

Radical Aminomethylation of
Unactivated Alkenes

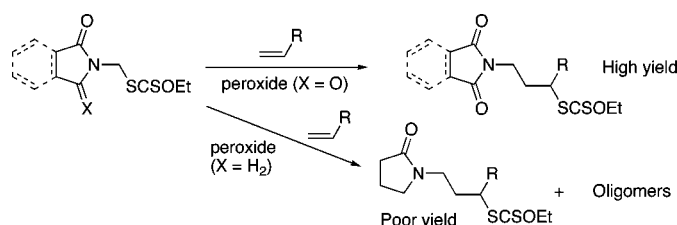
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ABSTRACT

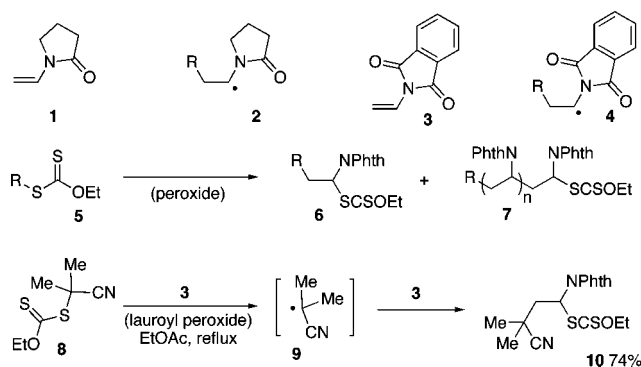


S-Succinimidomethyl- and S-phthalimidomethyl xanthates are added efficiently to various alkenes resulting in an overall aminomethylation process. In contrast, under similar conditions, S-pyrrolidonyl xanthate gives rise mostly to oligomers. This unexpected difference in reactivity is attributed to the more important allylic character of the intermediate radical in the case of the imide derivative as compared to the lactam.

In the course of our work on the radical xanthate transfer reaction,¹ we made a puzzling observation: while clean radical additions to *N*-vinyl pyrrolidone **1** could be achieved in the usual manner,² similar reactions with the synthetically more interesting *N*-vinyl phthalimide **3** furnished mostly oligomers **7**, instead of the desired adducts **6** (Scheme 1; PhthN = phthalimido).³ Only with xanthates such as **8**, leading to highly stabilized radicals (e.g., **9**), could we obtain a reasonable yield of the desired monoadduct (**10** in this case).

The extensive formation of oligomers is often the result of the adduct radical **11** being *more stable* than radical **R•** derived from the starting xanthate **5**, as can be seen in the simplified mechanistic manifold of Scheme 2. The relative stabilities of the starting and adduct radicals in the xanthate addition process is a key element for success.¹ Intermediate

Scheme 1



radical **12** has to fragment preferentially into starting radical **R•** and not back to adduct radical **11**, because otherwise the latter will accumulate, causing oligomer formation by further additions to the alkene component.

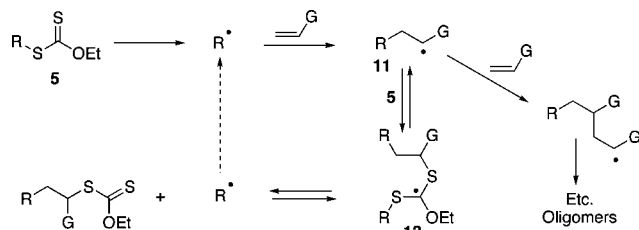
Thus, the easy, and for our purposes unwanted, oligomer formation in the case of *N*-vinyl phthalimide pointed to a *significantly greater stability* of adduct radical **4** as compared with the structurally closely related *N*-vinyl pyrrolidone

(1) For reviews of the xanthate transfer chemistry, see: (a) Zard, S. Z. *Angew. Chem., Int. Ed. Engl.* **1997**, 36, 672. (b) Zard, S. Z. In *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.

(2) See for example: Gagosz, F.; Zard, S. Z. *Org. Lett.* **2003**, 5, 2655.

(3) *N*-Vinylphthalimide has very recently been polymerized using xanthates by what is now called the RAFT/MADIX process: Maki, Y.; Mori, H.; Endo, T. *Macromol. Chem. Phys.* **2007**, 208, 2589.

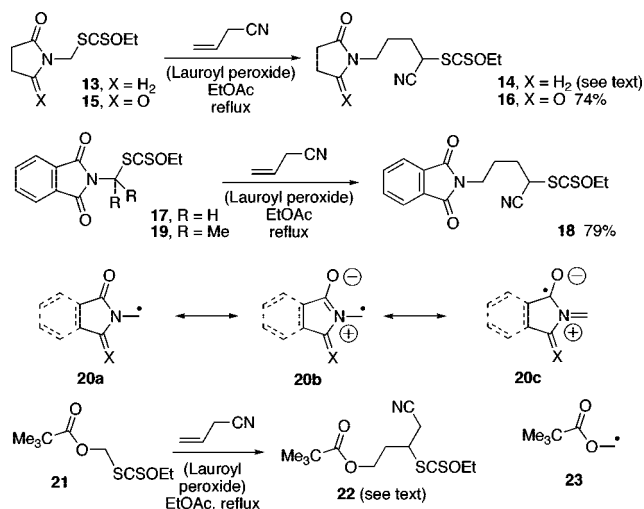
Scheme 2



derived radical **2**. This is *opposite* to what one would have predicted upon a superficial examination since the lone pair on the nitrogen should be more available to stabilize the radical in **2** than in **4**.⁴

This unanticipated difference in stability was confirmed when the radical addition of xanthate **13** to allyl cyanide was found to proceed sluggishly, giving a poor yield of the corresponding adduct **14** and important quantities of oligomers, which made purification difficult (Scheme 3). In

Scheme 3



dramatic contrast, the addition of succinimido- and phthalimido-methyl xanthates **15** and **17** took place smoothly and cleanly to furnish the respective adducts **16** and **18** in good yield and without untoward formation of oligomers. The most plausible rationalization appears to be a more significant contribution of canonical forms **20b** and **20c** when $X = O$ than when $X = H_2$,⁵ causing a significant increase in the allylic character radical in the former case and therefore an increase in its stability. *This difference in stability is, in all*

(4) The stabilization of aminoalkyl radicals is due to a favorable two-orbital–three-electron interaction. When the availability of the lone pair on nitrogen is decreased, for example, by protonation, the result is a *destabilization* of the aminoalkyl radical. See: Mayer, P. M.; Glukhovtsev, M. N.; Gauld, J. W.; Radom, L. *J. Am. Chem. Soc.* **1997**, *119*, 12889.

likelihood, small but sufficient to allow control of the radical process and to curtail the formation of unwanted oligomers.

Furthermore, phthalimidomethyl xanthate **17** proved only marginally more reactive (a factor of 1.3) than the succinimido analogue **15**, as shown by a competition experiment between the two reagents. The stabilization due to the second carbonyl group thus appears to be more important than the presence of the aromatic ring in the phthalimido derivative. Finally, pivaloyl xanthate **21** reacted sluggishly with allyl cyanide to furnish mostly oligomers and returned starting material but almost no monoadduct **22**. This militates against polar factors playing a predominant role in the success of the imide derivatives,⁶ since radical **23** should exhibit a similar, if not more, electron-withdrawing character as compared to **20**, where $X = O$.⁷

We had occasion, in the context of a different project, to perform radical additions starting with the isopropyl phthalimido xanthate **19**,⁸ but because the radical generated in this case is a tertiary radical, and therefore necessarily more stable than the (usually) secondary adduct radical, its addition to a nonactivated alkene did not surprise us. The fact that the addition is successful even with the parent *primary* xanthate **17** opens a major avenue in synthesis because of the enormous importance of primary amines in organic and medicinal chemistry.

The radical additions of reagents **15** or **17** can be viewed as the overall synthetic equivalent of a hydroaminomethylation of an alkene, a transformation traditionally accomplished through the tandem combination of a hydroformylation reaction with a reductive amination (eq 1, Scheme 4).⁹ The hydroaminomethylation and related trans-

(5) It is interesting to note that, in contrast to the corresponding lactams, cyclic imides exhibit *two* carbonyl stretching frequencies in the infra red spectrum, which may be separated by as much as 70 cm^{-1} , and which have been attributed to the existence of a strong coupling between the two carbonyl groups due to conjugation of the type pictured in structure **20b**. Furthermore, the stretching frequencies are sensitive to the substituents on the nitrogen atom indicating a possible interaction of the type shown in structure **20c**. See: Hargreaves, M. K.; Pritchard, J. G.; Dave, H. R. *Chem. Rev.* **1970**, *70*, 439, and references cited therein.

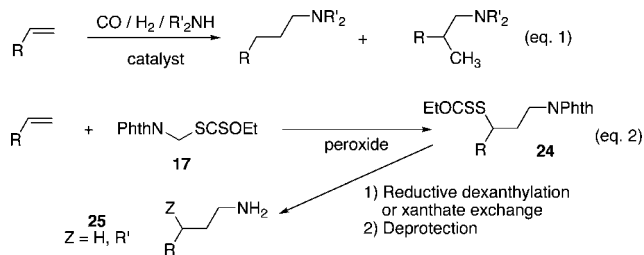
(6) In its recent use in a RAFT/MADIX controlled radical polymerization, the relative efficiency of xanthate **17** was attributed simply to the electrophilic nature of radical **20a**: (a) Postma, A.; Davis, T. P.; Evans, R. A.; Li, G.; Moad, G.; O'Shea, M. S. *Macromolecules* **2006**, *39*, 5293. (b) Postma, A.; Davis, T. P.; Evans, R. A.; Li, G.; Moad, G.; O'Shea, M. S. *Macromolecules* **2006**, *39*, 5307.

(7) The ^1H chemical shift signal of the $\text{N-CH}_2\text{-S}$ protons in **17** appears at δ 5.35 ppm, whereas that of the $\text{O-CH}_2\text{-S}$ in **21** appears at δ 5.65 ppm, which is 0.30 ppm more *downfield*, reflecting the slightly stronger electron-withdrawing effect of the pivalate in comparison to that of the phthalimido group.

(8) This xanthate was generated in situ by decarbonylation of the corresponding *S*-acyl xanthate: Heinrich, M.; Zard, S. Z. *Org. Lett.* **2004**, *6*, 4969.

(9) (a) Eilbracht, P.; Bäracker, L.; Buss, C.; Hollmann, C.; Kitsos-Rzychon, B. E.; Kranemann, C. L.; Rische, T.; Roggenbuck, R.; Schmidt, A. *Chem. Rev.* **1999**, *99*, 3329. For some recent studies, see: (b) Briggs, J. R.; Klosin, J.; Whiteker, G. T. *Org. Lett.* **2005**, *7*, 4795. (c) Beller, M.; Seayad, J.; Tillack, A.; Jiao, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 3368. (d) Ahmed, M.; Seayad, A. M.; Jackstell, R.; Beller, M. *J. Am. Chem. Soc.* **2003**, *125*, 10311. (e) Angelovski, G.; Eilbracht, P. *Tetrahedron* **2003**, *59*, 8265. (f) Seayad, A. M.; Ahmed, M.; Klein, H.; Jackstell, R.; Gross, T.; Beller, M. *Science* **2002**, *297*, 1676. (g) Rische, T.; Eilbracht, P.; Muller, K.-S. *Tetrahedron* **1999**, *55*, 9801. (h) Rische, T.; Eilbracht, P. *Tetrahedron* **1999**, *55*, 1915–1920. (i) Bergmann, D. J.; Campi, E. M.; Jackson, W. R.; Patti, A. F.; Saylik, D. *Tetrahedron Lett.* **1999**, *40*, 5597. (j) Zimmermann, B.; Herwig, B.; Beller, M. *Angew. Chem., Int. Ed.* **1999**, *38*, 2372. (k) Ojima, I.; Tzamarioudaki, M.; Eguchi, M. *J. Org. Chem.* **1995**, *60*, 7078.

Scheme 4



formations apply, with very rare exceptions,^{9,9b} to simple alkenes, and the use of ammonia in these processes, which would lead to primary amines in principle, is highly problematic in practice because of the rapid reaction of the primary amine product with the aldehyde generated in the hydroformylation step.^{9,9i} A further problem is the frequent obtention of mixtures of linear and branched products as implied by eq 1 in Scheme 4. The utility of this route to the synthesis of complex, densely functionalized structures is thus severely limited.

The present, radical-based approach¹⁰ complements, and often surpasses, the organometallic route, owing to the compatibility of radical processes with many functional groups and the mildness of the reaction conditions.¹¹ For the remainder of this study, we used xanthate **17** since it is nicely crystalline and readily prepared in essentially quantitative yield in one step from commercially available and cheap *N*-chloromethylphthalimide.¹² If the xanthate group in adduct **24** is reductively removed and the phthalimide cleaved off with hydrazine or other reagents, the overall process becomes strictly equivalent to a hydroaminomethylation of an alkene (eq 2, Scheme 4).

The presence of the xanthate in **24** can of course be exploited in numerous other ways to introduce further functionality ($Z \neq H$ in **25**).¹ The varied examples collected in Table 1 are self-explanatory and demonstrate unequivocally the tremendous power of this technology. Yields in parentheses correspond to yields based on recovered starting material. In the case of compounds **30**, **33**, **36**, **39**, **45**, and **46**, approximately 1:1 mixtures of diastereomers were obtained.

The xanthate group in the products can be removed by various methods.¹ We introduced a few years ago a reductive dexanthylation procedure involving lauroyl peroxide/isopropanol.¹³ An application illustrating its compatibility with the phthalimido group, as well as the synthesis of new hexaflu-

Table 1. Radical Aminomethylation of Alkenes

olefin	radical adduct with xanthate 17	yield
		69%
		68%
		82%
		86%
		87%
		56%
		85%
		78%
		74%
		64%
		46% (70%)
		91%
		79%
		77%
		78%
		57%
		89%
		54%
		84%
		46%

(10) Intermolecular radical hydroaminoalkylations of alkenes with simple amines under initiation with peroxides or UV light are known but are often low yielding and very limited in scope, working best, not unexpectedly, with electron-poor alkenes. See: (a) Hoffmann, N. *Chem. Rev.* **2008**, *108*, 1052. (b) Renaud, P.; Giraud, L. *Synthesis* **1996**, 913.

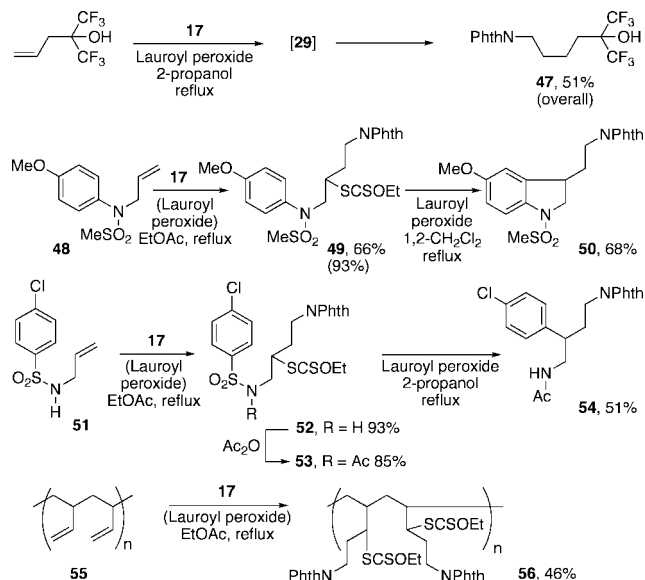
(11) Radical **20** has been generated from the corresponding bromide and iodide using stannane chemistry, and two examples of its addition to electrophilic olefins have been reported: (a) Campbell, E. F.; Park, A. K.; Kinney, W. A.; Fengl, R. W.; Liebeskind, L. S. *J. Org. Chem.* **1995**, *60*, 1470. (b) Receveur, J.-M.; Guiramand, J.; Récasens, M.; Roumestant, M.-L.; Viallefont, P.; Martinez, J. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 127.

(12) C.-P., Lo T. *J. Org. Chem.* **1961**, *26*, 3591.

orinated protected amino alcohol **47**, is displayed in Scheme 5. The isolation of the initial addition product **29** is not necessary: the two operations can be carried out in one pot

(13) Liard, A.; Quiclet-Sire, B.; Zard, S. Z. *Tetrahedron Lett.* **1996**, *37*, 5877.

Scheme 5



using 2-propanol as the solvent. The possibility of obtaining differentially protected diamine derivatives such as **32–34** is worth underscoring.

Other types of substituted diamines can be obtained as shown in Scheme 5. Thus, addition to *N*-allylsulfanilide **48** can be followed by ring closure to the aromatic ring to give indoline **50**, a structure that is useful as a precursor of melatonin.¹⁴ In the case of addition to sulfonamide **51**, acetylation of primary adduct **52** and further treatment with lauroyl peroxide in isopropanol cause a shift of the aromatic ring¹⁵ to give orthogonally protected diamine **54**. Such

(14) Quiclet-Sire, B.; Sortais, B.; Zard, S. Z. *Chem. Commun.* **2002**, 1692.

(15) Georghe, A.; Quiclet-Sire, B.; Vila, X.; Zard, S. Z. *Org. Lett.* **2005**, 7, 1653.

primary diamines are relatively uncommon. They are generally made by reduction of the corresponding dinitrile,¹⁶ and it is necessary to perform the reduction sequentially to be able to distinguish between the two amino groups.¹² The present approach is in contrast straightforward and concise. Finally, polyamines can be produced by multiple additions of reagent **17** to poly(1,2-butadiene) **55** leading to **56**, which was isolated by precipitation in 46%.¹⁷ Essentially, all the terminal olefins in the polymer can be saturated.

In summary, we have now in hand a very practical, efficient, and quite general process for the regioselective aminomethylation of alkenes. On a more fundamental level, we have uncovered a hitherto unsuspected mechanism for stabilizing an aminoalkyl radical that exploits the coupling of the two carbonyls in an imide structure through mesomeric forms such as **20b,c**. The success of the present method and all the consequent synthetic implications hinge on a small, but nevertheless decisive, difference in stabilization energy provided by the imide group. This effect should also apply, in principle, to structures related to imides (e.g., imidazolidinediones), but whether its magnitude in these cases will be sufficient to tip the balance in the desired direction remains to be seen.

Acknowledgment. We dedicate this paper to the memory of Jacques Levisalles and Jean-Louis Gras.

Supporting Information Available: Experimental procedures, full spectroscopic data, and copies of ¹H and ¹³C 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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(16) (a) Harley-Mason, J.; Jackson, A. H. *J. Chem. Soc.* **1954**, 1165. (b) White, J. D.; Yager, K. M.; Yakura, T. *J. Am. Chem. Soc.* **1994**, 116, 1831. (c) Lebarbier, C.; Carreaux, F.; Carboni, B. *Tetrahedron Lett.* **1999**, 40, 6233.

(17) Poly(1,2-butadiene), purchased from Aldrich, is constituted of 62 mol % 1,2-addition. In structure **55**, partial cyclization is possible but is not indicated for clarity.