ORGANIC LETTERS

2012
Vol. 14, No. 8
2018–2021

Desulfonylative Radical Ring Closure onto Aromatics. A Modular Route to Benzazepin-2-ones and 5-Arylpiperidin-2-ones

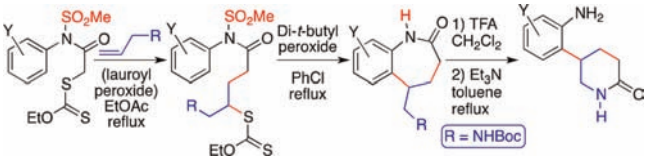
Nicolas Charrier, Zhibo Liu, and Samir Z. Zard*

Laboratoire de Synthèse Organique, CNRS UMR 7652 Ecole Polytechnique, 91128 Palaiseau Cedex, France

zard@poly.polytechnique.fr

Received March 1, 2012

ABSTRACT



Adducts from the intermolecular radical addition of *N*-xanthylacetyl-*N*-methanesulfanilides to Boc-protected allylamine undergo ring closure with loss of a methanesulfonyl radical to give benzazepin-2-ones. Upon deprotection and exposure to triethylamine, these compounds rearrange into 5-aryl-2-piperidones. This approach also represents a useful route to benzazepin-2-ones unsubstituted on the nitrogen atom of the azepinone ring.

Ready access to novel, variously substituted heterocyclic and heteroaromatic compounds is a central concern in medicinal chemistry.[1] In this respect, 3-arylpiperidines, and related structures, are of particular importance in view of their interesting opioid[2] and dopaminergic activity.[3] One example is preclamol (Figure 1), noted to be the first selective D_2-like dopamine autoreceptor agonist. Such dopaminergic substances have potential for the treatment of depression and drug addiction, Parkinson's and Alzheimer's diseases, and schizophrenia.

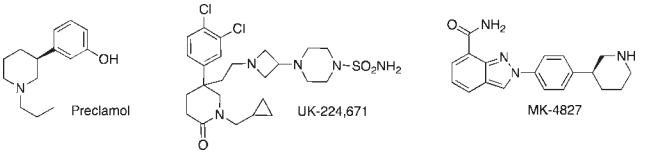


Figure 1. Examples of 3-aryl-piperidine drugs.

The identification of 3-arylpiperidines as inhibitors of the steroid 5α-reductase,[4] as ligands of the σ receptor,[5] and as antagonists of the tachykinin system[6] increases their importance as a class with privileged pharmacological structures. Thus, piperidone UK-224,671 is a potent,

(1) (a) Ward, R. A.; Kettle, J. G. *J. Med. Chem.* **2011**, *54*, 4670. (b) Pitt, W. R.; Parry, D. M.; Perry, B. G.; Groom, C. R. *J. Med. Chem.* **2009**, *52*, 2952. (c) Lovering, F.; Bikker, J.; Humblet, C. *J. Med. Chem.* **2009**, *52*, 6752.

(2) Iorio, M. A. *J. Med. Chem.* **1978**, *21*, 812.

(3) (a) Wikström, H.; Sanchez, D.; Lindberg, P.; Hacksell, U.; Arvidsson, L.-E.; Johansson, A. M.; Thorberg, S.-O.; Nilsson, J. L. G.; Svensson, K.; Hjorth, S.; Clark, D.; Carlsson, A. *J. Med. Chem.* **1984**, *27*, 1030. (b) Liljefors, T.; Wikström, H. *J. Med. Chem.* **1986**, *29*, 1896. (c) Liljefors, T.; Bøgesø, K. P.; Hyttel, J.; Wikström, H.; Svensson, K.; Carlsson, A. *J. Med. Chem.* **1990**, *33*, 1015. (d) Sonensson, C.; Lin, C.-H.; Hansson, L.; Waters, N.; Svensson, K.; Carlsson, A.; Smith, M.; Wikström, H. *J. Med. Chem.* **1994**, *37*, 2735. (e) Hansson, L. O.; Waters, N.; Holm, S.; Sonesson, C. *J. Med. Chem.* **1995**, *38*, 3121. (f) Macchia, M.; Cervetto, L.; Demontis, G. C.; Longoni, B.; Minutolo, F.; Orlandini, E.; Ortoce, G.; Papi, C.; Sbrana, A.; Macchia, B. *J. Med. Chem.* **2003**, *46*, 161.

(4) Abell, A. D.; Prince, M. J.; McNulty, A. M.; Neubauer, B. L. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1909.

(5) Ablordeppey, S. Y.; Fischer, J. B.; Law, H.; Glennon, R. A. *Bioorg. Med. Chem.* **2002**, *10*, 2759.

(6) (a) Giardina, G. A. M.; Grugni, M.; Rigolio, R.; Vassallo, M.; Erhard, K.; Farina, C. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2307. (b) Allan, G.; Carnell, A. J.; Escudero Hernández, M. L.; Pettman, A. *Tetrahedron* **2001**, *57*, 8193. (c) Mackenzie, A. R.; Marchington, A. P.; Middleton, D. S.; Newman, S. D.; Jones, B. C. *J. Med. Chem.* **2002**, *45*, 5365.

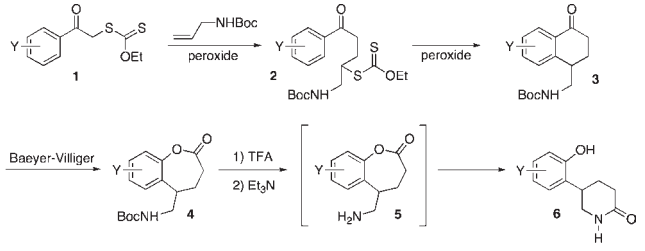
(7) Jones, P.; Altamura, S.; Boueres, J.; Ferrigno, F.; Fonsi, M.; Giomini, C.; Lamartina, S.; Monteagudo, E.; Ontoria, J. M.; Orsale, M. V.; Palumbi, M. C.; Pesci, S.; Roscilli, G.; Scarpelli, R.; Schultz-Fademrecht, C.; Toniatti, C.; Rowley, M. *J. Med. Chem.* **2009**, *52*, 7170.

10.1021/ol3005276
Published on Web 03/30/2012

selective antagonist of the neurokinin 2 receptor,[6c] while MK-4827 developed by Merck has entered clinical trials as an antitumor drug (Figure 1).[7]

Most routes to 3-arylpiperidines involve organometallic couplings starting with pyridines.[8] Examples include Heck[9] or Suzuki[10] couplings and nickel catalyzed cross-couplings between arylmagnesium bromides and 3-bromopyridines,[11] followed by complete or partial reduction of the resulting 3-aryl-substituted pyridine nucleus.

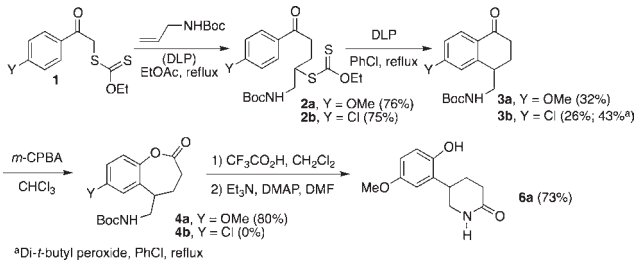
Scheme 1. Initial Strategy



We recently reported a radical based approach relying on a 1,4-aryl group migration from sulfonamides.[12] In continuation of our study of the degenerative radical exchange of dithiocarbonates (xanthates) and related derivatives,[13] we have conceived of an alternative route that takes advantage of the possibility of annelation by a radical cyclization onto aromatic rings.

Our initial plan, portrayed in Scheme 1, involves formation of an α-tetralone **3** by addition−cyclization of a phenacyl xanthate **1** and Boc-protected allylamine,[14] followed by ring expansion into lactone **4** through a Baeyer−Villiger reaction and, finally, spontaneous rearrangement of the free amine **5** into the more stable 5-aryl-piperidin-2-one **6** after deprotection of the amino group and treatment with base.

Scheme 2. First Example of an Aryl-piperidone Synthesis



This plan was readily reduced to practice on example **6a** depicted in Scheme 2. However, while the first dilauroyl peroxide (DLP)[15] initiated intermolecular radical addition to give **2a** and **2b** was efficient, the ring closure step leading to the tetralone proceeded in variable and also in significantly lower yields in comparison to our earlier study.[14] One possible explanation was the partial destruction of the Boc-protecting group by the lauric acid produced in the medium. Prolonged heating in refluxing chlorobenzene in the presence of even a weak acid such as lauric acid could result in slow decomposition of the relatively sensitive Boc-group. Indeed, in the case of **2b**, its cyclization into **3b** was markedly improved (from 26% to 43%) by replacing DLP with di-*tert*-butyl peroxide (DTBP), which does not liberate any acidic product upon thermolysis or induced decomposition (see also below).

Nevertheless, our hopes for expanding the scope of this approach were ultimately dashed by the unreliability of the Baeyer−Villiger reaction. For reasons still unclear, the Baeyer−Villiger reaction on α-tetralones **3** proved highly capricious.[16] For instance, no lactone **4b** was formed upon treatment of **3b** with peracid under otherwise identical conditions to those used for cyclizing **3a**.

Faced with this unexpected setback, we decided to examine in parallel another potentially efficient strategy relying this time on the ability to construct benzazepinones by direct radical ring closure.[17] This approach is illustrated by the transformation pictured in Scheme 3 starting from xanthate **7**. The radical addition to Boc-protected allylamine furnished a high yield of the normal adduct **8**. Further exposure to stoichiometric amounts of DLP in refluxing chlorobenzene accomplished the cyclization and delivered benzazepinone **9** in 50% yield. Finally, deprotection of the amine with TFA and heating with triethylamine induced an efficient rearrangement into piperidone **10**.

(8) For recent syntheses of 3-arylpiperidines, see: (a) Wong, Y.-S.; Marazano, C.; Gnecco, D.; Génisson, Y.; Chiaroni, A.; Das, B. C. *J. Org. Chem.* **1997**, *62*, 729. (b) Lindermann, U.; Reck, G.; Wulff-Molder, D.; Wessig, P. *Tetrahedron* **1998**, *54*, 2529. (c) Klumpp, D. A.; Garza, M.; Jones, A.; Mendoza, S. *J. Org. Chem.* **1999**, *64*, 6702. (d) Johnson, T. A.; Curtis, M. D.; Beak, P. *J. Am. Chem. Soc.* **2001**, *123*, 1004. (e) Liu, D.-G.; Gao, Y.; Wang, X.; Kelley, J. A.; Burke, T. R., Jr. *J. Org. Chem.* **2002**, *67*, 1448. (f) Amat, M.; Cantó, M.; Llor, N.; Ponzo, V.; Pérez, M.; Bosch, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 335. (g) Amat, M.; Cantó, M.; Llor, N.; Escolano, C.; Molins, E.; Espinosa, E.; Bosch, J. *J. Org. Chem.* **2002**, *67*, 5343. (h) Colpaert, F.; Mangelinckx, S.; De Kimpe, N. *J. Org. Chem.* **2011**, *76*, 234.

(9) (a) Nilsson, K.; Hallberg, A. *J. Org. Chem.* **1992**, *57*, 4015. (b) Büchner, I. K.; Metz, P. *Tetrahedron Lett.* **2001**, *42*, 5381.

(10) (a) Ali, N. M.; McKillop, A.; Mitchnell, M. B.; Rebelo, R. A.; Wallbank, P. J. *Tetrahedron* **1992**, *48*, 8117. (b) Tagata, T.; Nishida, M. *J. Org. Chem.* **2003**, *68*, 9412. (c) Cioffi, C. L.; Spencer, W. T.; Richards, J. J.; Herr, R. J. *J. Org. Chem.* **2004**, *69*, 2210.

(11) (a) Hacksell, U.; Arvidsson, L.-E.; Svensson, U.; Nilsson, L. G. *J. Med. Chem.* **1981**, *24*, 1475. (b) Tagat, J. R.; McCombie, S. W.; Barton, B. E.; Jackson, J.; Shortall, J. *Bioorg. Med. Chem. Lett.* **1995**, *18*, 2143.

(12) (a) Georghe, A.; Quiclet-Sire, B.; Vila, X.; Zard, S. Z. *Org. Lett.* **2005**, *7*, 1653. (b) Georghe, A.; Quiclet-Sire, B.; Vila, X.; Zard, S. Z. *Tetrahedron* **2007**, *63*, 7187. For a synthesis of 4-arylpiperidinones, see: Vila, X.; Zard, S. Z. *Heterocycles* **2006**, *70*, 45.

(13) For reviews on the xanthate radical addition-transfer process, see: (a) Zard, S. Z. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 672. (b) Quiclet-Sire, B.; Zard, S. Z. *Chem.—Eur. J.* **2006**, *12*, 6002. (c) Quiclet-Sire, B.; Zard, S. Z. *Top. Curr. Chem.* **2006**, *264*, 201. (d) Zard, S. Z. *Aust. J. Chem.* **2006**, *59*, 663. (e) Zard, S. Z. *Org. Biomol. Chem.* **2007**, *5*, 205. (f) Quiclet-Sire, B.; Zard, S. Z. *Pure Appl. Chem.* **2011**, *83*, 519.

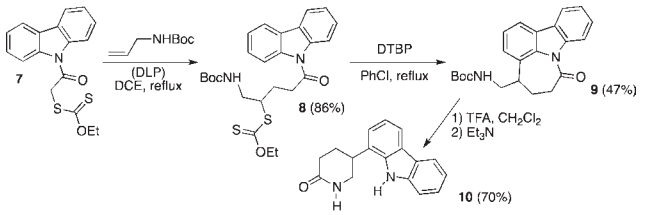
(14) Liard, A.; Quiclet-Sire, B.; Saicic, R.; Zard, S. Z. *Tetrahedron Lett.* **1997**, *38*, 1759.

(15) Dilauroyl peroxide is sometimes sold under lauroyl peroxide. Placing the peroxide between parentheses in the reaction schemes indicates that it is used in substoichiometric amounts as an initiator. Otherwise, it is both the initiator and the stoichiometric oxidant in mediating ring closure on the aromatic ring and rearomatization.

(16) For a recent review, see: ten Brink, G.-J.; Arends, I. W. C. E.; Sheldon, R. A. *Chem. Rev.* **2004**, *104*, 4105.

(17) Kaoudi, T.; Quiclet-Sire, B.; Seguin, S.; Zard, S. Z. *Angew. Chem., Int. Ed.* **2000**, *39*, 731.

Scheme 3. Second Route to Aryl-piperidones



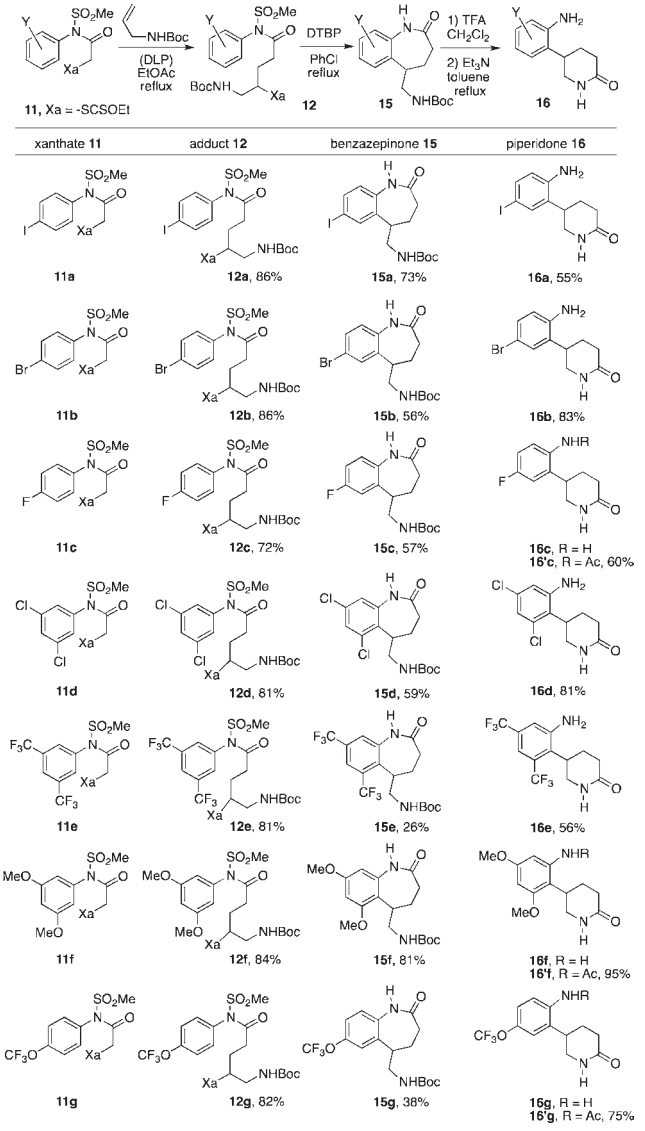
Expanding the range of substrates is crucial if this approach is to have any utility in medicinal chemistry. We therefore examined anilines as potential precursors since numerous substituted anilines are commercially available. To this end, we prepared a number of xanthates **11a**–**g** (Scheme 4 and Table 1) from a range of anilines, using a methanesulfonamide as the blocking group on nitrogen. It is necessary to have a substituent on the nitrogen for the radical cyclization on the aromatic ring to occur. The choice of the sulfonamide was made initially because of the simplicity of their synthesis and the desire to avoid rotamers which complicate spectroscopic description. Furthermore, the presence of the sulfonyl group should facilitate the transamidation step by improving the leaving group ability of the aniline nitrogen.

The synthesis of the xanthates and the first intermolecular addition to Boc-protected allylamine proceeded uneventfully to give adducts **12a**–**g** (Scheme 4 and Table 1). However, when the ring closure was performed by heating adduct **12a** with DLP in refluxing chlorobenzene, we were surprised to find that the sulfonamide group was absent in the product **15a**, which was obtained in 27% yield (Scheme 4). Following our observation above concerning the possible deleterious role of lauric acid, we replaced DLP with DTBP and were pleased to find that the yield of benzazepinone **15a** jumped to a respectable 73%.

The intermediate radical **13a** clearly undergoes a fragmentation of the N–SO_2Me bond with the formation of a methanesulfonyl radical. This latter can extrude sulfur dioxide to give a methyl radical, which could in principle participate in propagating the radical chain since the thermal decomposition of DTBP also leads to methyl radicals. The resulting intermediate **14a** then tautomerizes to give the observed benzazepinone **15a**.

We had extensively used methanesulfanilides in the synthesis of indolines without observing such a fragmentation.[18] For a more direct comparison, we prepared adduct **19** by addition of cyanomethyl xanthate **18** to *N*-allyl-*N*-methanesulfonyl-4-iodoaniline **17** and subjected it to the same cyclizing conditions as those used for **12a** (Scheme 4). This furnished *N*-methanesulfonylindoline **21** in 66% yield and none of the desulfonoylated material **22**. Presumably, the more flexible benzazepinone structure in **13a** allows the correct alignment of the orbital containing the free electron with the antibonding orbital of the N–S bond, and the scission can occur. A similar arrangement in intermediate radical **20**, with the smaller indoline ring, is significantly more strained and therefore energetically more costly.

Table 1. Examples of *N*-Unsubstituted 5-Aryl-2-piperidones

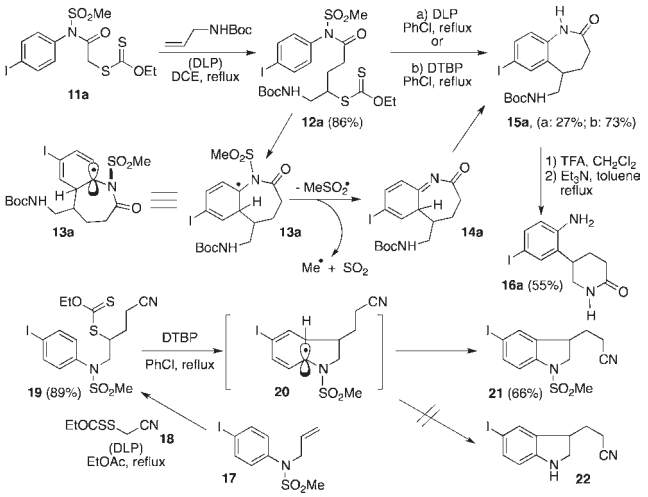


The loss of the sulfonamide group eliminated the need for a subsequent deprotection step and had otherwise no deleterious effect on the rest of the sequence. The equilibrium still favored the formation of the desired aryl piperidones. Thus, in the case of **15a**, removal of the Boc-protecting group and treatment with triethylamine afforded the desired arylpiperidone **16a** in 55% yield (Scheme 4).

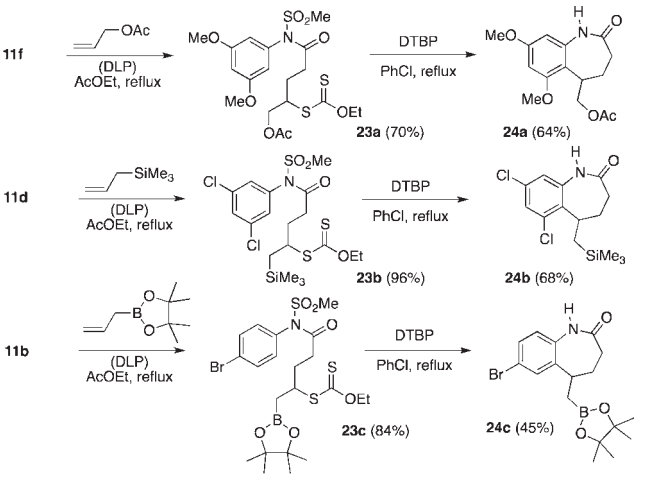
Substitution of the aromatic ring allows the introduction of a broad diversity in the structures, as shown by the examples collected in Table 1. In some cases (**16′c**,**f**,**g**), we found that acetylation of the liberated aniline with acetic anhydride increased the efficiency of the product isolation.

(18) (a) Quiclet-Sire, B.; Sortais, B.; Zard, S. Z. *Chem. Commun.* **2002**, 1692. (b) Ly, T.-M.; Quiclet-Sire, B.; Sortais, B.; Zard, S. Z. *Tetrahedron Lett.* **1999**, *40*, 2533.

Scheme 4. Unexpected Loss of a Methanesulfonyl Group



Scheme 5. Examples of Benzazepinones



The possibility of introducing fluorine groups, as in **16e**, **16′c**, and **16′g**, is particularly noteworthy, in view of the importance of organofluorine derivatives for the pharmaceutical and agrochemical industries. Finally the tolerance of the process to the presence of chlorine, bromine, and especially iodine (**16a**,**b**,**d**) opens up further avenues for diversification through numerous powerful organometallic couplings (e.g., Suzuki, Sonogashira, Heck, Stille, and Buchwald−Hartwig couplings).

While the purpose of this work was originally to establish an easy access to arylpiperidones, the importance of the benzazepinone intermediates **15** must nevertheless be underscored. Indeed, benzazepines and benzazepinones belong to one of the most studied classes of pharmacophores.[19] The present route to *N*-unsubstituted benzazepinones **15** allies simplicity, cheapness, convergence, and flexibility. The Boc-protected allylamine used as the olefinic trap in the above transformations can be replaced with other alkenes, in line with our earlier work on the degenerative radical addition−transfer of xanthates and related derivatives. This provides a simple means for introducing side chains bearing various functional groups into the benzazepinone skeleton. Three examples are depicted in Scheme 5, as an illustration of the possibilities.[20] The rapid synthesis of the boronate substituted benzazepinone **24c** is particularly interesting as such derivatives would be exceedingly tedious to make by traditional routes.

In summary, we have described a convenient approach to both benzazepinones and 5-aryl-2-piperidinones, unsusbtituted on the ring nitrogen. It illustrates the potential of radical chemistry in providing medicinal and heterocyclic chemists with a concise access to novel compounds not readily available by more established methods.

Acknowledgment. We dedicate this paper with respect and admiration to Dr. Stuart W. McCombie, formerly of Schering-Plough. N.C. and Z.L. thank Ecole Polytechnique for a scholarship. We thank Xuan Xiao and Aurélie Josselin, who participated in this project as undergraduate interns.

Supporting Information Available. Experimental procedures, full spectroscopic data and copies of ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(19) See for example: Zhang, A.; Neumeyer, J. L.; Baldessarini, R. J. *Chem. Rev.* **2007**, *107*, 274.

(20) It is interesting to note that benzazepin-2-ones may also be obtained by a Beckmann rearrangement of the oximes derived from α-tetralones such as **3**. For an example, see: Cordero-Vargas, A.; Quiclet-Sire, B.; Zard, S. Z. *Bioorg. Med. Chem.* **2006**, *14*, 6165.

The authors declare no competing financial interest.