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A convergent, modular access to complex amines

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This paper is dedicated with respect and admiration to Professor Steven V. Ley, recipient of the 2009 Tetrahedron Prize

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ABSTRACT

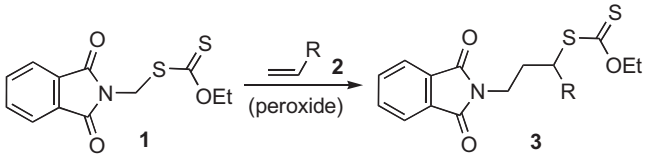
Various xanthates can be added to *N*-vinyl phthalimide with little formation of oligomers, if the xanthate is used in excess and the medium slightly diluted. The adduct xanthates thus obtained can in turn undergo radical additions to numerous olefins, providing a convergent and modular access to densely functionalized amines.

1. Introduction

The amino group occupies a central position in organic chemistry, and the synthesis of numerous natural products, such as amino-acids or alkaloids, or medicinal compounds, the vast majority of which contain one or more nitrogen atoms, hinges heavily on the ability to access functionalized amine intermediates or end products. As a consequence, the development of new flexible routes to amines remains a very worthwhile endeavor. We now report what we believe is an exceedingly powerful extension of an earlier approach, allowing the expedient assembly of highly functional internal primary amines conveniently protected as their phthalimido derivatives.

Recently, we described a versatile, practical radical aminomethylation of alkenes based on the degenerative xanthate transfer reaction,[1] namely the addition of xanthate **1** to alkene **2** to give adduct **3**, as summarized by the first equation in Scheme 1.[2] We later expanded this strategy to the arylaminomethylation of alkenes and to the synthesis of usefully functionalized amines starting from aminoacids.[3]

At the origin of our work in this area was a puzzling and frustrating observation: in contrast to additions to vinyl acetate or *N*-vinyl pyrrolidone, the corresponding radical additions of xanthates **4** to



Scheme 1.

N-vinyl phthalimide **5** furnished mostly oligomers **7** and only a small yield of the desired adducts **6** (Scheme 2; PhthN=phthalimido throughout). All three alkenes readily polymerize,[4] yet no difficulties were encountered in controlling the addition with the first two. In only one case, namely addition of AIBN derived xanthate ($Me_2C(CN)SCSOEt$, **4a**)[5] could we secure a good yield of mono-adduct under the usual conditions. Since xanthate additions to *N*-vinyl phthalimide **5** would constitute a simple, convergent, and flexible route to a vast number of variously functionalized, phthalimido protected primary amines **6**, we decided to re-examine this addition.

The difference in the behavior of *N*-vinyl phthalimide **5**, as compared to that of vinyl acetate and *N*-vinyl pyrrolidone, was attributed to the existence of resonance structures **8a** and **8b**, which impart a certain degree of allylic character to the adduct radical **8**.[6] Such conjugation is expected to be much less significant in the case of an acetate or a pyrrolidone group. The deleterious consequence of this stabilization in the present context can be understood by examining the fragmentation tendency of key intermediate **9** in Scheme 2. The formation of desired addition

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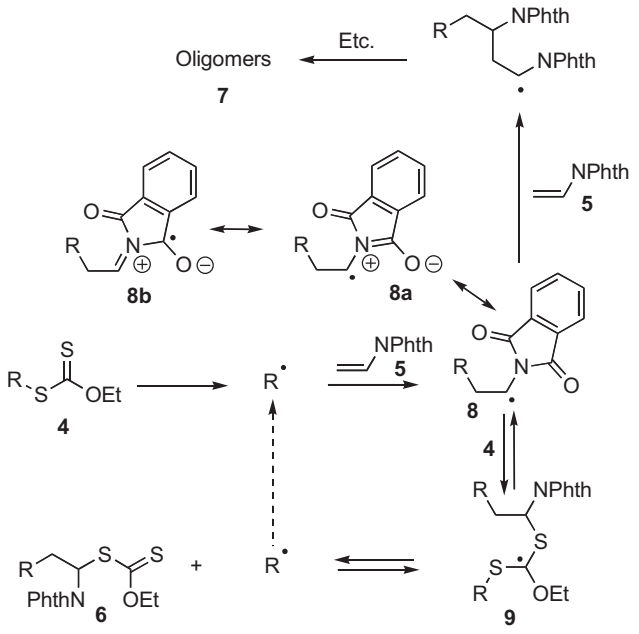


Scheme 2.

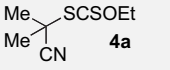
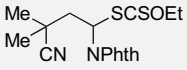
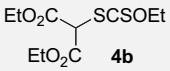
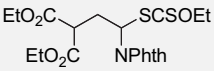
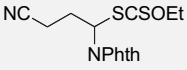
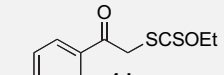
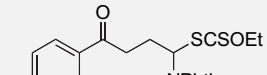
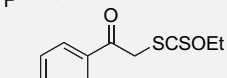
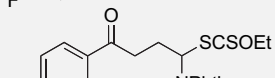
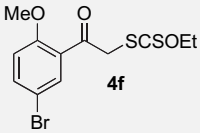
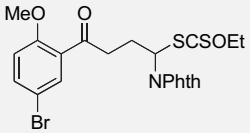
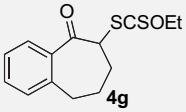
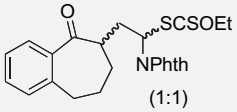
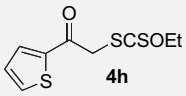
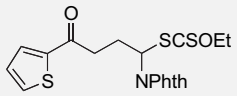
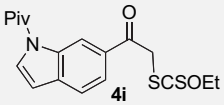
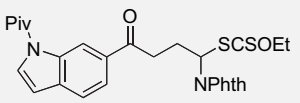
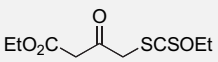
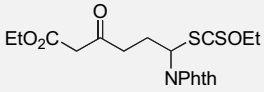
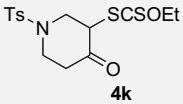
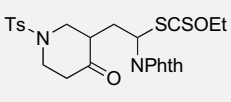
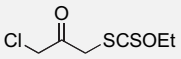
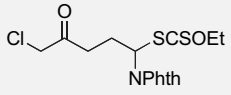
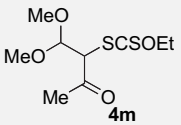
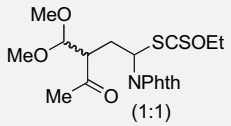
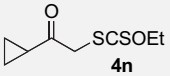
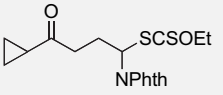
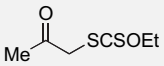
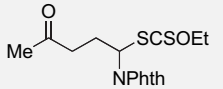
product **6** is favored when the collapse of this intermediate leads preferentially to radical R• and not back to adduct radical **8**. Unfortunately, the enhanced stabilization of **8** provided by the phthalimido group promotes the unwanted back fragmentation. This causes a build up in the concentration of **8** and encourages the formation of oligomer **7** by further additions to *N*-vinyl phthalimide **5**. In the case of AIBN derived xanthate **4a**, the corresponding radical ($Me_2C{\cdot}(CN)$) is sufficiently more stable than adduct radical **8** to shift the equilibrium in the right direction and allow clean obtention of mono-adduct **6a** (**6**, R=($Me_2C(CN)$–)).

While decisive, the extra stabilization provided by the phthalimido group is nevertheless expected to be small in absolute energy terms. It appeared therefore possible to curtail the unwanted oligomerization by a modification of the experimental parameters.

The additions of xanthates are normally conducted under a high concentration of 1–4 M and the olefinic partner is normally used in 1.5 to 3-fold and sometimes up to 5-fold excess, depending on its reactivity and volatility. If, instead, xanthate **4** is used in excess, the equilibrium should shift to increase the concentration of tertiary radical **9** at the expense of adduct radical **8**. This lowering of the concentration of **8** would automatically cause a decrease in the rate of oligomer formation. The rate of the bimolecular oligomerisation pathway may be further diminished by diluting the reaction medium. Thus, instead of using the usual two-fold excess of olefin, a two-fold excess of the xanthate and a 0.5 M concentration were employed instead.

We were gratified to find that these modified conditions worked quite nicely for xanthates derived from for diethyl malonate, acetonitrile, and functionalized ketones (Table 1, **6a**–**m**). The yield remained modest or poor with simpler xanthates **4n** and **4o** derived from cyclopropyl methyl ketone and from acetone, respectively. In these two cases, the efficiency was significantly improved to 72% and 82%, respectively, by increasing further the excess of xanthate to four-fold and further decreasing the dilution to 0.25 M. The same observation was made for *N*-acetyl oxazolidone derived xanthate **4p**. For the *N*,*O*-dimethyl acetylhydroxamic acid xanthate **4q**, a three-fold excess and a 0.33 M concentration were sufficient to secure a good yield (76%) of the desired adduct **6q**. With acetate or acetanilide xanthates, **4r** and **4s**, which otherwise add efficiently to ordinary terminal alkenes (e.g., allyl acetate), the extensive formation of oligomers could not be avoided unfortunately.

Table 1

Xanthate **4**	Radical adduct **6**	Yield[a] (%)
 **4a**		**6a**, 74
 **4b**		**6b**, 95
 **4c**		**6c**, 73
 **4d**		**6d**, 69
 **4e**		**6e**, 79
 **4f**		**6f**, 50
 **4g**	 (1:1)	**6g**, 87
 **4h**		**6h**, 64
 **4i**		**6i**, 72
 **4j**		**6j**, 62
 **4k**		**6k**, 86
 **4l**		**6l**, 72
 **4m**	 (1:1)	**6m**, 73
 **4n**		**6m**, 23 57[b]
 **4o**		**6o**, 22 72[b]

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