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Tin-Free Radical Sequences under Acidic Conditions. Convergent Access to Azole-Containing Structures

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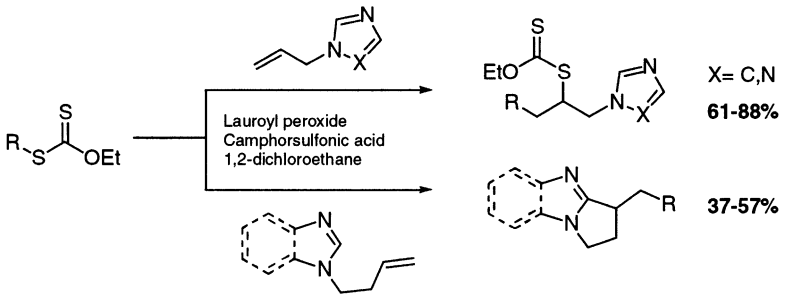
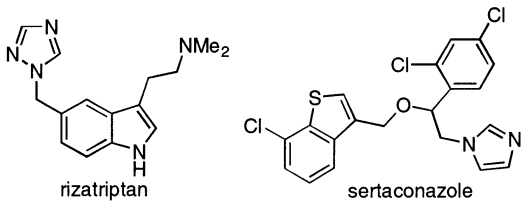
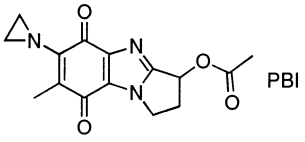
ABSTRACT



Various xanthates add efficiently to olefins bearing [1,2,4]triazole, imidazole, or benzimidazole moieties in the presence of camphorsulfonic acid via a radical chain reaction initiated by a small amount of lauroyl peroxide. The adducts may be transformed to more complex molecules by implementing a further radical cyclization.

Azole subunits are frequently present in biologically active compounds. This is the case for the marketed drugs rizatriptan[1] used in the treatment of migraine and the antifungal sertaconazole[2] or the promising PBI antitumor agent.[3] As a consequence, much ongoing effort has been devoted to the development of practical synthetic routes to the various classes of such heteroarenes. In this context, new free radical methods for the synthesis of heterocyclic compounds are gaining increasing importance.[4] However, with the exception of the cyclization protocols extensively developed by Bowman and co-workers,[5] general approaches for the introduction of azole and related heteroaromatic structures have not been widely studied.





Furthermore, most of the reported procedures concern cyclization with triazoles,[6] pyrazoles,[5a] indoles,[7] pyrroles,[5b,c,e,8] imidazoles,[5c−e] and benzimidazoles[5d,f] and are based on the use of tin reagents leading to the well-known difficulties with purification and toxicity.

(1) Street, L. J.; Baker, R.; Davey, W. B.; Guiblin, A. R.; Jelley, R. A.; Reeve, A. J.; Routledge, H.; Sternfeld, F.; Watt, A. P.; Beer, M. S.; Middlemiss, D. N.; Noble, A. J.; Stanton, J. A.; Scholey, K.; Hargreaves, R. J.; Sohal, B.; Graham, M. I.; Matassa, V. G. *J. Med. Chem.* **1995**, *38*, 1799.

(2) Raga, M. M.; Moreno-Manas, M.; Cuberes, M. R.; Palacin, C.; Castello, J. M.; Ortiz, J. A. *Arzneim. Forsch.* **1992**, *42*, 691.

(3) Sternfeld, F.; Baker, R.; Broughton, H. B.; Guiblin, A. R.; Jelley, R. A. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1825.

(4) For reviews, see: (a) Bowman, W. R.; Cloonan, M. O.; Krintel, S. L. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2885. (b) Bowman, W. R.; Bridge, C. F.; Brookes, P. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1. (c) Aldabbagh, F.; Bowman, W. R. *Contemp. Org. Synth.* **1997**, *4*, 261.

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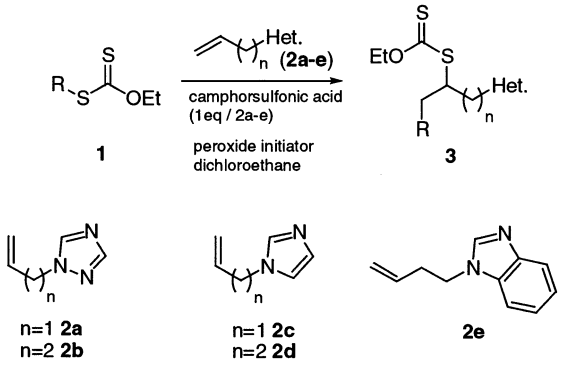
As part of our continuing work in radical chemistry, we have devised a flexible and efficient approach to the synthesis of [1,2,4]triazole, imidazole, and benzimidazole derivatives. Our synthetic design, depicted in Scheme 1, relies on the

Scheme 1. Synthetic Route to Functionalized Nitrogen Heterocycles



rich chemistry of xanthates.[9] Thus, radical addition of xanthate **1** to olefin **2** would lead directly to a variety of functionalized nitrogen heterocycles **3**. However, since the xanthate functionality is sensitive to nucleophilic attack, this radical addition fails with substrates containing basic nitrogen functionality. We therefore modified our normal experimental procedure by adding 1 equiv of camphorsulfonic acid (CSA) for each basic site on the olefin. Under these conditions, the reaction proceeded more cleanly in the case of olefins **2a**,**b** and the presence of acid was indispensable to obtaining xanthate adducts with olefins **2c**−**e**.

Indeed, when a solution of xanthate **1a**, olefin **2a** (2 equiv), and CSA (2 equiv) in 1,2-dichloroethane (1 M) was heated to reflux in the presence of a catalytic amount of lauroyl peroxide (DLP), the 60% yield of adduct **3a** obtained without the presence of the acid was improved to 75% yield. In the case of xanthate **1d** and olefin **2d**, the presence of the acid proved to be more crucial since the 79% yield of adduct **3f** dramatically falls to 0% yield when addition of CSA was omitted.[10] This modified protocol turned out to be quite efficient, as demonstrated by the examples shown in Table 1. Many functional groups may be tolerated in the xanthate as well as in the olefinic partner, allowing the synthesis of a variety of functionalized nitrogen heterocycles.

Table 1. Radical Additions of Xanthates to Olefins **2a**−**d** in the Presence of Camphorsulfonic Acid

olefin 2	xanthate 1	adduct 3	yield of 3
2a	**1a**	**3a**	75%[a]
2a	**1b**	**3b**	88%[b]
2a	**1c**	**3c**	65%
2b	**1d**	**3d**	82%
2c	**1e**	**3e**	61%
2d	**1d**	**3f**	79%[c]

[a] The adduct was obtained in 60% yield without addition of CSA. [b] Tetralone **4** was also isolated in 10% yield. [c] Rapid degradation was observed and no adduct was obtained when CSA was not added.

More complex molecules may be constructed by further transformation of the xanthate adduct. In the case of adducts **3b** and **3c**, refluxing in 1,2-dichloroethane with 1 equiv of CSA and the gradual addition of a stoichiometric amount of peroxide induced ring closure onto the aromatic ring to give the corresponding tetralone **4** in 75% yield and benz-

(5) (a) Allin, S. A.; Barton, W. R. S.; Bowman, W. R.; McInally, T. *Tetrahedron Lett.* **2002**, in press. (b) Allin, S. A.; Barton, W. R. S.; Bowman, W. R.; McInally, T. *Tetrahedron Lett.* **2001**, *42*, 7887. (c) Aldabbagh, F.; Bowman, W. R.; Mann, E.; Slawin, A. M. Z. *Tetrahedron* **1999**, *55*, 8111. (d) Aldabbagh, F.; Bowman, W. R. *Tetrahedron* **1999**, *55*, 4109. (e) Aldabbagh, F.; Bowman, W. R.; Mann, E. *Tetrahedron Lett.* **1997**, *38*, 7937. (f) Aldabbagh, F.; Bowman, W. R. *Tetrahedron Lett.* **1997**, *38*, 3793.

(6) Marco-Contelles, J.; Rodríguez-Fernández, M. *J. Org. Chem.* **2001**, *66*, 3717.

(7) (a) Bennasar, M.-L.; Roca, T.; Griera, R.; Bosch, J. *J. Org. Chem.* **2001**, *66*, 7547. (b) Byers, J. H.; Kosterlitz, J. A.; Steinberg, P. L. *C. R. Acad. Sci. Paris, Chem.* **2001**, *4*, 471. (c) Ziegler, F. E.; Belema, M. *J. Org. Chem.* **1997**, *62*, 1083. (d) Moody, C. J.; Norton, C. L. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2639. (e) Moody, C. J.; Norton, C. L. *Tetrahedron Lett.* **1995**, *36*, 9051.

(8) Antonio, Y.; De La Cruz, E.; Galeazzi; E.; Guzman, A.; Bray, B. L.; Greenhouse, R.; Kurtz, L. J.; Lustig, D. A.; Maddox, M. L.; Muchowski, J. M. *Can. J. Chem.* **1994**, *72*, 15.

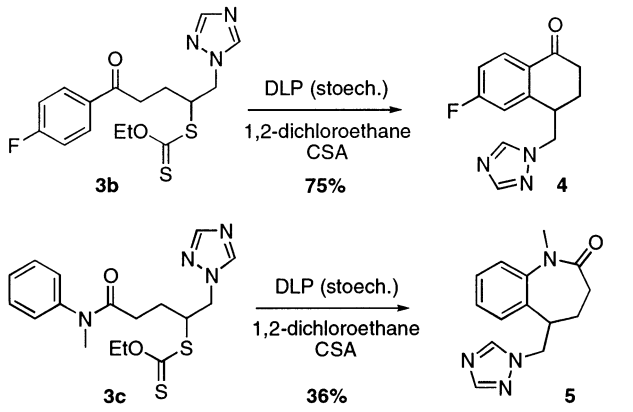
(9) (a) Quiclet-Sire, B.; Zard, S. Z. *Phosphorus, Sulfur Silicon* **1999**, 137. (b) Quiclet-Sire, B.; Zard S. Z. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 672.

(10) Rapid degradation of the starting material was observed.

(11) For the synthesis of tetralones by radical cyclisation, see: Liard, A.; Quiclet-Sire, B.; Saicic, R. N.; Zard, S. Z. *Tetrahedron Lett.* **1997**, *38*, 1759.

(12) For the synthesis of benzazepinones by radical cyclization, see: Kaoudi, T.; Quiclet-Sire, B.; Seguin, S.; Zard S. Z. *Angew. Chem., Int. Ed.* **2000**, *39*, 731.

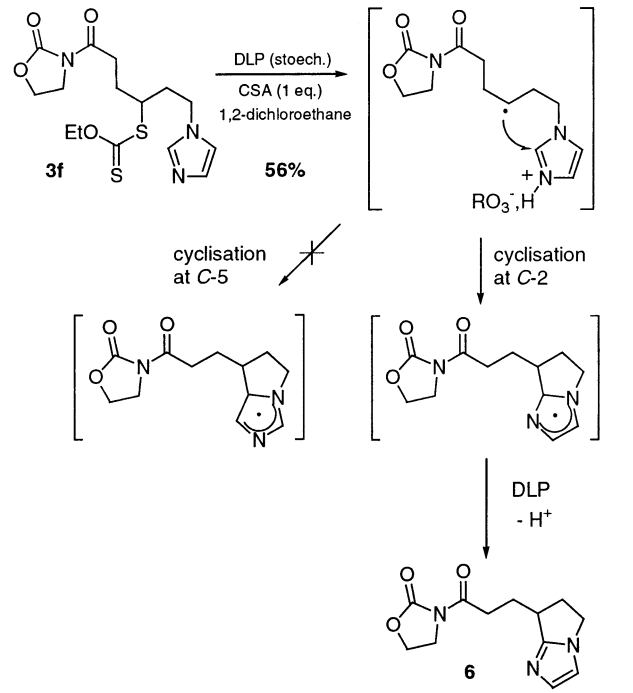
Scheme 2. Radical Transformation of Adducts **3b** and **3c**



azepinone **5** in 36% yield, respectively (Scheme 2).[11,12] Interestingly, the yield of tetralone **4** is higher than the average yield (30−70%) observed earlier[11] and may be attributed to an activation of the carbonyl function by CSA, making the aromatic more reactive toward the attack of an alkyl radical with nucleophilic character. Indeed, in an ancillary study, we found that adding CSA increased significantly the yield of tetralone.

Alternatively, the xanthate group in adduct **3f** may be used to implement a radical cyclization on the imidazole ring. Under the same conditions of radical cyclization, regioselective ring closure occurred at the C-2 position of imidazole as shown in Scheme 3. This selectivity must be contrasted with observations made by Bowman and coworkers, who found that the presence of activating groups

Scheme 3. Radical Cyclization of Xanthate Adduct **3f**

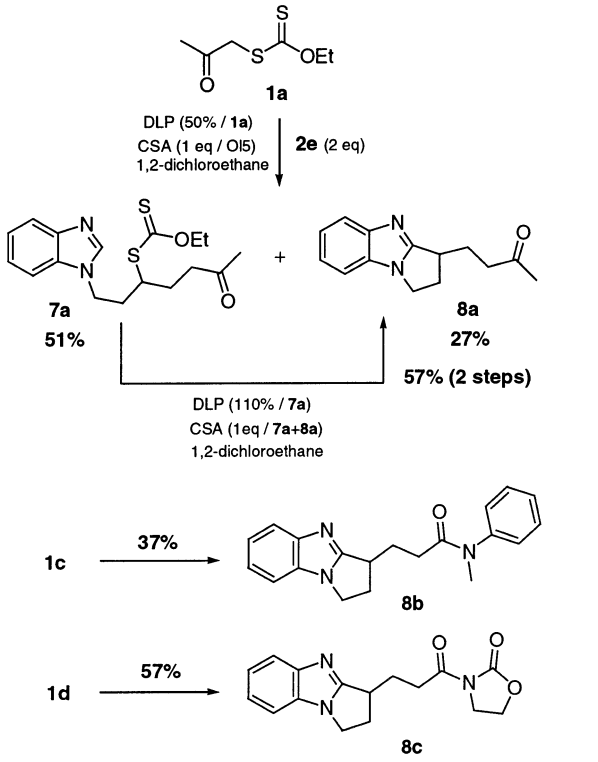


such as a phenyl or an aldehyde on the imidazole ring was necessary to perform the oxidative radical cyclization with Bu_3SnH.[5c,e] In the present case, CSA plays a double role by externally activating and directing the cyclization to give pyrrolo[1,2-*a*]imidazole **6** as the sole product in 56% yield.[13]

The same transformation was attempted with xanthate adduct **3d**, but in this case, no cyclized product was formed. This might be explained by a negligible activating effect of CSA on the much less basic [1,2,4]triazole.

Benzimidazole derivatives in contrast proved to be as good substrates as imidazoles for the radical cyclization. The combined activating effect of the acid and the fused phenyl group resulted in significant ring closure from the outset. Thus, when a solution of xanthate **1a**, olefin **2e** (2 equiv), and CSA (2 equiv) in 1,2-dichloroethane (1 M) was refluxed in the presence of lauroyl peroxide (DLP), an inseparable mixture of xanthate adduct **7a** (51%) and pyrrolo[1,2*a*]-benzimidazole **8a** (27%) was produced. This mixture was submitted again to radical cyclization conditions to finally give tricycle **8a** in 57% over the two steps (Scheme 4). The

Scheme 4. Radical Cascades with Olefin **2e**

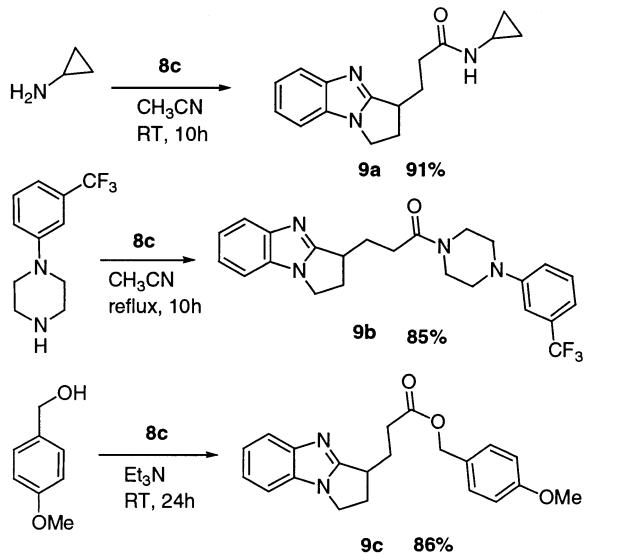


same sequence of addition/cyclization was applied to xanthates **1c** and **1d** to respectively give pyrrolo[1,2*a*]benzimidazole **8b** and **8c** in 37 and 57% yields.

It is worth pointing out that this simple protocol gives a rapid access to polyfunctionalized compounds possessing the

(13) For radical additions to positively charged heteroaromatics, see: (a) Minisci, F.; Citterio, A.; Vismara, E.; Giordano, C. *Tetrahedron* **1985**, *41*, 4157 and references cited therein. (b) Minisci, F.; Vismara, E.; Romano, V. *Tetrahedron Lett.* **1985**, *26*, 4803. (c) Barton, D. H. R.; Garcia, B.; Togo, H.; Zard, S. Z. *Tetrahedron Lett.* **1986**, *27*, 1327.

Scheme 5. Transformation of Pyrrolo[1,2*a*]benzimidazole **8c**



tricyclic core of the potent PBI antitumor agents.[3,14] Pyrrolo-[1,2*a*]benzimidazole **8c** is especially interesting since it possesses an activated carboxylic acid functionality that is ideally suited for further transformations. In the presence of nucleophiles such as amines or alcohols, the oxazolidine moiety is easily displaced. Amides **9a**,**b** and ester **9c** were thus readily prepared in excellent yield (Scheme 5).

In summary, these preliminary results demonstrate the compatibility of the xanthate methodology with an anhydrous acidic medium and its potential for the convergent construction of nitrogen-containing heteroaromatics. This tin-free protocol is quite general, proceeds under mild conditions, and tolerates many functional groups.

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Supporting Information Available: Detailed experimental procedures and spectral data for olefins **2a**−**e**, radical adducts **3a**−**f**, and cyclized compounds **4**−**6**, **8a**−**c**, and **9a**−**c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) For a review of the synthesis of the pyrrolo[1,2-*a*]benzimidazole antitumor agents, see: Skibo, E. B.; Islam, I.; Schultz, W. G.; Zhou, R.; Bess, L.; Boruah, R. *Synlett* **1996**, 297.