ORGANIC LETTERS

2005
Vol. 7, No. 17
3817−3820

An Unusual Radical Smiles Rearrangement

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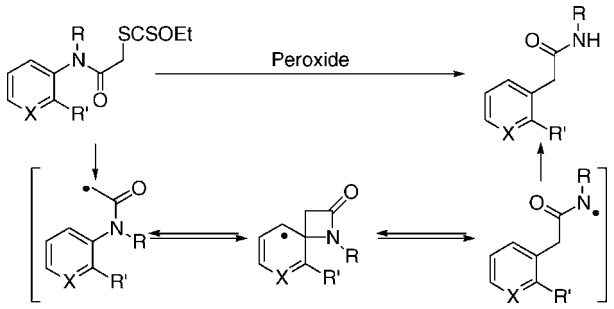
Received July 5, 2005

ABSTRACT



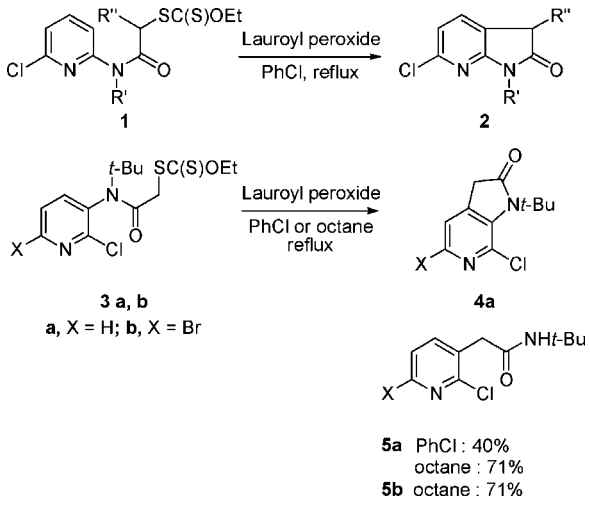
Radicals derived from *N*-(α-xanthyl)acetanilides or *N*-(α-xanthyl)acetylaminopyridines possessing a substituent next to the nitrogen undergo a hitherto undocumented Smiles rearrangement proceeding through a four-membered ring. It was also found that under certain conditions the amidyl radical produced by cleavage of the four-membered ring intermediate can undergo fragmentation to give an isocyanate. Such fragmentations are unprecedented at temperatures corresponding to refluxing benzene or chlorobenzene.

We recently embarked on a program for the synthesis of bicyclic azapyridines using the xanthate transfer technology and were able to construct azaoxindoles of type **2** starting from 2-chloro-6-aminopyridine precursors **1** (Scheme 1).[1,2]

Such derivatives are in great demand by medicinal chemists and are accessible only with difficulty by more traditional routes. In a logical extension of our initial study, we attempted the synthesis of azaoxindole **4a** from xanthate **3a** by the same radical process. We were surprised to find that treatment of this compound with lauroyl peroxide in refluxing chlorobenzene gave no azaoxindole **4a**. The major product turned out to be **5a**, isolated in 40% yield.

Apparently, carbon-centered radical **6a**, derived from the starting xanthate, underwent a Smiles rearrangement through spiroazetidinone **7a** and amidyl radical **8a**, as outlined in Scheme 2. Cases of radical Smiles rearrangements involving five-membered cyclic intermediates are well documented,[3]

Scheme 1. Unexpected Radical Smiles Rearrangement



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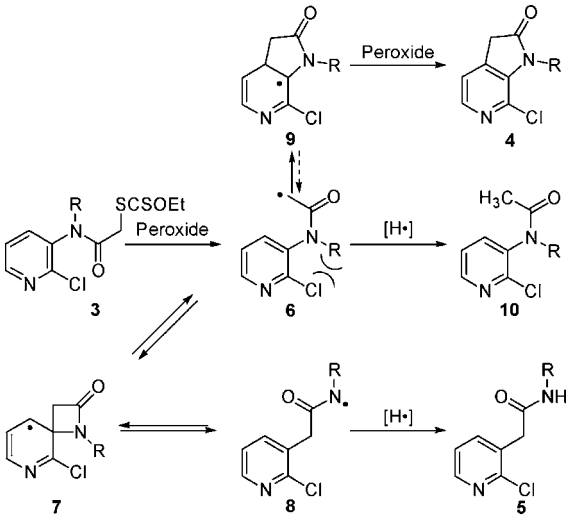
(1) Bacqué, E.; El Qacemi, M.; Zard, S. Z. *Org. Lett.* **2004**, *6*, 3671−3674.

(2) For general reviews on the xanthate transfer, see: (a) Zard, S. Z. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 672. (b) S. Z. Zard. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, 2001; Vol. 1, pp 90−108.

10.1021/ol051568l CCC: $30.25
Published on Web 07/23/2005

Scheme 2. Smiles Rearrangement through a Spiroazetidinone



3-10 : a, R = *t*-Bu; **c**, R = Me; **d**, R = *i*-Pr; **e**, R = cyclohexyl

but we are not aware of any report claiming a radical Smiles rearrangement proceeding through a four-membered ring. In the present case, steric repulsion between the chlorine atom and the bulky *tert*-butyl group hinders the desired ring closure of radical **6a** into **9a**. The *tert*-butyl group further compresses the radical terminus toward the pyridine ring and favors an otherwise difficult 4-*exo*-cyclization, as a prelude to the unusual Smiles rearrangement. As depicted in Scheme 2, a reactive amidyl radical **8a** is generated which abstracts a hydrogen atom from the medium but which can also undergo a number of undesired side reactions accounting for the modest yield of **5a**. The yield of amide **5a** increased to 71% when chlorobenzene was replaced with octane, a solvent with better hydrogen atom donating ability. The choice of octane is important because it behaves as a good hydrogen atom donor toward the reactive amidyl radical **8a** but as poor hydrogen atom donor toward the less electrophilic initial radical **6a**, thus giving the latter enough lifetime to undergo the Smiles rearrangement. Otherwise, premature reduction of **6a** would result in the generation of uninteresting amide **10a**. In the same manner, xanthate **3b** furnished the corresponding rearranged amide **5b** in 71% yield.

The importance of the steric bulk of the *tert*-butyl group was revealed by studying the behavior of xanthates **3c**−**e** under similar conditions. For instance, in the case of **3c** with a comparatively small methyl group on the nitrogen, the Smiles rearrangement was not observed. The corresponding azaoxindole **4c** now became the major product and could be isolated in 39% yield, along with smaller amounts of the reduced acetamide **10c** (9%). The higher analogues **3d** and **3e**, with moderately bulky isopropyl and cyclohexyl groups, gave a mixture of all three compounds **4d**, **5d**, and **10d** in 18, 31, and 9% yield and **4e** (traces), **5e**, and **10e** in 42 and 10% yield, respectively. These series of experiments were carried out in refluxing chlorobenzene; in octane, the major compound was the corresponding acetamide **10c**−**e**. Thus, in contrast to the *tert*-butyl substituted radical **6a**, where the Smiles rearrangement is faster than reduction with octane, radicals **6c**−**e**, possessing a smaller group on the nitrogen, underwent the 4-*exo* addition less rapidly than hydrogen abstraction from the solvent, which must proceed at comparable rates for radicals **6a** and **6c**−**e**.

Further compelling evidence for the intermediacy of a spiroazetidinone and amidyl radicals **7** and **8** emerged when we examined the extension to benzene derivatives. Xanthate **12** was prepared by reaction of 2-chloroaniline with *tert*-butyl trichloroacetimidate in the presence of $BF_3{\cdot}OEt_2$,[4] followed by chloroacetylation and displacement of the chlorine with potassium *O*-ethyl xanthate. We expected **12** to be less reactive than the analogous pyridine derivative **3a**, but our worries proved unfounded. Exposure of **12** to lauroyl peroxide in refluxing octane also produced a good yield (73%) of the rearranged product **13**. Unexpectedly, under the same conditions, toluidine analogue **14** furnished the rearranged dimer **16** in 55% yield, along with the product of direct reduction **15** (23%). Dimer **16** can only arise from coupling of benzylic radicals **18**, themselves derived by an internal 1,6 hydrogen atom abstraction by the intermediate amidyl radical **17** (Scheme 3). We had found that a clean formation of dimers is possible in the xanthate transfer process when a stabilized radical is generated,[5] and this has profound mechanistic implications which set the xanthate transfer apart from other Kharasch-type reactions. Replacing the methyl with a trifluoromethyl group blocked the hydrogen abstraction step and the "normal" product **20** was now obtained in 46% yield from xanthate **19**.

A further interesting observation arose when we examined the case of xanthate **22a**, with two chlorine atoms in the ortho positions. The substitution step itself from the chloride precursor **21a** proved problematic, and we had to switch to the corresponding neopentyl xanthate. We have in the past resorted to the more robust *O*-neopentyl xanthates in difficult cases.[6] The sluggish substitution reflects the severe steric congestion and the consequent conformational restrictions in that part of the molecule. When xanthate **22a** was subjected to the action of the peroxide in refluxing octane (0.1 M), the Smiles product **23a** was formed, accompanied this time by the unexpected symmetrical diarylethane **24** in a 75:25 ratio as determined by NMR. The isolated yield of **23a** was 55%, but the rather nonpolar **24** could not be obtained completely pure because of contamination by residues from lauroyl peroxide. No dichloroacetanilide **25a**, the product of simple reduction of the xanthate, was observed.

The formation of compound **24** can, logically, only arise through the dimerization of radical **28**, itself generated by loss of *tert*-butyl isocyanate either by rupture of the azeti-

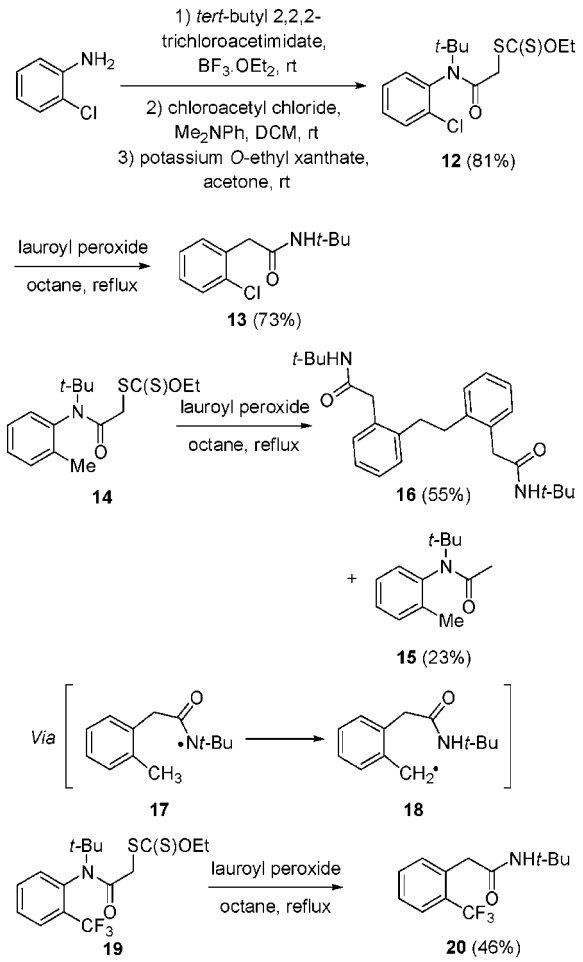
(3) (a) Studer, A. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, 2001; Vol. 2, pp 44−60. (b) Studer, A.; Bossart, M. *Tetrahedon* **2001**, *57*, 9649−9667.

(4) Anderson, J. C.; Cran, J. W.; King, N. P. *Tetrahedron Lett.* **2002**, *21*, 3849−3852.

(5) For a mechanistic discussion, see: Tournier, L.; Zard, S. Z. *Tetrahedron Lett.* **2005**, *46*, 455−459.

(6) See for example: Quiclet-Sire, B.; Zard, S. Z. *J. Am. Chem. Soc.* **1996**, *118*, 9190−9191.

Scheme 3. Smiles Rearrangement and a 1,6-Hydrogen Abstraction

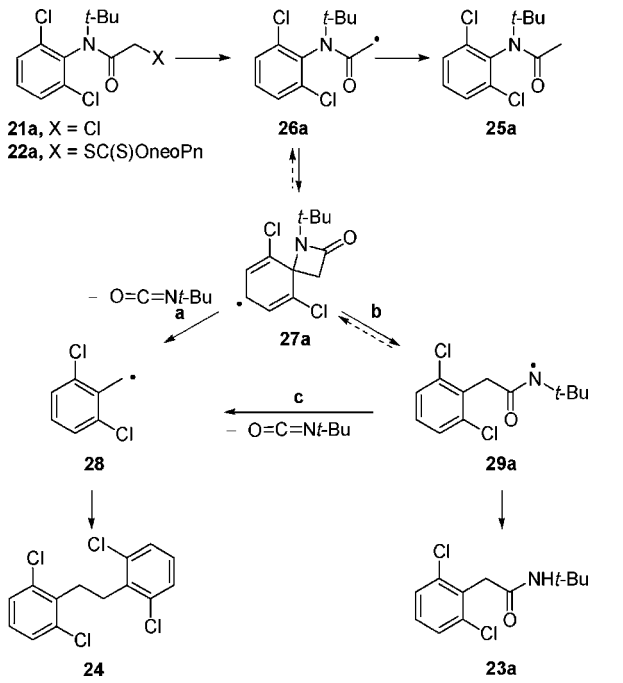


dinone ring in intermediate **27a** (path **a**) or through β-scission of radical **29a** (path **c**) (Scheme 4). Both of these steps, occurring at relatively moderate temperatures, are unprecedented as far as we are aware.

The route via path **c** appeared more reasonable. One would expect the formal retro [2 + 2] corresponding to path **a** to be many orders of magnitude slower than the various radical processes occurring in the medium. When the reaction was conducted in di-*n*-butyl ether at 130 °C, the Smiles rearrangement product **23a** was obtained in *98% isolated yield*. Di-*n*-butyl ether is a much better hydrogen atom donor than octane, and it is thus capable of efficiently intercepting radical **29a** *before* extrusion of a molecule of *tert*-butyl isocyanate occurs. This also means that the ring closure of radical **26a** into spiroazetidinone **27a** is quite fast in this system: the use of di-*n*-butyl ether with the other xanthates (e.g., **12**) with only one ortho substituent gave the corresponding acetanilide. The cyclization to the spiroazetidinone in these cases is too slow to compete with premature hydrogen abstraction from the solvent.

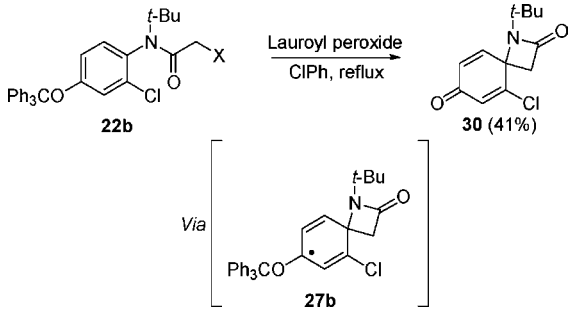
The existence of the spiroazetidinone intermediate was finally unambiguously ascertained by starting with xanthate **22b**. The reaction with the peroxide produced spirodienone **30** in 41% yield, along with some traces of Smiles product

Scheme 4. Smiles Rearrangement and Amidyl Radical Fragmentation



23b. In this case, the intermediate radical **27b** can rearrange into **23b** via **29b** or can proceed to spiro derivative **30** by expelling a stabilized triphenylmethyl radical,[7] which is ultimately converted to triphenyl carbinol (observed) (Scheme 5).

Scheme 5. Preparation of a Spirodienone



In summary, we have uncovered the first, clear case of a radical Smiles rearrangement going through a four-membered spiro intermediate. The scope and limitations of this process remain to be better delineated; nevertheless, a new and interesting access to various substituted aryl- or pyridylacetic acid derivatives is now at hand. In particular, hindered members such as **23a** can be obtained remakably efficiently by an appropriate choice of the reaction solvent. Last, but

(7) See, for example: (a) Leardini, R.; Nanni, D.; Pedulli, G. F.; Tundo, A.; Zanardi, G. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1591−1594. (b) de Turiso F. G.-L.; Curran, D. P. *Org. Lett.* **2005**, *7*, 151−154.

not least, we have also apparently documented the first instance of fragmentation of an amidyl radical into an isocyanate, occurring even in refluxing benzene.

Acknowledgment. We thank Sanofi-Aventis for generous financial support to one of us (M.E.). This paper is dedicated to the memory of Professor André Rassat.

Supporting Information Available: Full experimental data for the compounds described in this paper and ^{1}H and ^{13}C spectra of compounds **16** and **30**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL051568L