see: Chowdhury, M. A.; Senboku, H.; Tokuda, M. *Synlett* **2004**, *11*, 1933. Amal, I. S.; Itaru, N.; Yoshinori, Y. *J. Org. Chem.* **2004**, *69*, 3202.

(30) (a) Bernard, A. M.; Frongia, A.; Piras, P. P.; Secci, F. *J. Org. Chem.* **2004**, *69*, 5471. (b) Nordvik, T.; Miesusset, J.; Brinker, U. H. *Org. Lett.* **2004**, *6*, 715. (c) Satoh, T.; Saito, S. *Tetrahedron Lett.* **2004**, *45*, 347.

(31) Lima, C.; Julia, M.; Verpeaux, J.-N. *Synlett* **1992**, 133. In the originally described conditions, 2.0 equiv of CH_2I_2 was used. Our best results were obtained when using 1.8 equiv of CH_2I_2 in the methylenation step.

Scheme 4



substrate	R	R'	yield (%) (product)
6a	*n*-Bu	H	60 (**9a**)
6b	*t*-Bu	H	55 (**9b**)
7a	*n*-Bu	Me	70 (**10a**)
7b	*t*-Bu	Me	73 (**10b**)

In conclusion, in this paper we describe one of the most efficient methods for synthesizing optically pure cyclopropanes and alkylidenecyclopropanes containing a quaternary chiral center. It involves six steps from commercial alkynes, many of them evolving in quantitative yields. The key step is the thermal extrusion of the nitrogen from chiral pyrazolines, which contain a quaternary carbon (C-3) bearing an electron-withdrawing group (CN). This extrusion takes place in very high yields with complete retention of the configuration of all the chiral centers.

Acknowledgment. We thank CAICYT (Grant BQU2003-04012) for financial support.

Supporting Information Available: Experimental section containing characterization of compounds **4**−**10** and ^{1}H NMR spectra for compounds **8**−**10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(32) Chromatographic purification of these compounds was unsuccessful in our hands.