HETEROCYCLES, Vol. 74, 2007, pp. 211 - 218. © The Japan Institute of Heterocyclic Chemistry
Received, 31st August, 2007, Accepted, 3rd October, 2007, Published online, 4th October, 2007. COM-07-S(W)55

A PRACTICAL ROUTE TO PYRAZINES AND QUINOXALINES, AND AN UNUSUAL SYNTHESIS OF BENZIMIDAZOLES

Catherine Mougin, Julien Sançon, and Samir Z. Zard*

Department of Chemistry, Ecole Polytechnique, CNRS UMR 7652, 91128 Palaiseau, France. zard@poly.polytechnique.fr.

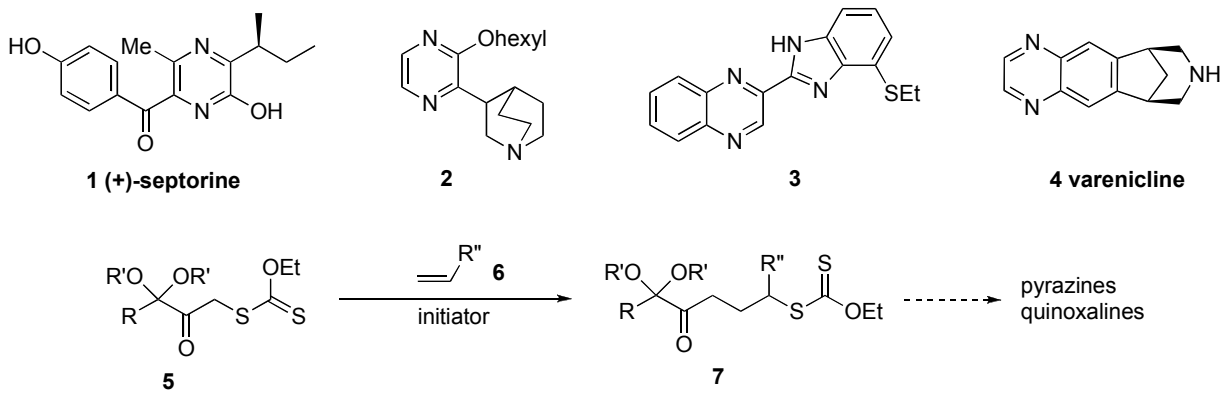
This paper is dedicated with respect and admiration to Prof. Ekkehard Winterfeldt on the occasion of his 75th birthday.

Abstract – 1,2-Dicarbonyl compounds can be accessed by a radical addition-transfer of xanthates and used for the synthesis of pyrazines and quinoxalines, as well as in an unusual approach to benzimidazoles.

INTRODUCTION

Pyrazines and quinoxalines represent basic heterocyclic ring structures that are found in numerous natural compounds and substances possessing interesting biological activities.[1] Examples include (+)-septorine **(1)**, an alkaloid isolated from the fungus *Septoria nodorum* Berk,[2] and synthetic pyrazine **(2)**, a selective agonist for the muscarinic receptor M1, which is apparently involved in the onset of Alzheimer's disease.[3] Quinoxaline **(3)** is a selective antagonist of the human adenosine receptor A1[4] whereas symmetrical quinoxaline **(4)**, varenicline, was recently reported to be a partial agonist of nicotinic receptor $\alpha 4\beta 2$ and useful in combating addiction to tobacco.[5]

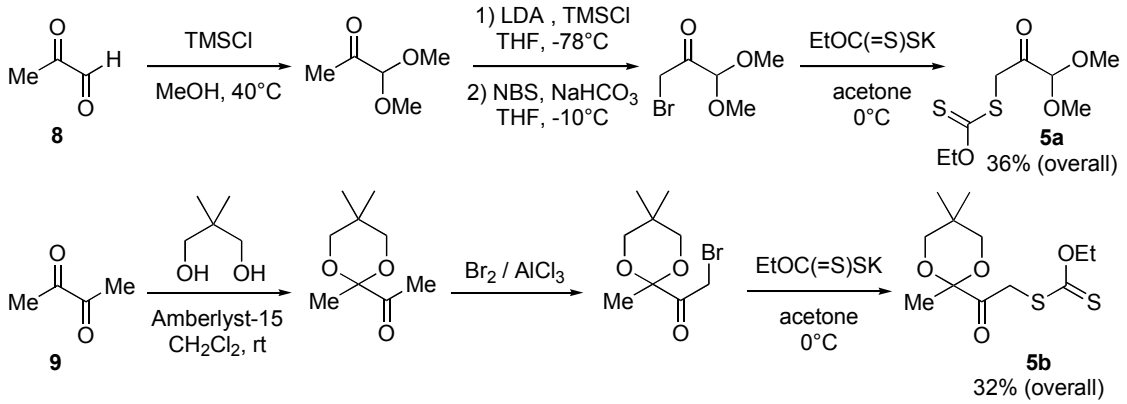
The simplest route to quinoxalines, pyrazines and related structures relies on the condensation of a 1,2-diamino-aromatic or heteroaromatic motif, or a 1,2-diaminoethene derivative, with 1,2-diketones or 1,2-ketoaldehydes.[1] The latter components are rather reactive species for which there are only few synthetic entries, and this severely limits access to the broad diversity of structures needed to explore and optimize biological activity. As part of our ongoing work on the degenerative radical transfer of xanthates and related substances,[6] we sought to expand the scope of this technology to encompass the synthesis of 1,2-diketones or 1,2-ketoaldehydes.



Scheme 1. Examples of pyridazines and quinoxalines and a new route to their precursors.

RESULTS AND DISCUSSION

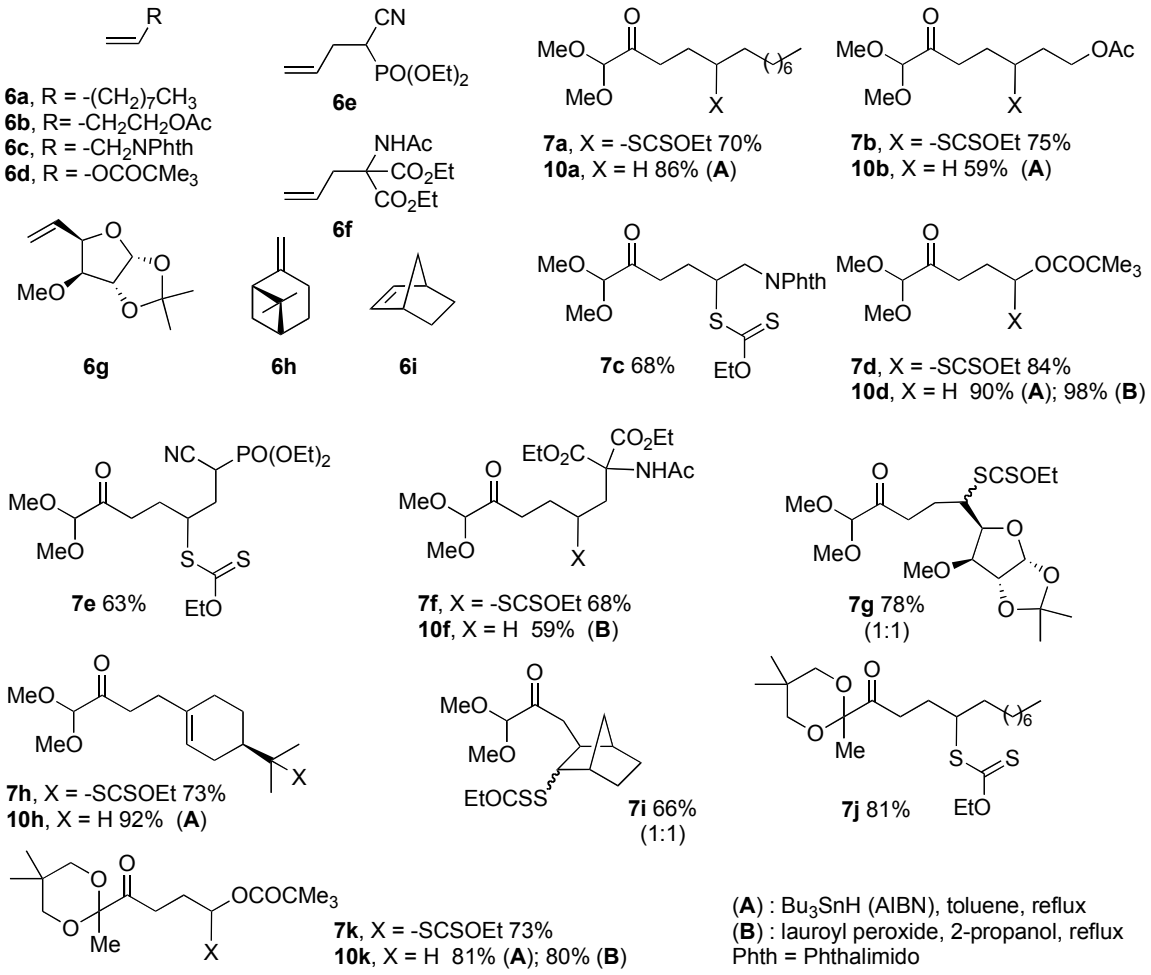
Our synthetic design was to use xanthates of general structure **(5)**, which should undergo a radical chain addition to an alkene **(6)** to give the corresponding adduct **(7)**, as outlined in Scheme 1. These adducts could then be converted into pyrazines and quinoxalines by classical condensation reactions. We began our study by the synthesis of compounds **(5a)** and **(5b)** as typical xanthates representative of this family. The preparation of xanthate **(5a)** proceeded readily from commercial pyruvaldehyde **(8)** by successive protection of the aldehyde function as the corresponding dimethyl acetal, bromination,[7] and displacement of the bromine with potassium *O*-ethyl xanthate. In the same manner, xanthate **(5b)** was obtained from 2,3-butanedione **(9)** in 32% overall yield.



Scheme 2. Synthesis of key xanthate reagents.

We were delighted to find that the radical addition took place readily upon refluxing a solution of xanthate **(5a)** or **(5b)** and the olefin in 1,2-dichloroethane (DCE), in the presence of a small amount of lauroyl peroxide. Good yields of adducts **(7)** were uniformly observed, as demonstrated by the examples in Scheme 3.[8] A broad range of alkenes **(6)** could be used bearing a number of synthetically useful functional groups, attesting to the mildness of the experimental conditions. Examples **(7c)**, containing a

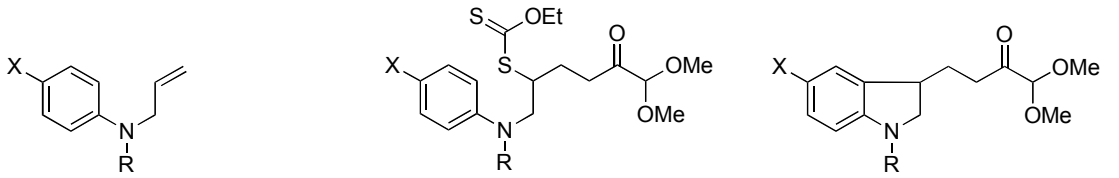
phthalimido group, and **(7g)**, produced by addition to the complex, glucose-derived olefin **(6g)**, are especially noteworthy. In the case of β-pinene **(6h)**, the radical addition to the olefin was followed, as expected, by the opening of the cyclobutane ring to give ultimately adduct **(7h)** in 73% yield. The simplicity, efficiency, and scope of this radical based approach to 1,2-diones and ketoaldehydes has to be contrasted with the fact that direct alkylation of the enolates of either pyruvaldehyde **(8)** or 1,2-butanedione **(9)**, as well as their ketal protected derivatives, is quite problematic. *Indeed, no actual examples of direct alkylation could be found in the Beilstein database; only very few Knoevenagel type condensations and even fewer aldol reactions have been reported.*[9]



Scheme 3. Synthesis of mono-protected keto-aldehydes and diketones.

The xanthate group, which has served so nicely to mediate the addition, is often not desired in the final product. It can be swiftly and smoothly removed using tributyltin hydride, as shown by the clean formation of dexanthylated derivatives **(10a)**, **(10b)**, **(10d)**, **(10h)**, and **(10k)**. Another convenient method, which avoids the use of toxic heavy metals, relies on a combination of stoichiometric lauroyl peroxide

and 2-propanol.[10] Examples **(10d)**, **(10f)**, and **(10k)** illustrate the utility of this latter technique in the present context.



6l, X = H, R = Boc
6m, X = Br, R = -SO_2Me
6n, X = CO_2Me, R = -SO_2Me
6o, X = OMe, R = -SO_2Me

7l, X = H, R = Boc
7m, X = Br, R = -SO_2Me
7n, X = CO_2Me, R = -SO_2Me
7o, X = OMe, R = -SO_2Me

11l, X = H, R = Boc 70%
11m, X = Br, R = -SO_2Me 52%
11n, X = CO_2Me, R = -SO_2Me 59%
11o, X = OMe, R = -SO_2Me 38%

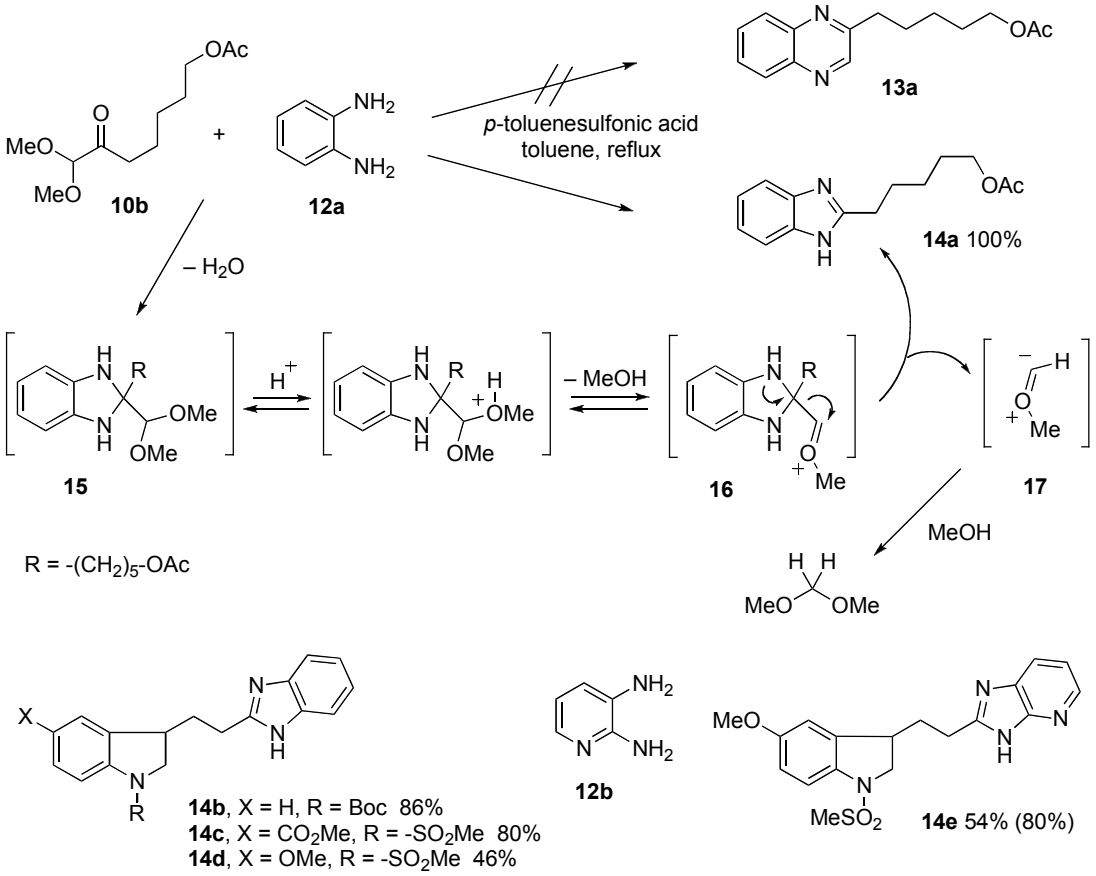
Scheme 4. Synthesis of methyl acetals of indoline ketoaldehydes.

The xanthate moiety can be converted by ionic or radical mechanisms into numerous other functional groups.[6] It provides, in particular, an easy entry into the exceptionally rich chemistry of sulfur. From a medicinal chemistry point of view, perhaps the most interesting feature concerns the use of the xanthate group for accomplishing a second radical process, namely closure onto an aromatic or heteroaromatic ring.[6] Thus, radical addition to *N*-allylanilines **(6l-o)** followed by further exposure of adducts **(7l-o)** to stoichiometric amounts of lauroyl peroxide in refluxing DCE leads to the formation of indolines **(11l-o)** in quite useful overall yields (Scheme 4).[11] In this transformation, the peroxide acts both as an initiator, to generate the radical from the xanthate, and as an oxidant, to oxidize the intermediate cyclohexadienyl radical and restore aromaticity.

With a number of mono-protected 1,2-ketoaldehydes and 1,2-diketones in hand, we set out to prepare the desired quinoxalines. When dexanthylated adduct **(10b)** was treated with *o*-phenylenediamine **(12a)** in refluxing toluene with a catalytic amount of *p*-toluenesulfonic acid, a clean reaction ensued but the product, isolated in quantitative yield, turned out to be benzimidazole **(14a)** and not the expected quinoxaline **(13a)** (Scheme 5). This surprising transformation is akin to the one recently observed by Baldwin *et al.*, whereby a benzimidazole was obtained from the reaction of *o*-phenylenediamine with a 1,2,3-tricarbonyl derivative.[12] However, the mechanism proposed by Baldwin *et al.* cannot be wholly transposed to our case. We therefore suggest an alternative mechanistic pathway, also displayed in Scheme 5.

Reaction of the diamine leads to imidazolidine **(15)**, which, by reversible acid catalyzed loss of methanol, is in equilibrium with intermediate **(16)**. Fragmentation of the latter gives rise to the observed benzimidazole **(14a)** and ylide **(17)**. The latter presumably reacts rapidly with the liberated methanol to give dimethoxymethane. Ylide **(17)** has an electronic structure similar to that of the active form of

thiamine diphosphate (vitamin B_1), which has inspired numerous acyl anion equivalents,[13] and is therefore less exotic than appears initially.

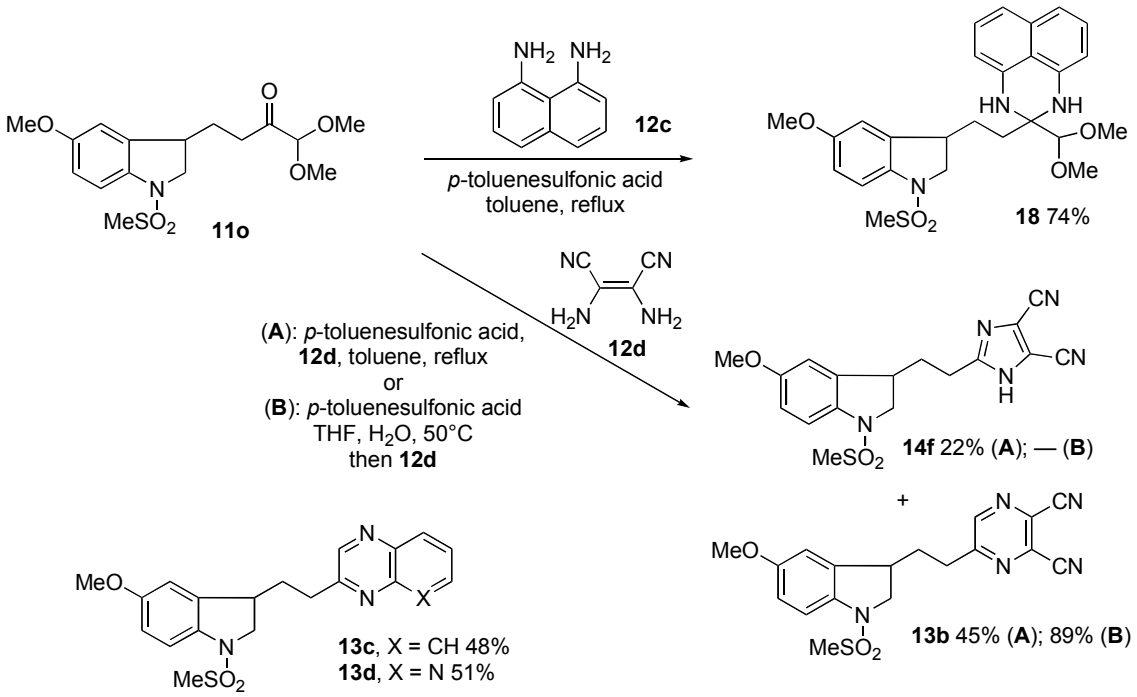


Scheme 5. Unexpected synthesis of benzimidazoles.

This unexpected synthesis of benzimidazoles seems to be fairly general. Four examples derived from indolines **(11l)**, **(11n)**, and **(11o)** are deployed at the bottom of Scheme 5, including the interesting case of aza-benzimidazole **(14e)**, produced by condensation with 2,3-diaminopyridine **(12b)** (the yield in parenthesis is based on recovered starting material). This route complements nicely more traditional approaches: its mildness (notice the complete survival of the Boc group in **(14b)**), coupled with the ready accessibility of the key precursors, should allow access to numerous new structures within this medicinally important class of compounds.[14]

In contrast, reaction of 1,8-diaminonaphthalene **(12c)** with mono-protected ketoaldehyde **(11o)** gave a good yield (74%) of diamino ketal **(18)** (Scheme 6). The fragmentation step, which in this case would have produced a pyridazine structure, did not occur under the reaction conditions. When the same masked ketoaldehyde **(11o)** was exposed to diaminomaleonitrile (DAMN, (**12d**)) in refluxing toluene with a catalytic amount of *p*-toluenesulfonic acid (conditions **A**), the corresponding imidazole **(14f)** was formed

in low yield (22%). The major product turned out to be quinoxaline **(13b)** (45%). This difference in behavior is no doubt due to the diminished nucleophilicity of the amino groups in DAMN, allowing time for the partial deprotection of the aldehyde function. In order to obtain the more interesting quinoxaline **(13b)** as the sole product, we first completely unmasked the aldehyde in compound **(11o)** by treatment with *p*-toluenesulfonic acid in THF / water at 50°C for 3 days. Addition of DAMN, without prior isolation of the free ketoaldehyde, resulted in the formation of quinoxaline **(13b)** in 89% yield (conditions **B**). Replacing DAMN with *o*-phenylenediamine **(12a)**, and 2,3-diaminopyridine **(12b)**, furnished quinoxalines **(13c)** and **(13d)** in 48 and 51% overall yield respectively. In the unprotected ketoaldehyde, the vastly more reactive aldehyde function engages the diamine first and hence conditions the outcome of the reaction. Thus, by modifying the experimental conditions, it is possible to obtain either benzimidazoles (or imidazoles such as **(14f)**) or pyazines and quinoxalines.



Scheme 6. Synthesis of pyrazines and quinoxalines.

In summary, we have developed a flexible approach to pyrazines and quinoxalines, as well as an unusual route to benzimidazoles (or imidazoles) from the same staring material. The required masked keto-aldehydes and diketones are themselves readily available by the powerful radical addition of xanthates. Indeed, the xanthate transfer technology represents a solution to a longstanding problem organic synthesis, namely the creation of a carbon-carbon bond in an *intermolecular* fashion on *non-activated* alkenes.

REFERENCES

1. A. E. A. Porter, in *Comprehensive Heterocyclic Chemistry* ed. by A. R. Katritzky and C. W. Rees, Pergamon: Oxford, 1984, Vol 3, part 2B, p 157; N. Sato, in *Comprehensive Heterocyclic Chemistry II*, ed. by A. R. Katritzky, C. W. Rees, and E. F. V. Scriven, Pergamon: Oxford,1996, Vol 6, p 233-278; G. Sakata, K. Makino, and Y. Kurasama, *Hetrocycles*, 1988, **27**, 2841.
2. M. Devys, M. Barbier, A. Kollmann, and J.-F. Bousquet, *Tetrahedron Lett.*, 1982, **23**, 5409.
3. J. S. Ward, L. Merrit, D. O. Calligaro, F. P. Bymaster, H. E. Shannon, B. D. Sawyer, C. H. Mitch, J. B. Deeter, S. C. Peters, M. J. Sheardown, P. H. Olesen, M. D. B. Swedberg, and P. Sauerberg, *J. Med. Chem*., 1995, **38**, 3469.
4. E. Novellino, B. Cosimelli, M. Ehlardo, G. Greco, M. Iadanza, A. Lavecchia, M. G. Rimoli, A. Sala, A. Da Settimo, G. Primofiore, F. Da Settimo, S. Taliani, C. La Motta, K.-N. Klotz, D. Tuscano, M. L. Trincavelli, and C. Martini, *J. Med. Chem*., 2005, **48**, 8253.
5. J. W. Coe, P. R. Brooks, M. G. Vetelino, M. C. Wirtz, E. P. Arnold, J. Huang, S. B. Sands, T. I. Davis, L. A. Lebel, C. B. Fox, A. Shrikhande, J. H. Heym, E. Schaeffer, H. Rollema, Y. Lu, R. S. Mansbach, L. K. Chambers, C. C. Rovetti, D. W. Schulz, F. D. Tingley III, and B. T. O'Neill, *J. Med. Chem*., 2005, **48**, 3474.
6. For reviews of this work, see: S. Z. Zard, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 672; B. Quiclet-Sire and S. Z. Zard, *Phosphorus, Sulfur, Silicon, Related Elem.*, 1999, 137; S. Z. Zard, in *Radicals in Organic Synthesis*, ed. by P. Renaud and M. P. Sibi, Wiley-VCH: Weinheim, 2001, Vol. 1, 90; B. Quiclet-Sire and S. Z. Zard, *Chem. Eur. J.*, 2006, **12**, 6002; B. Quiclet-Sire and S. Z. Zard, *Top. Curr. Chem.*, 2006, **264**, 201. (f) S. Z. Zard, *Org. Biomol. Chem.*, 2007, **5**, 205.
7. G. J. Bukovits, N. Mohr, H. Budkiewicz, H. Korth, and G. Pulverer, *Z. Naturforsch. B. Anorg. Chem. Org. Chem.*, 1982, **37**, 877; S. G. Levine and C. U. Mauney, *Synth. Commun.*, 1988, 689.
8. Typical experimental procedure for the radical adition: A solution of xanthate **(5a)** or **(5b)** (1 mmole) and olefin **(6)** (1.2 mmole) in DCE (1 mL) is degassed by refluxing under nitrogen for 20 minutes. Lauroyl peroxide (0.05 mmol) is added as a solid from the top of the condenser. Further portions are added every 1.5 h until almost complete consumption of the xanthate (typically 3-4 portions). The solvent is then evaporated and the residue purified by chromatography on silica gel.
9. K. Narasaka and F.-C. Pai, *Tetrahedron*, 1984, **40**, 2233; Y. Yoshida, N. Matsumoto, R. Hamasaki, and Y. Tanabe, *Tetrahedron Lett.*, 1999, **40**, 4227.
10. A. Liard, B. Quiclet-Sire, and S. Z. Zard, *Tetrahedron Lett.*, 1996, **33**, 5877.
11. T.-M. Ly, B. Quiclet-Sire, B. Sortais, and S. Z. Zard, *Tetrahedron Lett.*, 1999, **40**, 2533.
12. R. Adlington, J. Baldwin, D. Catterick, and G. Pritchard, *J. Chem. Soc., Perkin Trans.1*, 2001, 668; Dr. Joel Hawkins, of Pfizer, Groton, CT, USA, has kindly informed us that they have also observed

the formation of benzimidazoles by the condensation of 1,2-diaminobenzenes with glyoxal; J. Hawkins, private communication.

13. S. M. Mennen and S. J. Miller, *J. Org. Chem.*, 2007, **72**, 5260 and references there cited.
14. For very recent examples of benzimidazoles possessing interesting biological activities, see: Y.-F. Li, G.-F. Wang, P.-L. He, W.-G. Huang, F.-H. Zhu, He-Yong Gao, W. Tang, Y. Luo, C.-L. Feng, L.-P. Shi, Y.-D. Ren, W. Lu, and J.-P. Zuo, *J. Med. Chem.*, 2006, **49**, 4790; A. P. Combs, W. Zhu, M. L. Crawley, B. Glass, P. Polam, R. B. Sparks, D. Modi, A. Takvorian, E. McLaughlin, E. W. Yue, Z. Wasserman, M. Bower, M. Wei, M. Rupar, P. J. Ala, B. M. Reid, D. Ellis, L. Gonneville, T. Emm, N. Taylor, S. Yeleswaram, Y. Li, R. Wynn, T. C. Burn, G. Hollis, P. C. C. Liu, and B. Metcalf, *J. Med. Chem.*, 2006, **49**, 3774; V. I. Ognyanov, C. Balan, A. W. Bannon, Y. Bo, C. Dominguez, C. Fotsch, V. K. Gore, L. Klionsky, V. V. Ma, Y.-X. Qian, R.Tamir, X. Wang, N. Xi, S. Xu, D. Zhu, N. R. Gavva, J. J. S. Treanor, and M. H. Norman, *J. Med. Chem.*, 2006, **49**, 3719.