Halogen Atom Transfer Annulations Involving Iodomalonates and Allylamine Derivatives

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Received September 5, 1989

The use of carbon radical initiated cyclizations and annulations is currently a subject of intense synthetic research.[1-4] Recently, halogen atom transfer annulations have been described[1b] wherein initial halogen atom abstraction from a donor group is followed by intermolecular addition to an acceptor olefin, followed by intramolecular cyclization to afford a variety of annulated molecular frameworks. A representative example is shown in Scheme I.[5] This methodology is particularly useful when an initial slow addition reaction (e.g. **1′ + 2 → 3**) must precede a fast intramolecular closure (**3 → 4**). Additionally, since halogen is transferred to a new center in the product **5**, this retained functionality may be useful for subsequent reactions (vide infra).

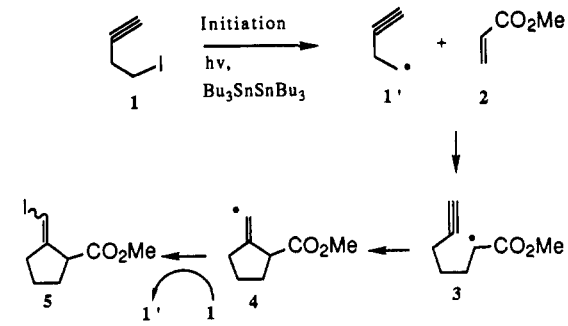
Particularly useful iodine atom donor groups are iodomalonates such as **6**, and their use has been described in synthesis of both carbocycles **7** and oxacycles **8**, as shown in Scheme II.[1b,6]

We recently set out to apply this iodine atom transfer annulation methodology to the formation of azabicycle systems.[7] Upon first trial, reaction of the known iodomalonate **6** with *N*-benzylallylamine **9a** (Scheme III, R = benzyl) did not afford any of the desired bicycle **13a** or its iodinated precursor **12a**.

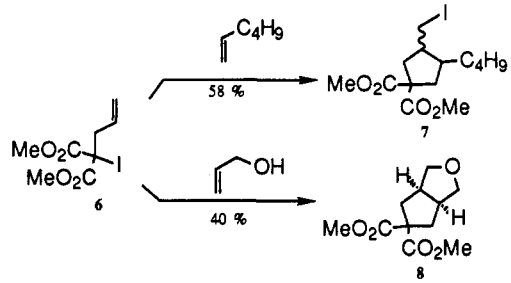
Instead, the aziridine **16** was formed in 45% isolated yield (Scheme IV). It seemed reasonable that an alternative reaction pathway had intervened due to the nucleophilicity of the *N*-benzylallylamine **9a**. Thus the iodomalonate in this case could serve as a source of positive iodine, forming **14** in situ. This *N*-iodo species could then suffer homolytic cleavage to form the nitrogen-based radical **14′**. Combination of **14′** with **14** would afford the radical adduct **15**, which upon closure would form aziridine **16**.[8]

In order to obviate this alternative pathway, it was reasoned that use of less nucleophilic allylamines might result in the desired atom transfer annulation shown in Scheme III. In fact, when the N-BOC allylamine **9b** was utilized, **12b** (R = BOC) was isolated in 28% yield, indicating that radical-initiated addition and cyclization had occurred as desired. Although the trans diastereomer of **12b** may have been formed as a minor product, none was isolated. That the cis product of **12b** was the major product (and the only one isolated) is in keeping with literature precedent.[6,9,10]

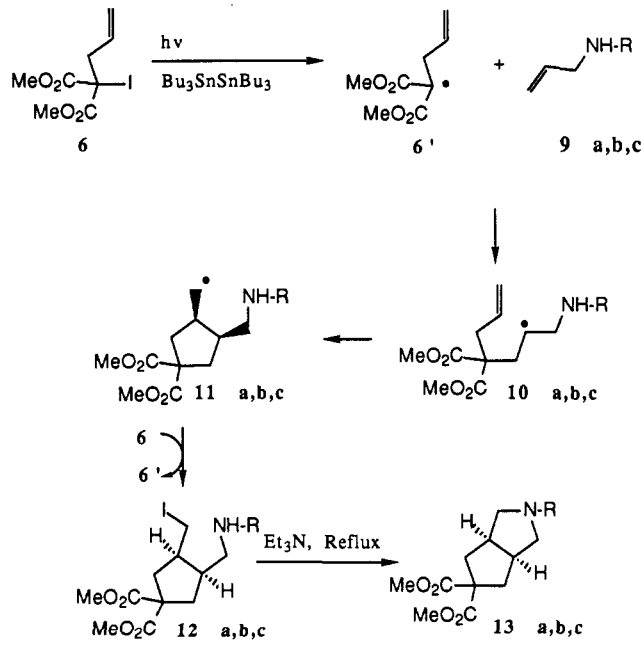
Scheme I



Scheme II



Scheme III



a R = benzyl
b R = t-BOC
c R = p-OMebenzene sulfonyl

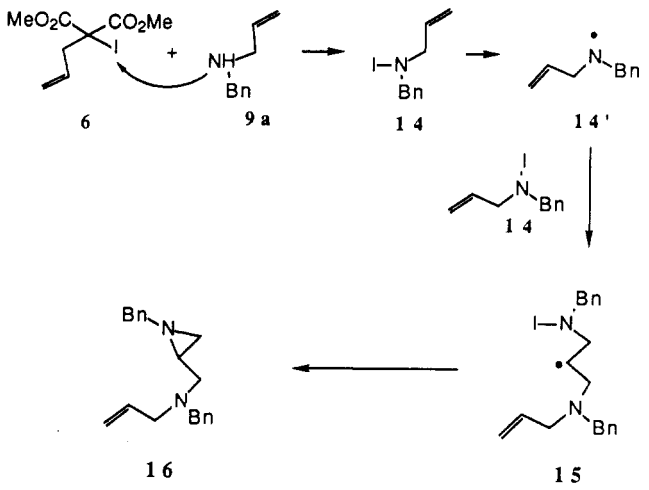
Although the iodinated adduct **12b** could be isolated and subsequently cyclized using triethylamine, this was not routinely done because of sensitivity in handling **12b**. Alternatively, the cyclization of **12b** to **13b** could be performed in situ simply by adding triethylamine to the reaction vessel after formation of **12b** was complete. Using this one-pot procedure, the azabicycle **13b** was isolated in 43% yield after chromatography.

By analogy, reaction of the iodomalonate **6** with the sulfonamide **12c** (R = (*p*-methoxyphenyl)sulfonyl) af-

(1) (a) Curran, D. P. *Synthesis* **1988**, 417. (b) Curran, D. P. *Synthesis* **1988**, 489.
(2) Hart, D. J. *Science* **1984**, *223*, 883.
(3) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*; Pergamon Press: Oxford, **1986**.
(4) Ramaiah, M. *Tetrahedron* **1987**, *43*, 3541.
(5) Curran, D. P.; Chen, M.-H. *J. Am. Chem. Soc.* **1987**, *109*, 6558.
(6) Curran, D. P.; Chen, M.-H.; Spletzer, E.; Seong, C. M.; Chang, C.-T. *J. Am. Chem. Soc.* **1989**, *111*, 8872.
(7) The work described herein represents a tandem atom-transfer annulation/cyclization strategy for the formation of azabicycles. For an example of atom-transfer cyclization as an approach to other azabicycle systems, see: Jolly, R. S.; Livinghouse, T. *J. Am. Chem. Soc.* **1988**, *110*, 7536.
(8) For an example of analogous cyclopropane formations, see: Hudlicky, T.; Ranu, B. C. *J. Org. Chem.* **1985**, *50*, 123.
(9) Beckwith, A. L. J. *Tetrahedron* **1981**, *37*, 3073.
(10) Spellmeyer, D. C.; Houk, K. N. *J. Org. Chem.* **1987**, *52*, 959.

0022-3263/90/1955-3673$02.50/0

Scheme IV



forded **13c** in 59% isolated yield.

Thus, iodomalonate-mediated atom-transfer annulations can be performed to give azacyclic systems, provided the nucleophilic character of the allylamine is low. Further application of this methodology is being pursued to form a variety of azabicycles. This work will be reported in due course.

Experimental Section

All reactions were performed under an atmosphere of argon in flasks which were oven-dried overnight. Tetrahydrofuran was distilled from sodium benzophenone ketyl. Benzene was degassed with argon. All reagents were purchased from Aldrich Chemical Co. and used without further purification. Merck silica gel 60 (230–400 mesh) was used for medium-pressure liquid chromatography (MPLC) and flash column chromatography. Macherey-Nagel precoated silica gel G/UV254 plates (0.25 mm) were used for thin-layer chromatography (TLC).

^{1}H NMR spectra were measured at 300 MHz on a General Electric QE-300 spectrometer in $CDCl_3$ using tetramethylsilane as a reference (0.00 ppm). ^{13}C NMR spectra were measured at 75 MHz on a General Electric QE-300 spectrometer in $CDCl_3$. High-resolution mass spectra were recorded on a Finnigan MAT8430 instrument. Microanalyses were conducted on a Control Equipment CEC240-XA instrument. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected.

***N*,1-Dibenzyl-*N*-allyl-2-(methylamino)aziridine (16).** To a solution of 250 mg (0.84 mmol) of allyliodomalonate **6**[6] in 2.5 mL of benzene were added 123 mg (0.84 mmol) of *N*-benzylallylamine **9a** and 53 μL (0.084 mmol) of bis(tributyltin). After exposing the homogeneous solution to light from a sunlamp (d = 8 cm) for 20 min, the brown-red homogeneous solution was cooled, diluted with 30 mL of dichloromethane, and washed with 20 mL of a 10% aqueous solution of potassium carbonate. The organic layer was separated, dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. MPLC (ethyl acetate–hexane, 1:3 to 1:1; 15 mm × 1000 mm diameter; flow rate 8 mL/min) provided 56 mg (45%) of aziridine **16** as an oil: R_f 0.27 (ethyl acetate–hexane, 1:2); ^{1}H NMR δ 1.38 (1 H, d, J = 6.4 Hz), 1.58 (1 H, d, J = 3.5 Hz), 1.70 (1 H, m), 2.45 (1 H, dd, J = 13.4, 6.3 Hz), 2.57 (1 H, dd, J = 13.4, 5.0 Hz), 3.02 (1 H, dd, J = 14.2, 6.6 Hz), 3.16 (1 H, dd, J = 14.2, 6.1 Hz), 3.40 (2 H, AB q, J = 13.2 Hz, $\Delta\nu$ = 41.6 Hz), 3.59 (2 H, AB q, J = 13.8 Hz, $\Delta\nu$ = 50.1 Hz), 5.13 (2 H, m), 5.84 (1 H, m), 7.30 (10 H, m); ^{13}C NMR 32.43, 38.00, 56.57, 58.02, 58.16, 64.66, 117.18, 126.70, 127.00, 128.06, 128.22, 128.29, 128.80, 135.88, 139.02, 139.54; HRMS $C_{20}H_{24}N_2$ M$^+$ calcd 292.1939, found 292.1936.

***N*-BOC-7,7-dicarbomethoxy-3-azabicyclo[3.3.0]octane (13b).** To a solution of 1.27 g (4.26 mmol) of allyliodomalonate **6** and 1.34 g (8.52 mmol) of *N*-BOC-allylamine **9b** in 10 mL of benzene was added via syringe 0.16 mL of bis(tributyltin). After the clear homogeneous solution was exposed to light from a sunlamp (d = 8 cm) for 30 min, the light source was removed and 5 mL of triethylamine was added. The solution was heated at reflux for 20 h, at which time the dark brown-red mixture was concentrated under reduced pressure. Flash chromatography on 150 g of silica gel (ethyl acetate–hexane, 1:5 to 1:3) provided 0.606 g (43%) of azabicycle **13b** as a clear oil: R_f 0.34 (ethyl acetate–hexane, 1:4); ^{1}H NMR 1.46 (9 H, s), 2.04 (2 H, dd, J = 13.2, 6.8 Hz), 2.56 (2 H, m), 2.72 (2 H, m), 3.25 (2 H, m), 3.44 (2 H, m), 3.72 (3 H, s), 3.74 (3 H, s); ^{13}C NMR 28.52, 39.29, 43.56, 52.77, 53.81, 62.25, 79.31; MS $C_{16}H_{25}NO_6$ M$^+$ 327. Anal. Calcd for $C_{16}H_{25}NO_6$: C, 58.69; H, 7.71; N, 4.28. Found: C, 58.25; H, 7.55; N, 4.06.

***N*-((*p*-Methoxyphenyl)sulfonyl)-7,7-dicarbomethoxy-3-azabicyclo[3.3.0]octane (13c).** Starting with 0.35 g (1.17 mmol) of **6** and 0.53 g (2.35 mmol) of *N*-((*p*-methoxyphenyl)sulfonyl)-allylamine **9c**, the crude product, formed from the identical reaction conditions described in the above paragraph, was purified on 30 g of silica gel (ethyl acetate–hexane, 1:2.5) to afford 0.275 g (59%) of azabicycle **13c** as a solid: mp 132.0–134.0 °C (ethyl acetate); ^{1}H NMR δ 1.98 (2 H, dd, J = 12.7, 7.4 Hz), 2.52 (2 H, m), 2.69 (2 H, m), 2.81 (2 H, m), 3.16 (2 H, br d, J = 8.8 Hz), 3.70 (3 H, s), 3.72 (3 H, s), 3.89 (3 H, s), 7.01 (2 H, d, J = 9.2 Hz), 7.73 (2 H, d, J = 9.2 Hz); HRMS $C_{18}H_{23}NO_7S$ M$^+$ calcd 397.1287, found 397.1222.

Acknowledgment. Thanks are extended to Professor D. P. Curran for helpful discussions regarding this work and for providing experimental details for the formation of the iodomalonate **6**.[6]

Stereoselective Synthesis of 6-Fluoropenicillanate Analogues of β-Lactamase Inhibitors†

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Received April 24, 1989 (Revised Manuscript Received November 6, 1989)

6β-Bromopenicillanic acid (**1a**)[2] and penicillanic acid 1,1-dioxide (**1b**)[3,4] have been extensively studied as β-lactamase inhibitors, and some aspects of the mechanism of action have been elucidated.[5-7]

The use of selectively fluorinated substrate is of considerable interest at the present time for the study of enzyme substrate interactions,[8] and the use of fluorinated analogues of biologically active compounds has recently been reviewed.[9] For these reasons the synthesis of regio- and stereospecifically fluorinated penicillanates is of interest. 6β-Fluoropenicillanates are known in the patent literature,[10] and we recently reported a procedure for the synthesis of (pivaloxyloxy)methyl (POM) 6α-fluoropenicillanate (**3d**).[11] We now describe new methods for the conversion of POM 6-diazopenicillanate (**2**) into POM 6β-bromo-6α-fluoro- and 6β-chloro-6α-fluoropenicillanates (**3a–b**) using a *N*-halosuccinimide and tetrabutylammonium bifluoride. In our hands these were considerably more efficient than the procedures currently available and may have application in other areas. We also describe the stereoselective conversion of these compounds into the POM 6β-fluoropenicillanate (**3e**) together with a procedure for the one-pot conversion of the POM 6-diazopenicillanate (**2**) into the 6α-fluoro compound **3d**.

† Dedicated to the memory of Professor Orfeo O. Orazi.

0022-3263/90/1955-3674$02.50/0