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A New Class of Ammonium Ylid for [2,3]-Sigmatropic Rearrangement Reactions: *ene*-*endo*-Spiro Ylids

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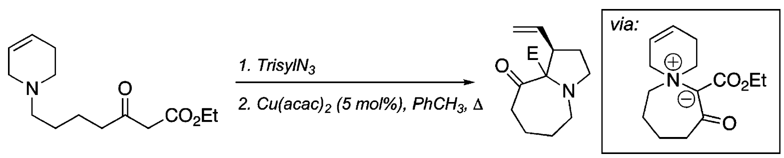
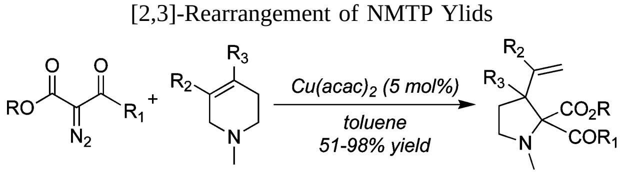
ABSTRACT



The first examples of sigmatropic rearrangements of *ene-endo*-spirocyclic, tetrahydropyridine-derived ammonium ylids are reported. Thus, *spiro*[6.7]-ylids rearrange primarily by a [2,3]-pathway, whereas the analogous [6.6]-ylids rearrange by [1,2]- and [2,3]-mechanisms in roughly equal proportions. This method serves as a rapid entry to the core of a range of alkaloids bearing a pyrrolo[1,2-*a*]azepine or octahydroindolizidine nucleus.

Due to their excellent potential for selective synthetic transformations, much attention has been focused upon the rearrangement reactions of ylids generated from diazo compounds.[1] We have previously reported the use of metal catalysis to mediate [2,3]-rearrangements of NMTP ("*N*-methyltetrahydropyridine") ylids (Scheme 1).[2]

Scheme 1. Functionalized Pyrrolidines via [2,3]-Rearrangement of NMTP Ylids



Among the panoply of excellent research carried out by others in this area, the rearrangement of spiro-ylids has been shown to be an elegant synthetic tool, and the processes reported by West and Clark particularly held our attention. Thus, West et al. reported that spiro[4.5]-ylid **1** rearranges by stereoselective Stevens ([1,2]-) rearrangement,[3] whereas Clark et al. demonstrated that spiro[4.4]-ylid **2** rearranges by a [2,3]-process onto its pendant exocyclic alkene[4] (Figure 1); in both cases, the reactions are highly diastereo- and enantioselective, due to the influence of the adjacent (proline-derived) chiral α-carbon. A reaction corresponding to

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(1) For reviews of the area, see: (a) Davies, H. M. L. (Ed.) *Tetrahedron: Asymmetry* **2003**, *14*, 763−949. (b) Clark, J. S., Ed. *Nitrogen, Oxygen and Sulfur Ylide Chemistry*; Oxford University Press: Oxford, 2002. (c) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; Wiley & Sons: New York, 1998.

(2) [2,3]-Sigmatropic rearrangements of NMTP ylids were first reported by Ollis: (a) Mageswaran, S.; Ollis, W. D.; Sutherland, I. O. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1953. (b) Mageswaran, S.; Ollis, W. D.; Sutherland, I. O. *J. Chem. Soc., Chem. Commun.* **1973**, 656.

(3) (a) West, F. G.; Naidu, B. N. *J. Am. Chem. Soc.* **1994**, *116*, 8420−8421. (b) West, F. G.; Naidu, B. N. *Tetrahedron* **1997**, *53*, 16565−16574. (c) Beall, L. S.; Padwa, A. *Tetrahedron Lett.* **1998**, *39*, 4159−4162. (d) Vanecko, J. A.; West, F. G. *Org. Lett.* **2002**, *4*, 2813−2816. (e) Saba, A.; *Tetrahedron Lett.* **2003**, *44*, 2895−2898. (f) Muroni, D.; Saba, A.; Culeddu, N. *Tetrahedron: Asymmetry* **2004**, *15*, 2609−2614.

(4) (a) Clark, J. S.; Hodgson, P. B. *J. Chem. Soc., Chem. Comun.* **1994**, 2701−2702. Clark, J. S.; Hodgson, P. B. *Tetrahedron Lett.* **1995**, *36*, 2519−2522. (b) Wright, D. L.; Weekly, R. M.; Groff, R.; McMills, M. C. *Tetrahedron Lett.* **1996**, *37*, 2165−2168. (c) Clark, J. S.; Hodgson, P. B.; Goldsmith, M. D.; Blake, A. J.; Cooke, P. A.; Street, L. J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 3225−3337.

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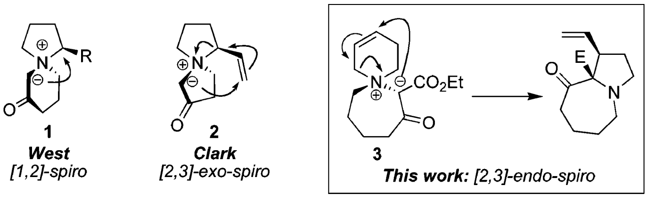
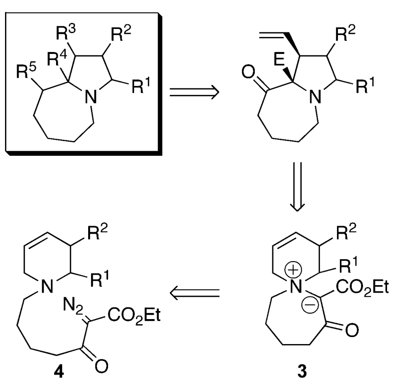


Figure 1. New ammonium [2,3]-rearrangement: *endo*-spiro-ylids.

Clark's, in which the alkene component of the ylid is endocyclic, has not been reported: we reasoned that such a [2,3]-rearrangement (i.e., of a 6-aza-7-carboxyspiro[5.6]-dodecan-8-one ylid, typified by **3**) would, in addition to providing an informative tool in understanding the mechanism of such processes (vide infra), allow a rapid entry to pyrroloazepines such as those at the core of the *Stemona* alkaloids; we report here the realization of our proposal, which represents a novel addition to the class of [2,3]-rearrangement reactions of ammonium ylids.

The pyrrolo[1,2-*a*]azepine structural motif forms the core of a range of alkaloids exhibiting potent biological activity: more than 40 *Stemona* alkaloids (including croomine and tuberostemonine) have been isolated, possessing a diverse range of therapeutic properties.[5] These properties, married to the significant synthetic challenges presented by the molecules, have led to a considerable interest in the design of synthetic routes to enable their synthesis.[6] As detailed in Scheme 2, [2,3]-rearrangement of spiro-ylid **3** (prepared in

Scheme 2. Pyrroloazepines via [2,3]-Rearrangement of *endo*-Spiro Ammonium Ylids



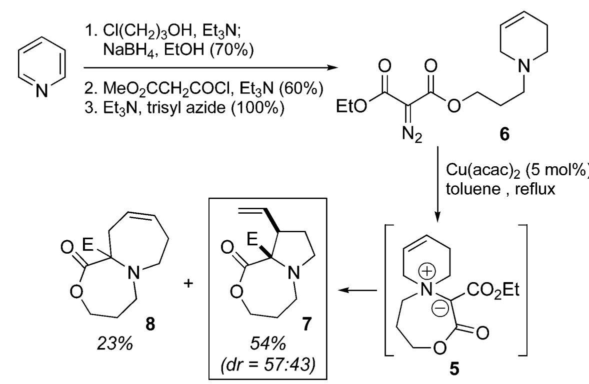
situ from diazoester **4**) would give the pyrroloazepine core directly, while also providing peripheral functionality to enable subsequent preparation of the more densely functionalized members of the class. The proposed reaction would also act as a probe for the scope of the *endo*-alkene class of [2,3]-rearrangements to which the NMTP reactions belong:

(5) For a review of the structures and properties of *Stemona* alkaloids, see: Pilli, R. A.; Ferreira de Oliveira, M. C. *Nat. Prod. Rep*. **2000**, *17*, 117−127.

given the relative rigidity of this class of ylid, when compared to "normal" NMTP ylids, the reactive centers are constrained by the geometry of the spiro-linkage to be more distant from each other than is usual. One might logically conclude that this structural feature would, therefore, disfavor the [2,3]-rearrangement and enhance [1,2]-rearrangement (normally not seen in the rearrangements of NMTP ylids). Thus, we commenced our synthetic studies with the hope of resolving this intriguing mechanistic condundrum, in addition to further defining the scope of ammonium [2,3]-rearrangement chemistry and developing a useful synthetic tool.

We initially chose to carry out a model study of the proposed, "all-carbon", rearrangement, using a more readily prepared oxazepinone analogue (Scheme 3). The synthetic

Scheme 3. [2,3]-Rearrangement of Oxazepinone Spiro-ylid **5**



route to model ylid **5** began with hydroxypropylation of pyridine, followed by reduction with $NaBH_4$; subsequent acylation with methylmalonyl chloride and diazo transfer reaction gave key intermediate **6**, in 42% yield over the four steps of the sequence.

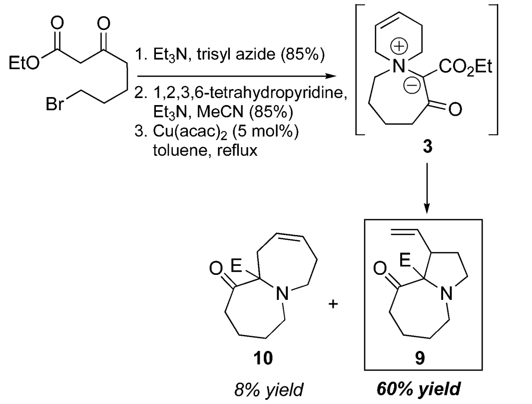
Thus, we were set to carry out the key rearrangement reaction: we observed that treatment of **6** with a substoichiometric amount of $Cu(acac)_2$ in refluxing toluene gave [2,3]-rearrangement product **7** (dr = 57:43, major isomer as shown; we define this isomer as being cis-configured and use this terminology throughout the manuscript) in 54% yield (unoptimized), along with the product of [1,2]-rearrangement **8** (23% yield) (Scheme 3). This is, to our knowledge, the first example of a [2,3]-sigmatropic rearrangement of spiro-NMTP ylids. The mixture of diastereoisomers probably

(6) For recent reports, see: (a) Morimoto, Y.; Iwahashi, M.; Kinoshita, T.; Nishida, K. *Chem. Eur. J.* **2001**, *7*, 4107−4116. (b) Ginn, J. D.; Padwa, A. *Org. Lett.* **2002**, *4*, 1515−1517. (c) Martin, S. F. *Acc. Chem. Res.* **2002**, *35*, 895−904. (d) Jacobi, P. A.; Lee, K. *J. Am. Chem. Soc.* **2000**, *122*, 4295−4303. (e) Gurjar, M. K.; Reddy, D. S. *Tetrahedron Lett.* **2002**, *43*, 295−298. (f) Kende, A. S.; Hernando, J. I. M.; Milbank, J. B. J. *Tetrahedron* **2002**, *58*, 61−74. (g) Williams, D. R.; Fromhold, M. G.; Earley, J. D. *Org. Lett.* **2001**, *3*, 2721−2724. (h) Lindsay, K. B.; Pyne, S. G. *Synlett* **2004**, 779−782. (i) Bruggemann, M.; McDonald, A. I.; Overman, L. E.; Rosen, M. D.; Schwink, L.; Scott, J. P. *J. Am. Chem. Soc.* **2003**, *125*, 15284−15285. (j) Williams, D. R.; Shamin, K.; Reddy, J. P.; Amato, G. S.; Shaw, S. M. *Org. Lett.* **2003**, *5*, 3361−3364. (k) Booker-Milburn, K. I.; Hirst, P.; Charmant, J. P. H.; Taylor, L. H. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 1642−1644. (l) Wipf, P.; Rector, S. R.; Takahashi, H. *J. Am. Chem. Soc.* **2002**, *124*, 14848−14849.

results from the possibility of two different secondary orbital interactions (known to be important in these rearrangements) with either of the two carbonyl groups present in the ylid.

The preparation of the all-carbon ylid **3** was best executed via the introduction of the NMTP subunit at a late stage of the sequence (Scheme 4).[7] Given the intimacy of the

Scheme 4. Efficient Preparation of Pyrrolo[1,2-*a*]azepines by [2,3]-Rearrangement of *endo*-Spiro Ammonium Ylids

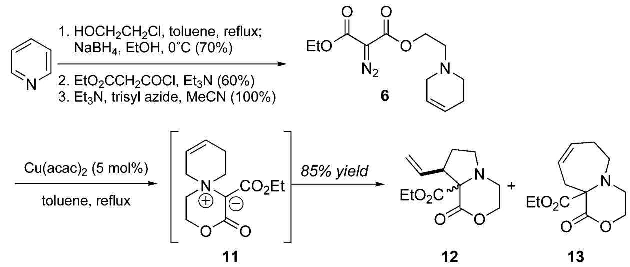


proposed transition state in NMTP ammonium ylid rearrangements, we were encouraged to hope that the presence of a more sterically demanding methylene group, rather than the endocyclic oxygen atom of **5**, would lead to a higher selectivity in the [2,3]-rearrangement step: thus, we were pleased to witness that the rearrangement of carbon ylid **3** (Scheme 4) proceeded to give azepinones **9** and **10** but with improved regioselectivity (**9**:**10** = 88:12) and with better diastereocontrol in the [2,3]-process (*cis*-**9**:*trans*-**9** = 70:30; this stereochemical assignment was confirmed by X-ray crystallography). Compared to existing methods, this represents a highly efficient entry into the pyrrolazepine architecture, and the method also allows a facile introduction of a quaternary center to the ring junction of such structures.

To better define the scope of the reaction, we next investigated this new rearrangement reaction in two lower homologues. Thus, morpholinone spiro[5.5]-ylid **11** was prepared in a manner analogous to that used for synthesis of **5**; **11** underwent rearrangement in 85% yield to give the [2,3]- and [1,2]-rearrangement products (**12** and **13**, respectively) as a separable 1:1 mixture (Scheme 5); the [2,3]-product was itself obtained as a 1:1 mixture of diastereoisomers. Clearly, the extra rigidity of the [5.5]-system now *does* place unfeasible geometric constraints upon the [2,3]-reaction, resulting in an increased propensity for the Stevens [1,2]-process.

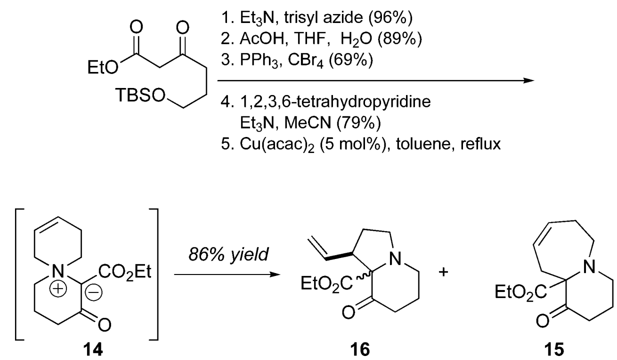
Once again, the synthesis of the analogous all-carbon [5.5]-ylid **14** was best accomplished using a late-stage introduction

Scheme 5. [2,3]-Rearrangement of Morpholinone [5.5]-Spiro Ammonium Ylids



of the heterocyclic subunit (Scheme 6). As seen previously in the higher homologue, the introduction of a methylene in

Scheme 6. [2,3]-Rearrangement of Piperidinone [5.5]-Spiro Ammonium Ylids



place of the lactonic oxygen atom improved the diastereoselectivity of the [2,3]-rearrangement, though the regiochemistry was unaltered: a 5:3:2 mixture of [1,2]- and cis- and trans-[2,3]-products (**15**, *cis*-**16**, and *trans*-**16**, respectively) was isolated in 86% combined yield. Though the reaction is less selective in this case, the diastereomeric [2,3]-products are easily purified and, given the resemblance of **16** to potent natural products (such as castanospermine, inter alia), the method nonetheless represents a very efficient entry into structures with potential biological significance.

Some comment upon the differences in the ratios of [2,3]- and [1,2]-rearrangement of these ylids is appropriate. In the rearrangement of [5.5]-ylids **11** and **14**, there are four possible structures available: two *endo*-conformed (A and B) and two *exo*-conformed (C and D) (Figure 2).

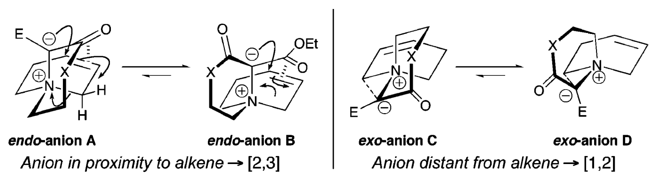


Figure 2. Rigidity of conformation controls the rearrangement of [6.6]-*endo*-spiro ylids.

(7) For an analogous strategy, see: Vanecko, J. A.; West, F. G. *Org. Lett.* **2002**, *4*, 2813.

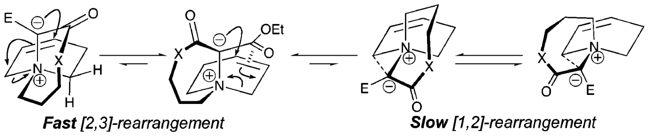


Figure 3. Flexibility in *endo*-spiro[6.7]-ylids favors [2,3]-rearrangement.

Only the *endo*-transition state allows a [2,3]-rearrangement: the alternative *exo*-TS has its anionic component geometrically constrained to be distant from the alkene, preventing [2,3]-rearrangement and favoring the (nonconcerted) [1,2]-process. If one assumes that ylid formation is irreversible, the observation that there is no regiocontrol in the reaction of the [5.5]-ylid implies two things: first, that ring-flip (the process by which the *endo*- and *exo*-anions are interconverted) is slow compared to C−C bond formation, and, second, that the *endo*- and *exo*-transition states have similar energy (meaning that they are formed at comparable rates). Under these constraints, a 1:1 ratio of [1,2]:[2,3] products must inevitably result. With regard to the preference for formation of the cis isomer in the rearrangement of the carbon ylid, we rationalize this as arising from a repulsive interaction between the X group (CH_2 in ylid **14**) and the methylene indicated (*endo*-anion A, Figure 2). In the rearrangement of ylid **11**, X = O and there is relatively little interaction between the smaller oxygen atom and the same methylene, leading to a 1:1 mixture of diastereomers.

In the case of spiro[5.6]-ylids **3** and **5** (Figure 3), we rationalize the enhanced yield of the [2,3]-rearranged product by assuming that its greater flexibility facilitates the [2,3]-process, meaning that interconversion between the possible conformers is rapid compared to the C−C bond-forming events and that the [2,3]-process is faster than the [1,2]-reaction.[8] Thus, the yield of [2,3]-rearrangement product is enhanced, at the expense of the [1,2]-byproduct. Once again, greater diastereoselectivity is observed when X = CH_2.

In summary, we have described the first [2,3]-sigmatropic rearrangements of spirocyclic ammonium ylids in which the alkene component is endocyclic. These ylids are efficiently prepared from readily available starting materials, and the method represents a novel and efficient route to the core structures of two classes of bicyclic alkaloids. In particular, the use of this reaction in the synthesis of a range of *Stemona* alkaloids is a current objective within our laboratories.

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Supporting Information Available: Experimental and spectroscopic data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) Where both processes are possible, [2,3]-rearrangement is usually more rapid than [1,2]-rearrangement. See, for instance: Workman, J. A.; Garrido, N. P.; Sançon, J.; Roberts, E.; Wessel, H. P.; Sweeney, J. B. *J. Am. Chem. Soc.* **2005**, *126*, 1066−1067.