## LETTERS 2006 Vol. 8, No. 14 3041–3043

ORGANIC

## Skeletal Rearrangements in the 2,3-Diazanorbornene Series. A Fast Access to Highly Functionalized Cyclopentanes

Chloée Bournaud, Martine Bonin, and Laurent Micouin\*

Laboratoire de Chimie Thérapeutique, UMR 8638 associée au CNRS et à l'Université René Descartes, Faculté des Sciences Pharmaceutiques et Biologiques, 4 av de l'Observatoire, 75270 Paris Cedex 06, France

laurent.micouin@univ-paris5.fr

Received April 24, 2006



Acid-catalyzed nucleophilic substitution of bicyclic hydrazine–epoxide involves nitrogen participation, leading to a skeletal rearrangement. This transformation enables the fast preparation of disubstituted bicyclic hydrazines in a regio- and stereoselective manner, leading to several polyfunctional diaminocyclopentanes after hydrogenolysis.

Skeletal rearrangements are powerful processes for generating molecular diversity with atom economy. Numerous transformations, involving neighboring group participation by  $\sigma$  or  $\pi$  bonds, have been reported in the chemistry of bicyclo-[2.2.1] heptanes (norbornanes),<sup>1</sup> and similar participation has also been established for the corresponding 7-azanorbornane skeleton, leading to compounds of high interest via a very short synthetic sequence.<sup>2</sup> In our ongoing work on the use of bicyclic hydrazines as starting material for the synthesis of polyfunctionalized aminocyclopentanes,<sup>3</sup> we recently reported a new route to aminocyclopentitols based on an acid-catalyzed rearrangement of compound **1** (Scheme 1).<sup>4</sup>

(3) (a) Pérez Luna, A.; Ceschi, M.-A.; Bonin, M.; Micouin, L.; Husson, H.-P.; Gougeon, S.; Estenne-Bouhtou, G.; Marabout, B.; Sevrin, M.; George, P. J. Org. Chem. 2002, 67, 3522. (b) Pérez Luna, A.; Bonin, M.; Micouin, L.; Husson, H.-P. J. Am. Chem. Soc. 2002, 124, 12098. (c) Pérez Luna, A.; Cesario, M.; Bonin, M.; Micouin, L. Org. Lett. 2003, 5, 4771.

We wish to report herein our results concerning acidcatalyzed skeletal rearrangements of the corresponding epoxide **4**.



<sup>(1)</sup> Pale, P.; Vogel, P. In *Comprehensive Organic Functional Group Transformations 2*; Katritzky, A. R., Taylor, R. J. K., Eds.; Elsevier: Amsterdam, 2005; Vol. 1, p 889.

<sup>(2)</sup> Malpass, J. R.; White, R. J. Org. Chem. 2004, 69, 5328 and references cited therein.

<sup>(4)</sup> Bournaud, C.; Robic, D.; Bonin, M.; Micouin, L. J. Org. Chem. 2005, 70, 3316.

Although the involvement of aziridinium intermediates in numerous substitution reactions is well recognized,<sup>5</sup> the participation of nitrogen lone pairs of hydrazines in similar transformations has been less described.<sup>6</sup> We therefore decided to first establish the formation of such a reactive intermediate before studying epoxide rearrangements.

The racemization observed during the solvolysis of optically active *exo*-brosylate **7** is now a textbook experiment for the characterization of a transient  $\sigma$ -delocalized symmetrical carbonium ion in the norbornane series (Figure 1).<sup>7</sup>



Figure 1. Racemizing solvolysis of brosylate 7.

We therefore investigated similar transformations starting from enantiomerically enriched hydrazino-alcohol 9 (Scheme 2).<sup>8</sup>



The use of Mitsunobu reaction conditions<sup>9</sup> with p-nitrobenzoic acid led to substituted compound **10** with

retention of relative configuration as a single diastereomer.<sup>10</sup> Alcohol **9** was then obtained after hydrolysis, however, in a partially racemized form. Not surprisingly, alcohol **9** was recovered without any racemization after a classical esterification—hydrolysis sequence, showing that racemization occurred during the substitution reaction.

A similar behavior was observed with p-nitrophenol as a nucleophile, leading to the largely racemized substituted bicycle **11** (Scheme 3).



In both cases, partial epimerization of the three stereogenic centers and the overall retention of relative configuration under Mitsunobu conditions clearly indicate that the substitution occurred via a transient *meso*-aziridinium intermediate.<sup>11</sup>

Having established that the nitrogen lone pairs of bicyclic hydrazines could be involved in the stabilization of bridged cationic species, we then turned our attention to the acid-catalyzed rearrangement of epoxide **4**. This reaction has been reported on norbornene oxide **12** to involve a skeletal rearrangement leading to 2,7-syn disubstituted norbornane **13** (Figure 2).<sup>12</sup>

According to our preliminary studies with nucleophilic substitutions, assisted ring opening should be followed by the formation of a transient aziridinium, leading to a rearranged skeleton after regioselective nucleophilic attack.

<sup>(5)</sup> Reviews: (a) Cossy, J.; Gomez Pardo, D. *Targets Heterocycl. Syst.* **2002**, 6, 1. (b) Dahanukar, V. H.; Zavialov, L. A. *Curr. Opin. Drug. Discovery Dev.* **2002**, 5, 918.

<sup>(6)</sup> For a NMR description of aziridinium imide, see: Poon, T. H. W.; Park, S. H.; Elemes, Y.; Foote, C. S. *J. Am. Chem. Soc.* **1995**, *117*, 10468. The bromination of diazanorbornenes has been described to occur with nitrogen participation and rearrangement in a seminal study: Raasch, M. S. *J. Org. Chem.* **1975**, *40*, 161.

<sup>(7) (</sup>a) Winstein, S.; Trifan, D. S. J. Am. Chem. Soc. **1949**, 71, 2953. (b) Winstein, S.; Trifan, D. S. J. Am. Chem. Soc. **1952**, 74, 1147. (c) Winstein, S.; Trifan, D. S. J. Am. Chem. Soc. **1952**, 74, 1154. (d) For a general discussion on norbornyl cations, see: Olah, G. A. Acc. Chem. Res. **1976**, 9, 41.

<sup>(8)</sup> Enantiomerically enriched **9** was prepared by a reported procedure: see ref 3a.

<sup>(9)</sup> Mitsunobu, O. Synthesis 1981, 1.

<sup>(10)</sup> Nucleophilic substitutions with retention of configuration under Mitsunobu conditions involving aziridinium species are precedented. See for example: Freedman, J.; Vall, M. J.; Huber, E. W. J. Org. Chem. **1991**, 56, 670. For a rearrangement triggered by a Mitsunobu reaction, see: Dondoni, A.; Richichi, B.; Marra, A.; Perrone, D. Synlett **2004**, 1711.

<sup>(11)</sup> The solvolysis of brosylate **7** has been described to occur with complete racemization, whereas only partial epimerization was observed in our experiments. The partial retention of configuration could tentatively be explained by the formation of a meso, but not fully symmetrical, distorted aziridinium intermediate having unequal bond lengths and leading to the preferential attack of the nucleophile on the carbon that bared the leaving group. We observed that the enantiomeric ratio of the substituted hydrazine **11** was not solvent (THF, toluene) nor temperature (rt to 110 °C) dependent.

<sup>(12)</sup> Walborsky, H. M.; Loncrini, D. F. J. Org. Chem. 1957, 22, 1117.



Although the epoxidation of **1** had been described to be problematic and to require harsh conditions,<sup>13</sup> we were pleased to find that compound **4** could be obtained in 63% yield with optimized conditions on a multigram scale. Nucleophilic opening was then investigated under various acidic conditions (Scheme 4).<sup>14</sup>



As expected, acid-catalyzed epoxide substitution led to the rearranged bicyclic hydrazine **5a** in a regio- and stereose-

(13) Allred, E. L.; Anderson, C. L.; Smith, R. L. J. Org. Chem. 1966, 31, 3493.

lective manner. Sulfuric acid proved to be the best for Brønstedt acid-catalyzed rearrangements, leading to the introduction of a hydroxyl group in a nonnucleophilic solvent (trifluoroethanol)<sup>15</sup> or a methoxy group in methanol.<sup>16</sup> The best results were obtained with organoaluminum reagents in Lewis acid activated reactions, leading to the stereose-lective creation of carbon—halogen or carbon—carbon bonds.<sup>17</sup> In all the cases, only the rearranged skeleton was obtained, in a stereoselective manner.

As in our former studies, hydrogenolysis over platinum oxide of the hydrazine bond afforded the corresponding aminocyclopentanes **6b**,**c** in almost quantitative yields (Scheme 5).



In conclusion, several tetrasubstituted cyclopentanes can be prepared in a short synthetic sequence (four steps from cyclopentadiene) with good overall yield (30%). The key step involves an acid-catalyzed rearrangement of epoxide **4**, followed by a regio- and stereoselective nucleophilic attack, leading to control of the relative configuration of four contiguous stereogenic centers in a single operation. Involvement of an aziridinium intermediate during this process is supported by mechanistic studies on the stereochemical outcomes of nucleophilic substitutions on alcohol **9** under Mitsunobu conditions.

**Acknowledgment.** C.B. thanks the MRT for a grant. We thank the CNRS for financial support.

**Supporting Information Available:** Analytical data for all new compounds and NMR spectra of all synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

## OL060972X

<sup>(14)</sup> Typical procedure. Preparation of compound **5f** is representative: Compound **4** (200 mg, 0.53 mmol) was placed in a Schlenk tube, dried under vacuum for 1 h, and then placed under an argon atmosphere. After addition of freshly distilled anhydrous CH<sub>2</sub>Cl<sub>2</sub> (10 mL), a solution of PhCCAIMe<sub>2</sub> (1.48 M in heptane, 0.43 mL, 0.64 mmol) was added dropwise, and the reaction mixture was stirred at room temperature during 20 h. The reaction was quenched by a Rochelle's salt aqueous solution (2 M, 10 mL). The organic layer was separated, and the aqueous phase was extracted by CH<sub>2</sub>Cl<sub>2</sub> (3 × 10 mL). Organic phases were dried over MgSO<sub>4</sub>; the solvent was evaporated, and the crude was purified by silica gel chromatography (elution conditions: cyclohexane/ethyl acetate 80:20) to give **5f** as a yellow oil (160 mg, 0.33 mmol). The alane solution was prepared according to our previously reported procedure: Feuvrie, C.; Blanchet, J.; Bonin, M.; Micouin, L. Org. Lett. **2004**, *6*, 2333.

<sup>(15)</sup> For an excellent review on the use of trifluoroethanol as a solvent in cationic rearrangements, see: Bégué, J.-P.; Bonnet-Delpon, D.; Crousse, B. *Synlett* **2004**, 18.

<sup>(16)</sup> Acid-catalyzed aziridinium generation from 2,3-epoxy amines has been described: Liu, Q.; Marchington, A. P.; Rayner, C. M. *Tetrahedron* **1997**, *53*, 15729.

<sup>(17)</sup> The reaction of organoaluminum reagents with 2,3-epoxy amines has been described to involve aziridinium intermediates, leading to a C-2 ring-opened product with retention of configuration: Liu, C.; Hashimoto, Y.; Saigo, K. *Tetrahedron Lett.* **1996**, *37*, 6177.