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Stabilization of Radicals by Imides. A Modular Stereoselective Approach to Protected Functional 1,2-Diamines

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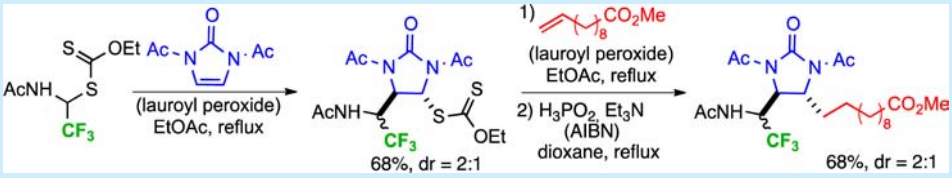
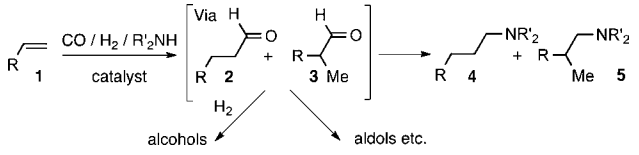
Supporting Information



ABSTRACT: Radical addition of various xanthates to *N*,*N*′-diacylimidazol-2-one occurs readily to give protected 1,2-diamines. The imide group stabilizes the adduct radical sufficiently to enable a second addition to unactivated alkenes. In some cases, the addition product could be converted into an indoline, a tetralone, or further added to an indole. Regioselective removal of one acyl group could also be accomplished.

The introduction of an amino group into organic molecules is often challenging, despite the numerous synthetic methods that have been devised over the years.[1] The limitations are acutely visible when alkenes are used as substrates. Bimolecular, transition-metal-catalyzed hydroaminations of alkenes are essentially confined to activated (styrenes, dienes) or to strained alkenes and are often not chemoselective, leading to mixtures of amine, enamines, and alkanes.[2] As for the much studied aminoalkylation of alkenes, which astutely combines a hydroformylation of an alkene such as **1** with a reductive amination of the resulting intermediate aldehydes **2** and **3**,[3] it still suffers from the shortcomings summarized in Scheme 1. In

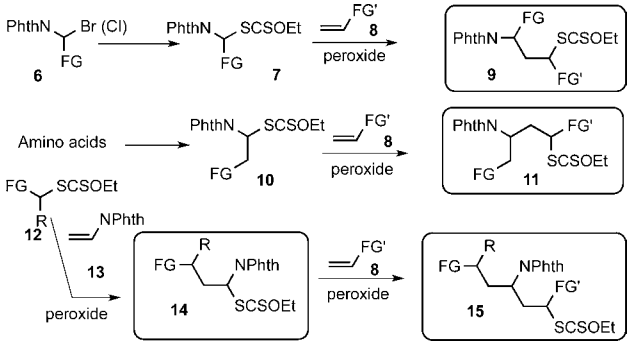
Scheme 1. Catalytic Aminoalkylation of Alkenes



addition to issues with regioselectivity, these include side reactions arising from premature reduction of the alkene or the intermediate aldehydes; from condensation of the aldehydes with themselves or with the product amines **4** and **5**, both leading ultimately to the formation of undesired higher amines; and from an intrinsic incompatibility with other functional groups. Even though the aminoalkylation is in principle an almost ideal process in terms of convergence and atom economy, it is in practice still largely limited to simple alkenes. In any case, the synthesis of vicinal diamines by any of these approaches remains especially problematic.[4]

We recently described efficient intermolecular radical chain additions of phthalimido-substituted xanthates to various alkenes allowing access to a plethora of highly functionalized phthalimido-protected amines.[5,6] The approaches we examined are outlined in Scheme 2 (PhthN = phthalimido and FG and FG′ indicate the presence of functional groups on the xanthate or the alkene).

Scheme 2. Xanthate Based Routes to Protected Amines



Initially, we explored the additions of the parent reagent **7** (FG = H),[5a] but routes to more functionalized starting xanthates **7** and **10** were later developed hinging on the bromination of substituted phthalimides and on the decarbonylative rearrangement of *S*-acyl xanthates of phthalimide-protected *α*-amino acids.[5b,d] Addition of these xanthates furnishes protected amines of types **9** and **11**. Another powerful strategy leading to more elaborate amines **15** consisted of first adding functional xanthates **12** to commercial *N*-vinylphthalimide **13** and incorporating adducts **14** in a second radical addition.[5c]

Addition products **9**, **11**, **14**, and **15** may be further transformed through ionic or radical methods. A broad variety of protected amines could be obtained by any of these

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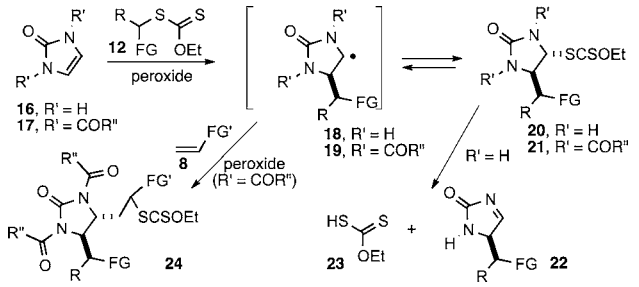
approaches, including 1,3-, 1,4-, and even 1,5-diamines (i.e., FG and FG′ could also contain protected amino groups). In the present paper, we describe a flexible, convergent route to protected 1,2-diamines, thus adding 1,2-diamines to the series.

The key element for the success of our process is the use of *N*,*N*′-diacylimidazol-2-one **17** as the alkene partner in the xanthate addition. The acyl groups play two crucial roles. In the first, they stabilize adduct **21** by preventing the ionic elimination of xanthic acid **23 to** give imine **22**, which happens readily with of an *N*-unsubstituted adduct **20** (Scheme 3). Xanthic acid **23** is an

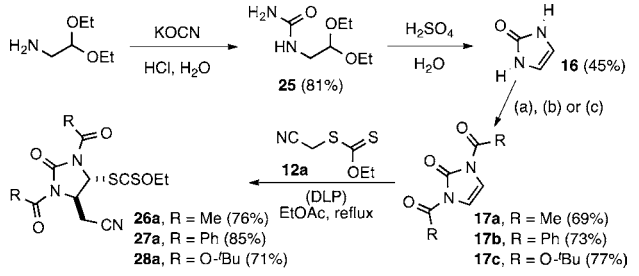
Scheme 3. Route to Protected 1,2-Diamines



unstable molecule and an inhibitor of the radical chain. In the second, and for reasons discussed below, the presence of the acyl groups would enable a subsequent addition to an external alkene **8**, thus providing complex protected 1,2-diamines of general structure **24**.

The synthesis of *N*,*N*′-diacylimidazol-2-ones **17a**−**c** is straightforward (Scheme 4). We confirmed that the non-

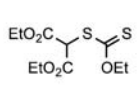
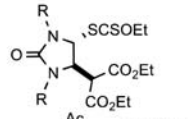
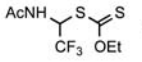
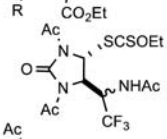
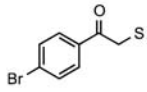
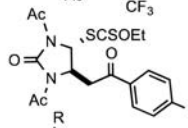
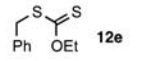
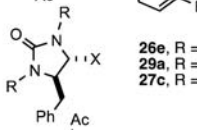
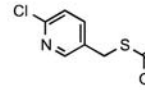
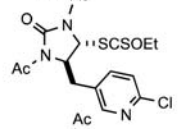
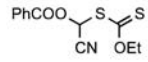
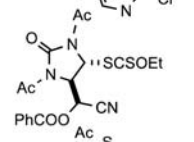
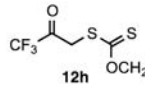
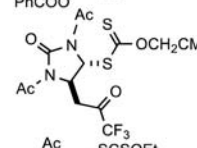
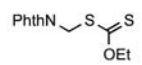
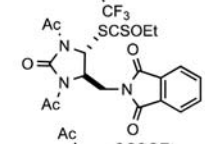
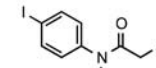
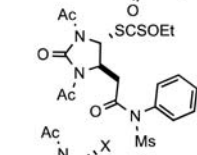
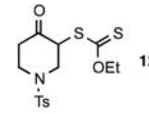
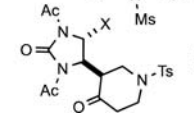
Scheme 4. First Examples of Intermolecular Radical Additions



acetylated intermediate **16** is indeed not a suitable olefinic trap for the radical addition, in contrast to **17a**−**c**, which reacted smoothly with xanthate **12a** to give the corresponding *trans*-addition products **26a**, **27a**, and **28a**, respectively (DLP = lauroyl peroxide throughout). The observed stereochemistry results from the shielding of one face of cyclic radical **19** by the entering group from the xanthate (FG = CN and R = H in this case).

A range of other xanthates could be added, leading to the products compiled in Table 1. Noteworthy examples are pyridine derivative **26f** and cyanohydrin benzoate **26g** (a masked aldehyde). Products **26c** and **26i** are protected 1,2,3-triamines, with the former bearing an interesting trifluoromethyl group. Another organofluorine derivative is trifluoro ketone **26h**. Trifluoromethyl ketones are highly valued, since they readily form hydrates that mimic the tetrahedral intermediate in the hydrolysis of esters and amides and are often potent reversible inhibitors of enzymes such as lipases.[7] Finally, adducts **26e** and **26k** were reductively dexanthylated by the Barton method using triethylammonium hypophosphite.[8] This allows access to protected *terminal* diamines **29a** and **29b**.

Table 1. Formation of Protected Diamines

xanthate **12**	adduct **26**	yield[a]
 **12b**		**26b**, R = Ac (88%) **27b**, R = Bz (92%)
 **12c**		**26c** (68%) (dr = 2:1)
 **12d**		**26d** (62%)
 **12e**		**26e**, R = Ac; X = SCSOEt (56%) **29a**, R = Ac; X = H (81%) **27c**, R = Bz; X = SCSOEt (56%)
 **12f**		**26f** (54%)
 **12g**		**26g** (68%) (dr = 2:1)
 **12h**		**26h** (71%) (as a 3:1 mixture with hydrate)
 **12i**		**26i**, R = Ac (61%) **27d**, R = Bz (62%)
 **12j**		**26j** (52%)
 **12k**		**26k**, X = SCSOEt (55%) **29b**, X = H (72%) (dr = 1:1)

One of the key conditions for a successful intermolecular addition of xanthates to alkenes is that the initial radical generated from the starting xanthate has to be more stable than the adduct radical corresponding to the product xanthate (neglecting polar effect in a first approximation).[6] Otherwise, a chain process cannot be efficiently sustained. This condition has been respected in all of the additions displayed in Table 1. This includes xanthate **12i**, the corresponding primary radical of which (**30a**, Scheme 5) would not seem, at first sight, to be more stable than the secondary adduct radical **19** (Scheme 3). In fact, radical **30** enjoys a special stabilization due to the coupling of the two carbonyls in the phtalimide structure (canonical structures **30b**−**d** in Scheme 5; structures involving the benzene ring have been omitted for clarity).[5a] This conjugation imparts a more significant allylic character to radical **30** than would be the case in a simple lactam. This phenomenon is largely responsible for the success of the additions of the phthalimide xanthates in Scheme 2.

Radicals **19** derived from xanthate adducts **26** (R″ = Ac) are also next to an imide and should also benefit, albeit to a lesser

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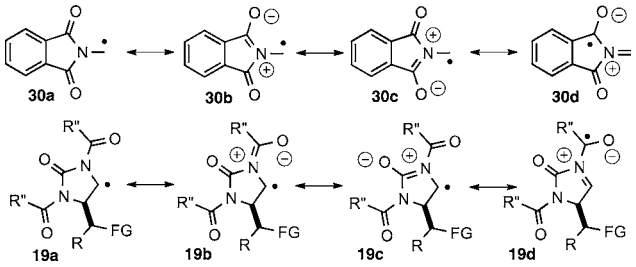
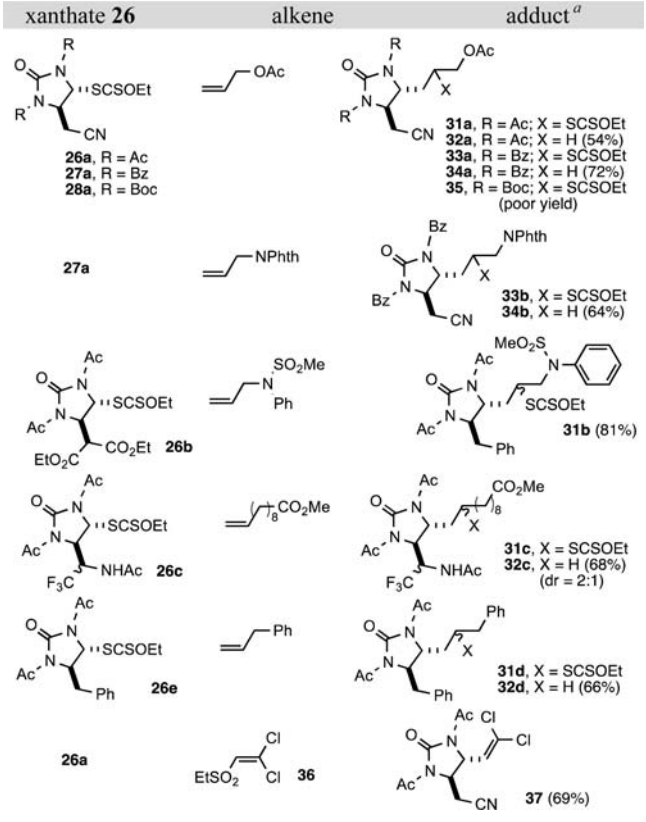
Scheme 5. Radical Stabilization by Imide Groups



extent, from a similar stabilizing effect through resonance forms **19b,c** (Scheme 5).[9] Xanthates **26** should therefore be capable of participating in a second addition to unactivated alkenes **8** (i.e., FG′ not a radical stabilizing group) to give adducts of general structure **24** (Scheme 3), since radicals **19** are now the initial radicals and the requirement stated above that the initial radical be more stable than the adduct radical is fulfilled.[5e]

This surmise proved indeed to be the case as indicated by the examples of additions collected in Table 2. Adducts **31a,c,d** and

Table 2. Further Additions of Xanthates 26



33a,b were not purified but subjected to the Barton reductive dexanthylation in order to eliminate one chiral center and simplify spectroscopic characterization. The overall yield for the two steps is therefore given for products **32a,c,d** and **34a,b**. As expected, all adducts were obtained as the *trans* isomers.

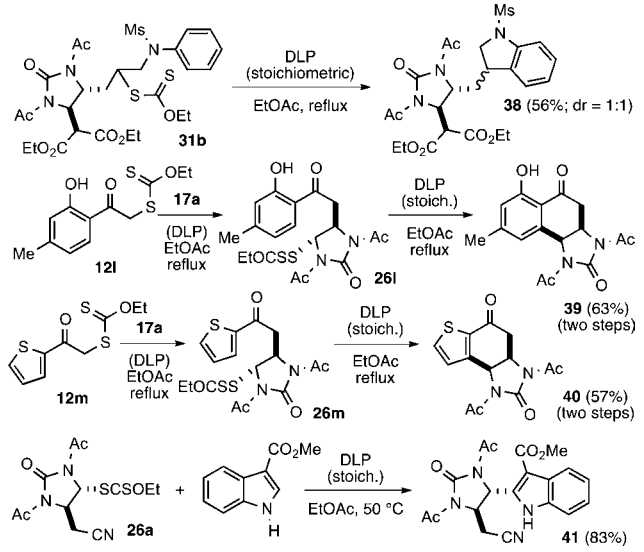
The influence of the acyl groups on the efficiency of the subsequent addition is apparent in the significantly better yield with the benzoyl adduct (72% for **34a** vs 54% for **32a**). This is almost certainly due to a slightly better stabilization of intermediate radical **19** (R″ = Ph) through further delocalization of the unpaired electron on the phenyl ring (note the benzylic character of the radical in canonical structure **19d**, R″ = Ph). More importantly, and in stark contrast, *the analogous di-Boc protected xanthate* ***28a*** *produced a complex mixture containing monoadduct* ***35a*** *but also higher addition products under identical reaction conditions.*

The formation of products of multiple additions to the alkene is an indication that the difference in stability of the initial and adduct radicals *is not sufficiently in favor of the former* to enable control of the chain process. Clearly, a carbamate-type imide does not provide sufficient stabilization for the radical through delocalization (**19b−d**, R″ = O-*t*-Bu) in comparison with an acetimide or a benzimide (**19b−d**, R″ = Ac or Ph). In chemistry, the path to success or failure often hinges on tiny differences in activation energy. In the present case, the nature of acyl group on the nitrogen atom *geminal* to the radical center is the decisive element for taming the radical addition.

Finally, the reaction with olefin **36** corresponds to an *ipso* substitution of an ethylsulfonyl radical. This process is not subject to the above condition of relative stability of the intermediate radicals[10] but nevertheless furnishes an interesting dichlorovinyl product **37** in good yield (69%; last example in Table 2).

Further variations are also possible. For example, treatment of adduct **31b** with a stoichiometric amount of peroxide results in ring closure to indoline **38** (Scheme 6).[11] Alternatively, reaction

Scheme 6. Further Reactions of Adducts 26



of imide **17a** with xanthates **12l** and **12m** provides first adducts **26l** and **26m** and subsequently tetralones **39** and **40** in good overall yield by further treatment with peroxide.[12] Finally, it is possible to perform an intermolecular addition to a substituted indole, as illustrated by the efficient synthesis of compound **41**.[13]

We made an unexpected observation while attempting to remove the acyl groups on adducts **26** or **27** (Scheme 7). Treatment of **26a,b** and **27b** with Hünig's base in methanol at rt cleaved cleanly the acyl group distal to the xanthate to give **42a,b** and **43a** respectively. The reasons for this regioselectivity are still not clear and the synthetic consequences have yet to be explored. Fortunately, the loss of the distal benzoyl group in **43a** did not affect its ability to undergo efficient radical addition to acetal-protected acrolein to give compound **45** after dexanthylation of the primary adduct **44**. This again confirms the importance of the

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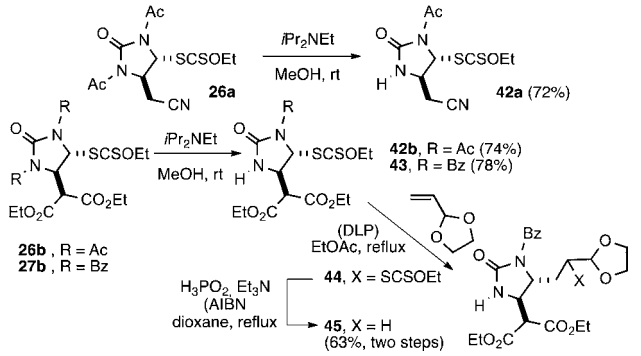
Scheme 7. Regioselective Deacylation of Adducts 26 and 27



proximal acyl group on the nitrogen in enabling the control over the radical addition.

The 1,2-diamino motif is found in numerous biologically active natural and synthetic substances.[14] Biotin is perhaps the most prominent example, but other representatives include antibiotics (e.g., mitomycins) as well as 1,4-benzodiazepines and various piperazine-containing drugs. Vicinal diamines are also valuable for the synthesis of ligands for metals.[15] Despite their importance, synthetic routes to these structures have remained relatively limited in variety and scope.[16] The present approach offers simplicity, flexibility, and modularity. Indeed, many of the compounds described herein would be tedious to obtain by more conventional syntheses.

■ ASSOCIATED CONTENT

Supporting Information

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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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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■ DEDICATION

This paper is dedicated with respect to the memory of Prof. John W. Cornforth (University of Sussex).

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