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Radical Arylaminomethylation of Unactivated Alkenes

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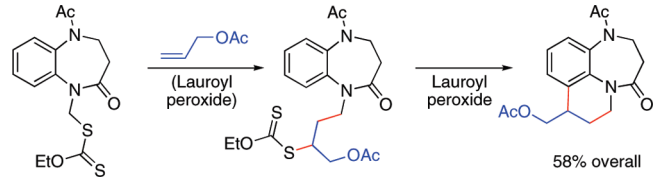
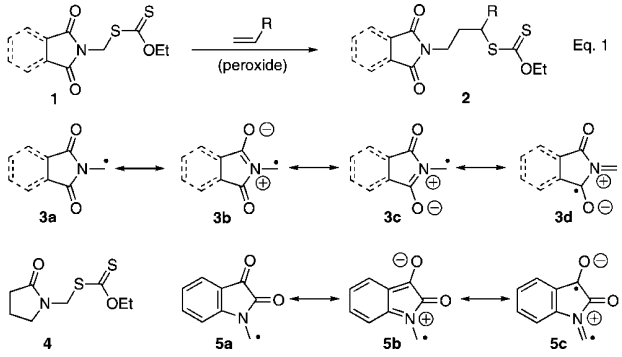
ABSTRACT



Xanthates derived from open chain or cyclic *N*-chloromethylanilides are capable of adding to various unactivated alkenes to give adducts which, in suitable cases, can be made to undergo ring closure onto the aromatic ring. This flexible arylaminomethylation of alkenes allows the rapid synthesis of open chain or polycyclic aniline derivatives.

We recently found that it was possible to accomplish the aminomethylation of unactivated alkenes through the use of the degenerative radical xanthate transfer reaction.[1] While xanthates such as **1** (succinimido- or phthalimido-residues) underwent the desired radical addition very efficiently to give adducts **2** (Scheme 1, eq 1), the reaction of xanthate **4**, derived from a pyrrolidone and not an imide, *produced mostly oligomers*. The successful addition in the case of xanthates **1** was attributed to the extra stabilization of radicals **3** by a more significant contribution of canonical forms **3b** and **3c**, giving the radical a greater "allylic character" (cf. structure **3d**), as compared to those derived from simple lactams, where a second carbonyl group is missing. The relative stabilities of the starting and adduct radicals in the xanthate addition process are a key element for success.[2] Normally, and absent special polar effects, the starting radical has to be more stable than the adduct radical. This is the case of radical **3**, which appears to be more stable than the simple secondary radical resulting from the addition to an ordinary alkene.

Scheme 1



To extend the synthetic utility of this process, we examined the case of isatin derivatives, where the fusion of an aromatic ring adjacent to the amide nitrogen and the presence of the extra carbonyl could still allow a similar but now a "vinylogous" type stabilization, as shown in canonical structures **5a**−**c** in Scheme 1. We hoped that such stabilization would be sufficient to allow control of the radical addition process. The required xanthate precursor **6** is readily

(1) Quiclet-Sire, B.; Zard, S. Z. *Org. Lett.* **2008**, *10*, 3279.

(2) For reviews of the xanthate transfer chemistry, see: (a) Zard, S. Z. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 672. (b) Zard, S. Z. *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, 2001; Vol. 1, p 90. (c) Quiclet-Sire, B.; Zard, S. Z. *Chem.—Eur. J.* **2006**, *12*, 6002. (d) Quiclet-Sire, B.; Zard, S. Z. *Top. Curr. Chem.* **2006**, *264*, 201. (e) Zard, S. Z. *Org. Biomol. Chem.* **2007**, *5*, 205.

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available from *N*-chloromethylisatin,[3] and this hypothesis could be easily tested. We were, however, rapidly disappointed.

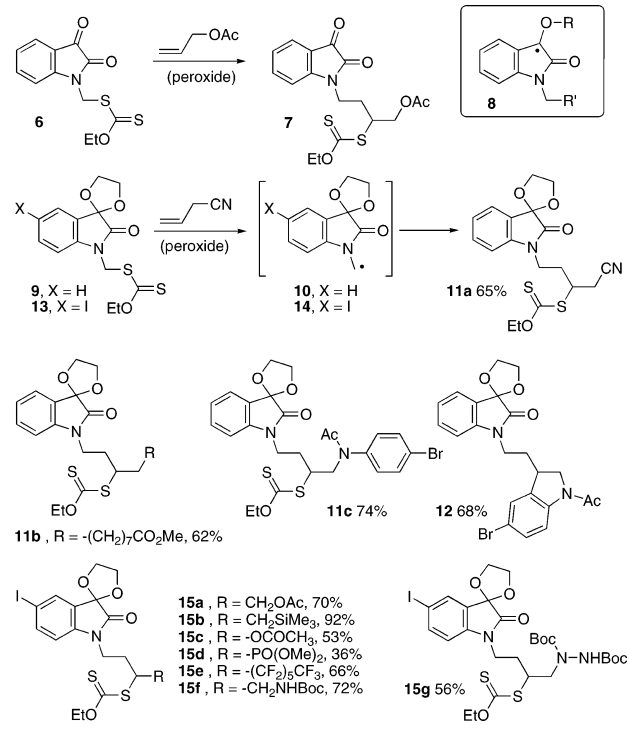
When xanthate **6** and allyl acetate were treated with lauroyl peroxide, a complex mixture was obtained, as indicated by TLC, from which only a small yield of the desired adduct **7** could be isolated by chromatography. More puzzling, the NMR spectrum of the crude mixture was very poorly resolved and exhibited broad signals suggesting the presence of paramagnetic impurities in the sample. The most reasonable explanation was that some radical addition was taking place on the activated ketone group of the isatin, leading to highly stabilized and perhaps even persistent radicals such as **8**.

Although this unexpected observation dashed our hopes of extending our radical process to a naked isatin structure, it raised the question of the actual need for the presence of the second carbonyl group. The aromatic ring itself may provide the necessary extra stabilization and thus replace conveniently one of the carbonyl groups. The ketone group in the isatin xanthate derivative **6** was therefore protected as the corresponding ketal **9**. Pleasingly, with the deleterious effect of the reactive ketone removed, the desired radical addition with allyl cyanide proceeded smoothly to give the expected adduct **11a** in 62% yield. Clearly, a phenyl group can indeed act as a surrogate for the carbonyl, and intermediate radical **10** is sufficiently stabilized to allow control of the degenerative xanthate transfer process.

In the same way, adducts **11b**,**c** were prepared by reaction with methyl 10-undecenoate and *N*-acetyl-*N*-allyl-4-bromoaniline, respectively. In the case of the last adduct, **11c**, further treatment with stoichiometric amounts of lauroyl peroxide in refluxing chlorobenzene furnished indoline **12** in 68% yield.[4] The cyclization could also be performed in refluxing ethyl acetate, but the yield was slightly lower (64%). No ring closure on the aromatic ring of the isatin portion was observed.

One notable advantage of this chemistry is its tolerance for the presence of aromatic iodides. This is illustrated by the normal reactivity displayed by 5-iodoisatin xanthate **13** (Scheme 2).[5] Additions to allyl acetate, allyl trimethyl silane, vinyl acetate, dimethyl vinylphosphonate, tridecafluorooctene, and *N*-Boc allylamine proceeded uneventfully to give the corresponding adducts **15a**−**f** in generally good yield. Addition to Boc-protected allylhydrazine provides a direct access to complex hydrazine **15g**.[6] Such a compound would be quite tedious to make by more conventional chemistry. The presence of the iodine atom in all these derivatives opens the way to combining the radical addition with some of the most powerful transition metal catalyzed processes, such as the Heck, Suzuki, Sonogashira, and Buchwald−Hartwig reactions. Numerous novel isatin derivatives may thus be accessed, some of which could have useful pharmacological properties.[7]

Scheme 2



The successful addition of the isatin derived xanthates gave rise to yet another question: is the flat bicyclic structure, with a maximized orbital overlap, necessary? In other words, can the xanthate transfer be extended to open chain anilides or to ones containing a more flexible ring such as benzazepinone? It must be remembered that in the present context the differences in energy between radicals useful in the xanthate transfer process, such as **3**, and inappropriate radicals, such as those derived from **4**, are quite small, and the crossover point, where oligomer formation becomes a serious problem, is easily reached.

We were gratified to find that, even though somewhat less effective than the isatin derivatives, xanthates **19**−**21**, prepared from the corresponding anilines, underwent reasonably smooth additions to various alkenes. The examples are assembled in Scheme 3. The superiority of the isatin-derived xanthates is best appreciated by comparing the yields of addition to vinyl pivalate, an olefin much more prone to polymerization than the other alkene partners. Thus, while with isatin xanthate **13** the expected adduct **15c** was obtained in 53% yield (Scheme 2), extensive oligomerization was observed with xanthate **20** as the reaction does not stop at

(3) El Ghammarti, S.; Rigo, B.; Mejdi, H.; Henichart, J.-P.; Couturier, D. *J. Heterocycl. Chem.* **1998**, *35*, 555.

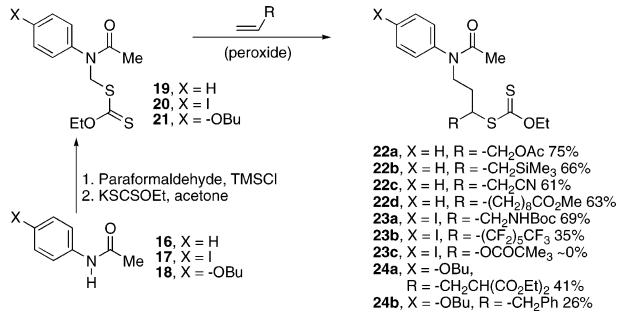
(4) Ly, T.-M.; Quiclet-Sire, B.; Sortais, B.; Zard, S. Z. *Tetrahedron Lett.* **1999**, *40*, 2533.

(5) Garden, S. J.; Torres, J. C.; Souza Melo, S. C.; Lima, A. S.; Pinto, A. C.; Lima, E. L. S. *Tetrahedron Lett.* **2001**, *42*, 2089.

(6) Quiclet-Sire, B.; Sortais, B.; Zard, S. Z. *Synlett* **2002**, 903.

(7) For some recent, medicinally oriented work on isatin derivatives, see: (a) Diaz, P.; Phatak, S. S.; Xu, J.; Astruc-Diaz, F.; Cavasotto, C. N.; Naguib, M. *J. Med. Chem.* **2009**, *52*, 433. (b) Chu, W.; Rothfuss, J.; Chu, Y.; Zhou, D.; Mach, R. H. *J. Med. Chem.* **2009**, *52*, 2188. (c) Hyatt, J. L.; Moak, T.; Hatfield, M. J.; Tsurkan, L.; Edwards, C. C.; Wierdl, M.; Danks, M. K.; Wadkins, R. M.; Potter, P. M. *J. Med. Chem.* **2007**, *50*, 1876. (d) Vine, K. L.; Locke, J. M.; Ranson, M.; Pyne, S. G.; Bremner, J. B. *J. Med. Chem.* **2007**, *50*, 5109. (e) Pirrung, M. C.; Pansare, S. V.; Sarma, K. S.; Keith, K. A.; Kern, E. R. *J. Med. Chem.* **2005**, *48*, 3045.

Scheme 3

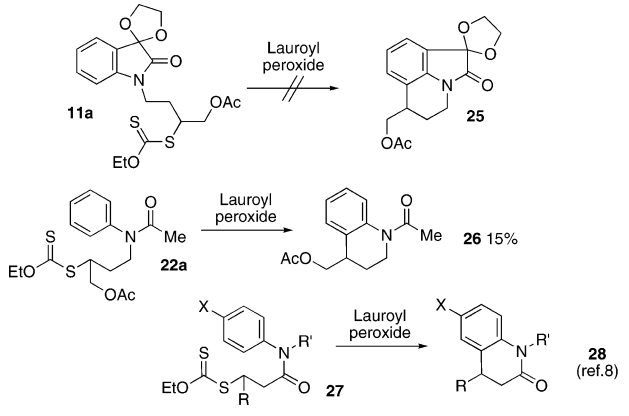


the desired monoadduct **23c** (Scheme 3). In the latter case, the difference in stability between the initial radical and the adduct radical (now stabilized by a three-electron interaction with the lone pair of the pivalate oxygen) is not sufficient to allow proper control of the addition process.

We also noticed that the presence of an electron-donating group on the aromatic ring, such as the butoxy group in **21**, caused a significant decrease in the efficiency of the addition, as indicated by the modest yield of adducts **24a** and **24b**. Furthermore, when a strong electron-withdrawing group was present on the aromatic ring, the required *N*-chloromethyl precursor could not be prepared by the usual procedure.

In the case of the isatin derivatives, no ring closure on the aromatic portion of the isatin residue, leading for example to **25**, was observed when the adducts were further exposed to stoichiometric amounts of peroxide (Scheme 4). The strain

Scheme 4

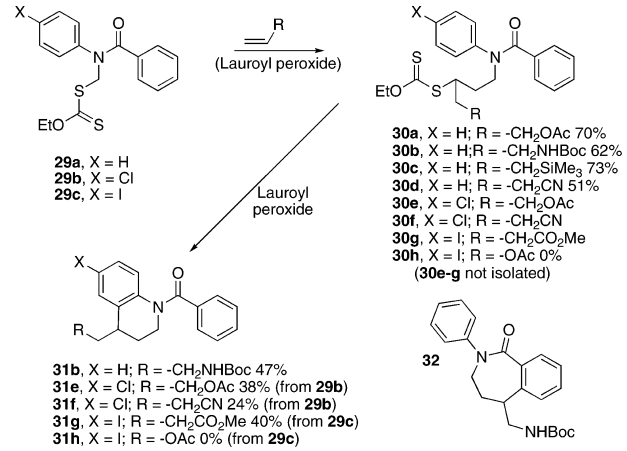


resulting from the fusion of a five- and six-membered ring around the aromatic nucleus must certainly raise the activation barrier of the cyclization. We hoped that the open chain derivatives would prove to be better substrates. Unfortunately, when compound **22a** was treated with lauroyl peroxide in refluxing chlorobenzene, only a small yield of desired tetrahydroquinoline **26** was obtained. This contrasted sharply with the ready formation of the analogous dihydroquinolones **28** from xanthates **27** (R′ = Me or even H) we examined a few years ago.[8]

The lack of propensity to ring close onto the aromatic ring is probably due to an unfavorable conformation in this case. The acetyl on the nitrogen atom was therefore replaced with a benzoyl to allow the radical another possibility of cyclization, namely on the aromatic ring of the benzoyl group. This would lead to the creation of a fused seven-membered ring benzazepinone structure (cf. **32**). Radical cyclizations onto aromatic rings to produce fused seven-membered rings are quite rare but nevertheless precedented.[9]

Xanthate **29a** was readily obtained from benzanilide by the same procedure as for *N*-acetyl xanthate **19**. This xanthate underwent a fairly smooth radical addition to a number of typical olefins to give the corresponding addition products **30a**−**d** in satisfactory yields (Scheme 5). Treatment of adduct

Scheme 5



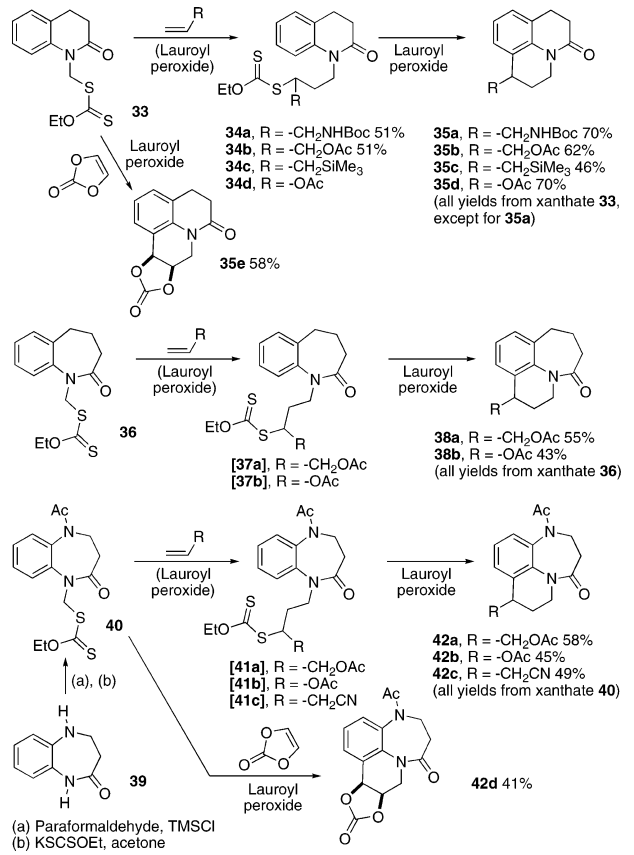
30b with stoichiometric amounts of lauroyl peroxide in refluxing chlorobenzene resulted in the formation of tetrahydroquinoline **31b** in 46% yield and none of benzazepinone **32**. Replacement of the acetyl group on the aniline nitrogen by a benzoyl group resulted thus in a very significant improvement in the cyclization step, without the competitive formation of benzazepinone **32**. In the same way, substituted xanthates **29b** and **29c** were converted into corresponding tetrahydroquinolines **31e**−**g** in a comparable overall yield, without isolation of intermediate adducts **30e**−**g**. As for **23c** above, the radical addition to vinyl acetate could not be controlled, and essentially no **30h** was obtained.

In a further example, lactam xanthate **33** not only underwent the radical addition to *N*-Boc-allylamine to give compound **34a** in 51% yield, but the corresponding tricyclic product **35a** started forming already at this stage (Scheme 6). Indeed, exposure of purified adduct **34a** to stoichiometric amounts of lauroyl peroxide furnished tricycle **35a** in 70%

(8) Binot, G.; Zard, S. Z. *Tetrahedron Lett.* **2005**, *46*, 7503.

(9) (a) Bacqué, E.; El Qacemi, M.; Zard, S. Z. *Org. Lett.* **2004**, *6*, 3671. (b) Kaoudi, T.; Quiclet-Sire, B.; Seguin, S.; Zard, S. Z. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 731, and references cited therein.

Scheme 6

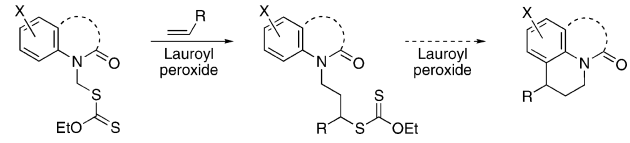


yield. It was in fact better to perform the intermolecular addition and cyclization in the same flask, as shown by the reaction with allyl acetate. The first adduct **34b** was obtained in 51% yield, whereas pushing the reaction all the way to the tricyclic structure gave **35b** in superior overall yield of 62%. In the same manner, compounds **35c**, **35d**, and **35d** were prepared in 46%, 70%, and 58% yield, respectively, using allyl trimethylsilane, vinyl acetate, and vinylidene carbonate as the olefinic traps. In the last case, the intermediate xanthate adduct was not even observed by thin-layer chromatography.

It was also pleasing to find that the homologous benzazepinone xanthate **36** underwent the same addition−cyclization, even if the efficacy was slightly lower. Thus, without isolation of the intermediate adducts **37a** and **37b** to allyl and vinyl acetate, respectively, it was possible to obtain the corresponding fused tricyclic derivatives **38a** and **38b** in 55% and 43% overall yield. The more rigid benzodiazepinone analogue **40**, obtained in good yield from known lactam **39**,[10] gave rise somewhat more efficiently to the very rare structures **42a**−**d**,[11] again without isolation of the intermediate addition products **41a**−**d**.

These preliminary results greatly extend our initial work on the radical aminomethylation of unactivated alkenes, summarized by eq 1 in Scheme 1. The replacement of one of the carbonyl groups in the original imide **1** with an aromatic ring maintains sufficient stabilization of the initial primary carbon radical to allow control of the radical chain and results in a simple yet powerful and flexible process for performing useful arylaminomethylations of unactivated alkenes. As encapsulated in Scheme 7, this approach can

Scheme 7



lead rapidly to open chain or cyclic aniline derivatives bearing varied and useful functionality, both in the xanthate and olefinic partners. Aniline-based structures are of considerable importance, especially in medicinal chemistry,[12] and many of the compounds described in the present work would not be readily available by more conventional routes. Compounds **35e** and **42d** are striking examples of the complexity that can rapidly be attained.

Acknowledgment. We respectfully dedicate this paper to Professor Rolf Huisgen (Ludwig Maximilians Universität, Munich). F.L. thanks Ecole Polytechnique for a scholarship.

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.

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(10) Dai-Il, J.; Tae-Wonchoi, C.; Yun-Young, K.; In-Shik, K.; You-Mi, P.; Yong-Gyun, L.; Doo-Hee, J. *Synth. Commun.* **1999**, *29*, 1941.

(11) A search of Beilstein returned only 15 structures. See: Katritzky, A. R.; Abonia, R.; Yang, B.; Qi, M.; Insuasty, B. *Synthesis* **1998**, 1487.

(12) For example, tricyclic amides closely related to compounds **35** have been found to be potent systemic fungicides. See: Bass, R. J.; Koch, R. H.; Richards, H. C.; Thorpe, J. E. *J. Agric. Food Chem.* **1981**, *29*, 576.