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Functional Primary Amines and Diamines from α-Aminoacids. A Concise Route to Substituted 2-Aminotetralins

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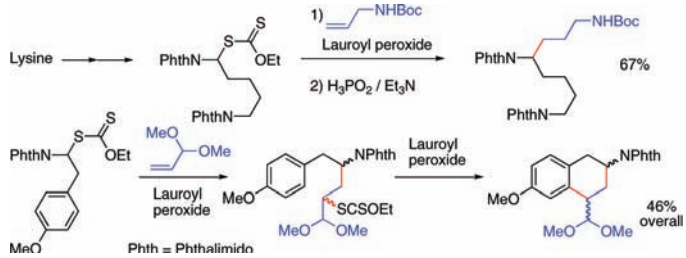
ABSTRACT

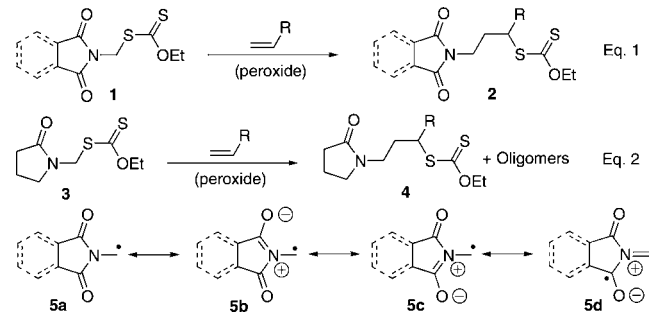


***S*-Phthalimidomethyl xanthates derived from various α-amino acids add efficiently to a range of unactivated alkenes to give a variety of highly functionalized, protected amines. In the case of phenylalanine and tyrosine derived xanthates, the adducts can be further converted into the rare 4-substituted 2-aminotetralines by a radical ring closure onto the aromatic ring.**

We recently described a flexible and quite general radical aminomethylation of alkenes by addition of *S*-succimidomethyl or *S*-phthalimidomethyl xanthate **1** to various alkenes to give adducts **2** (Scheme 1, eq 1).[1] The analogous pyrrolidone-derived xanthate **3** leads mostly to oligomer formation instead of desired adduct **4** (Scheme 1, eq 2). Success in the former case hinges on the apparent extra stabilization of the starting radical provided by the imide group, as indicated by canonical forms **5a**−**d**, which is less important in the simple lactam. It is essential, in the degenerative radical xanthate addition−transfer reaction, that in the absence of special polar effects the initial radical should be more stable than the adduct radical.[2]

In view of the fundamental importance of primary amines in organic chemistry, we considered extending this approach to more complex amine derivatives. This required a convenient access to the xanthate reagents. While the synthesis of the phthalimidomethyl derivative **1** is trivial,[3] since the *N*-chloromethylphthalimide precursor is commercially available, this is not the case for more elaborate derivatives.

Scheme 1



(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. 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.

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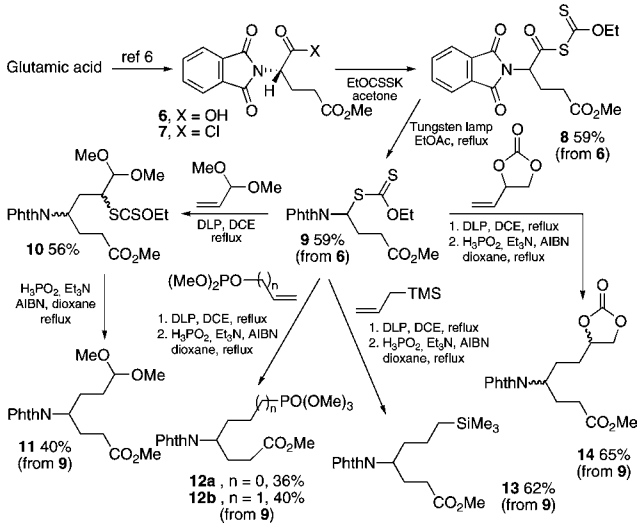
N-Chloromethylphthalimide is made by the addition of phthalimide to formaldehyde followed by treatment of the resulting *N*-hydroxymethylphthalimide with thionyl chloride.[3] Unfortunately, this approach, with perhaps very rare exceptions,[4] cannot be generalized to higher aldehydes.

The ready commercial availability of numerous α-amino acids offered a potentially simple and attractive solution to this problem. The possibility of replacing the carboxylic acid function with a xanthate group by way of the radical chain decarbonylation of the corresponding *S*-acyl xanthate would allow access to a variety of functionalized aminoalkyl precursors.[5] This strategy is illustrated by the synthesis and radical additions of the γ-aminobutyric acid (GABA) synthon **9** from L-glutamic acid as depicted in Scheme 2.

Scheme 2

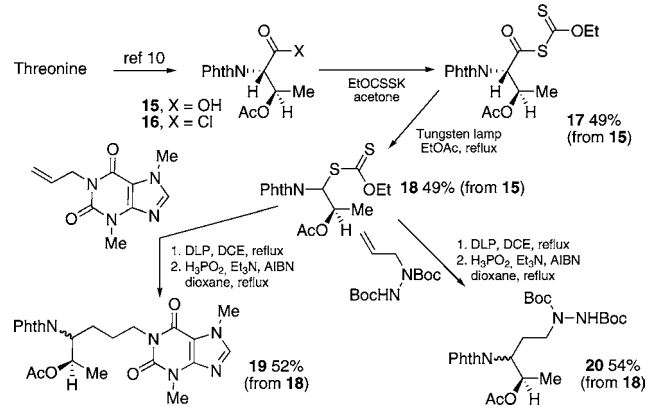


Thus, reaction of the acid chloride **7** derived from the known phthalimido acid **6**[6] with potassium *O*-ethyl xanthate furnished *S*-acyl xanthate **8**, which was not purified but simply irradiated with a tungsten lamp in refluxing ethyl acetate to give the desired xanthate **9** in good overall yield. This sequence was easily accomplished on a multigram scale, and xanthate **9** proved stable to storage, making its handling very convenient. It is worth underlining that in the synthesis of *S*-acyl xanthates in general it is important to resist the temptation to use the xanthate salt in excess with respect to the more valuable acid chloride. Any excess xanthate salt (or any potential nucleophile for that matter) can catalyze the decomposition of the *S*-acyl xanthate by way of an ionic chain reaction resulting in tedious purification and poor yields.[7]

With xanthate **9** in hand, its radical addition to a number of olefins, induced by lauroyl peroxide (DLP), could be examined. The results are summarized in Scheme 2. Thus, addition to the dimethylacetal of acrolein afforded adduct **10**. To avoid having to characterize mixtures of diastereoisomers, the xanthate group was reductively removed using triethylammonium hypophosphite[8] to give compound **11**, an amine with a carboxylate on one end and a masked aldehyde on the other. Other novel GABA analogues, with an extended chain and incorporating a number of useful functional groups, could thus be readily assembled and are displayed in Scheme 2. Several drugs now in clinical use (Baclophen, Pregabalin, etc.) embody the γ-aminobutyric acid core structure, underscoring the enormous importance of GABA analogues to the medical field.[9] It is interesting to note that compound **12a** can be viewed as both a γ-amino carboxylic acid and a γ-amino phosphonic acid derivative, a kind of double GABA analogue.

The use of other amino acid precursors provides xanthate reagents with different substituents. For instance, xanthate **18**, prepared from protected threonine **15**[10] via acid chloride **16** and the corresponding *S*-acyl xanthate **17** in the same manner, also underwent efficient radical additions, as indicated by the two examples in Scheme 3.

Scheme 3



In this case, the products, **19** and **20**, are valuable, latent β-aminoalcohols containing, respectively, a theobromine-

(4) For other hydroxyalkyl phthalimides derived from glyoxalic acid, methylglyoxal, and 2-phenylglyoxal, respectively, see: (a) Serino, A. J. *J. Org. Chem.* **1988**, *53*, 2661. (b) Egyud, L. G. US 4066650, see: *Chem. Abst.* **1978**, *88*, 152432. (c) Cosonni, P.; Favara, D.; Omodei-Sale, A.; Bartolini, G.; Ricci, A. *J. Chem. Soc., Perkin Trans. 2* **1983**, 967.

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(6) Wagner, J.; Kallen, J.; Ehrhardt, C.; Evenou, J. P.; Wagner, D. *J. Med. Chem.* **1998**, *41*, 3664.

(7) A mechanism for this ionic chain decomposition is proposed in ref.2a

(8) (a) Barton, D. H. R.; Jang, D. O.; Jaszberenyi, J. Cs. *Tetrahedron Lett.* **1992**, *33*, 5709. (b) Boivin, J.; Jrad, R.; Juge, S.; Nguyen, V. T. *Org. Lett.* **2003**, *5*, 1645.

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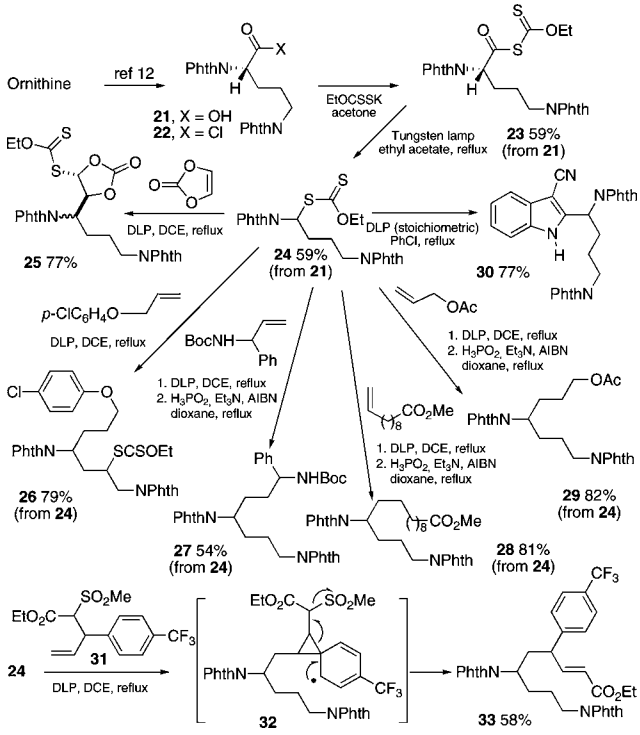
derived purine motif and a Boc-protected hydrazine.[11] While the chiral center bearing the methyl group initially present in threonine remains intact, its presence does not unfortunately allow any significant asymmetric induction at the adjacent center carrying the phthalimido group.

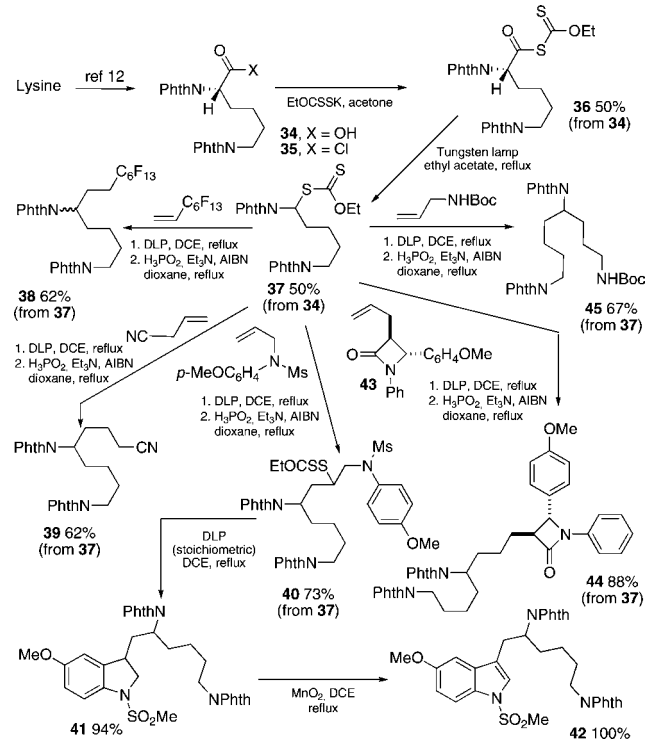
By starting with the known acid chlorides **22** and **35** derived, respectively, from ornithine and lysine,[12] a flexible and general route to 1,4- and 1,5-diamines can be implemented. The results, displayed in Schemes 4 and 5, demonstrate once again the power and flexibility of this approach in terms of functional group compatibility. The addition of xanthate **24** to Boc-protected α-phenyl-allylamine and xanthate **37** to Boc-protected allylamine leads, after dexanthylation, to triamines **27** and **45**, where one of the amine groups is protected differently from the other two. The synthesis of unsymmetrical polyamines by traditional routes is very tedious indeed,[13] contrasting starkly with the straightforwardness of the present approach.

Scheme 4



The intermolecular addition of xanthate **24** to 3-cyanoindole, mediated by stoichiometric amounts of lauroyl peroxide, occurred at the 2-position affording indole derivative **30** in 77% yield. The addition of xanthates to heteroaromatics is not general but can lead to interesting and otherwise inaccessible substances.[14] In the case of olefin **31**, a 1,2-shift of the aromatic ring via spirocyclohexadienyl radical

Scheme 5



32 followed by elimination of a methylsulfonyl radical furnished **33** in useful yield.[15] The obtention of fluorous diamine **38** and β-lactam **44** is also worthy of note. In adduct **40**, the xanthate was not reductively removed but used instead to accomplish a ring closure onto the aromatic ring to give indoline **41** in high yield.[16] Oxidation of the latter with activated manganese dioxide provided 3-substituted indole **42** quantitatively.

Diamines are highly valuable substances from a medicinal chemistry perspective. Du Bois and co-workers have recently described a route to 1,2- and 1,3-diamines involving an elegant rhodium-catalyzed intramolecular amination of C−H bonds starting with monoamine derivatives.[17] This strategy cannot, however, be easily extended to the preparation of 1,4- and 1,5-diamines. The xanthate transfer technology therefore nicely complements transition-metal-catalyzed insertion reactions.

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(14) Reyes-Gutiérrez, P. E.; Torres-Ochoa, R. O.; Martnez, R.; Miranda, L. D. *Org. Biomol. Chem.* **2009**, *7*, 1388. (b) Guerrero, M. A.; Miranda, L. D. *Tetrahedron Lett.* **2006**, *47*, 2517. (c) Osornio, Y. M.; Cruz-Almanza, R.; Jimenez-Montano, V.; Miranda, L. D. *Chem. Commun.* **2003**, 2316.
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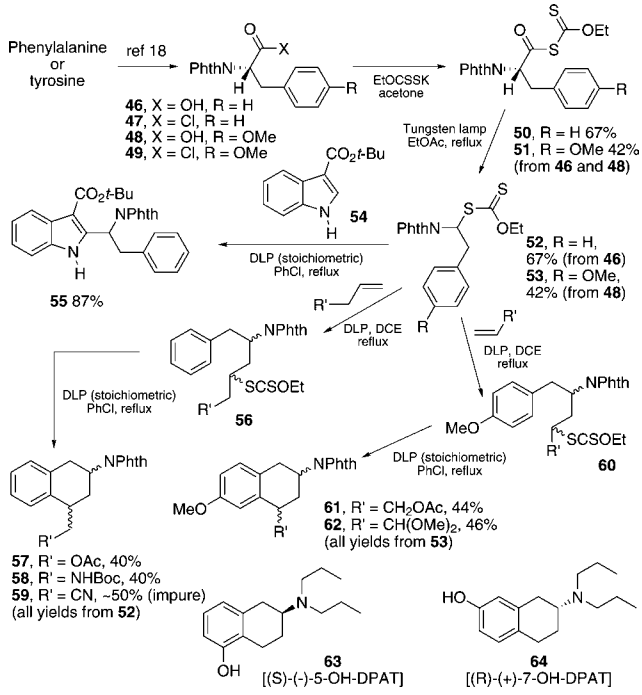
(16) Liard, A.; Quiclet-Sire, B.; Zard, S. Z. *Tetrahedron Lett.* **1996**, *37*, 5877.
(17) (a) Olson, D. E.; Du Bois, J. *J. Am. Chem. Soc.* **2008**, *130*, 11248. (b) Kurokawa, T.; Kim, M.; Du Bois, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 2777.

Another interesting feature of this chemistry was revealed in the study of xanthates **52** and **53**, derived, respectively, from acid chlorides **47** and **49** of protected phenylalanine and tyrosine (Scheme 6).[18] While the addition of xanthate

Scheme 6



52 to *t*-butyl 3-indolecarboxylate **54** to give indole **55** proved particularly effective, we found it possible to convert the usual olefin adducts into 2-aminotetralines by treatment with further amounts of lauroyl peroxide, as shown by the formation of compounds **57** and **58** and **61** and **62**. Such ring closures on an aromatic nucleus, leading to six-membered rings, are generally difficult if not impossible to perform with most radical processes and can be quite capricious even with the xanthate-based process.[2] In the present case, a small amount of dexanthylated material and compounds apparently derived from an *ipso*- ring closure mode were observed as side products, which sometimes complicated purification.

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2-Aminotetralins represent a family of compounds that is of high medicinal importance. For example, [(*S*)-(−)-5-OH-DPAT] **63** and [(*R*)-(+)-7-OH-DPAT] **64** are much studied dopamine agonists.[19] Yet, even though hundreds of analogues have been prepared, access to these structures remains surprisingly limited, hinging essentially on the reductive amination of 2-tetralones. The latter are generally prepared from 2-methoxynaphthalenes through a Birch reduction or, more seldom, using an intramolecular Friedel−Crafts reaction. The present radical based route is not only convergent and flexible but also provides ready access to derivatives substituted in the 4-position, which are difficult to obtain by existing routes and are consequently very rare.

The preliminary results described herein give only a glimpse of the synthetic potential attached to the use of α-amino acids as precursors of the corresponding xanthates. Not all the possibilities have been explored, and the approach is obviously not limited to naturally occurring α-amino acids. Amines associated with a very broad combination of functional groups can now be easily assembled, simply by modifying the reacting partners.

Acknowledgment. We respectfully dedicate this paper to Professor Larry E. Overman (University of California-Irvine). G. R. thanks Ecole Polytechnique for a studentship.

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.

OL901263T

(19) For the original work on isomeric OH-DPAT, see: (a) Wikstrom, H.; Lindberg, P.; Hjorth, S.; Carlsson, A.; Hacksell, U.; Svenason, U.; Nilsaon, J. L. G. *J. Med. Chem.* **1978**, *21*, 864. (b) Hacksell, U.; Svensson, U.; Nilsson, J. L. G.; Hjorth, S.; Carlsson, A.; Wikström, H.; Lindberg, P.; Sanchez, D. *J. Med. Chem.* **1979**, *22*, 1469. (c) McDermed, J. D.; McKenzie, G. M.; Freeman, H. S. *J. Med. Chem.* **1976**, *19*, 547. (d) Tedesco, J. L.; Seeman, P.; McDermed, J. D. *Mol. Pharmacol., I* **1979**, *16*, 369. (e) Arvidsson, L. E.; Hacksell, U.; Nilsson, J. L.; Hjorth, S.; Carlsson, A.; Lindberg, P.; Sanchez, D.; Wikström, H. *J. Med. Chem.* **1981**, *24*, 921. For some very recent references, see: (f) Butini, S.; Gemma, S.; Campiani, G.; Franceschini, S.; Trotta, F.; Borriello, M.; Ceres, N.; Ros, S.; Sanna Coccone, S.; Bernetti, M.; De Angelis, M.; Brindisi, M.; Nacci, V.; Fiorini, I.; Novellino, E.; Cagnotto, A.; Mennini, T.; Sandager-Nielsen, K.; Andreasen, J. T.; Scheel-Kruger, J.; Mikkelsen, J. D.; Fattorusso, C. *J. Med. Chem.* **2009**, *52*, 151. (g) Hatzenbuhler, N. T.; Baudy, R.; Evrard, D. A.; Failli, A.; Harrison, B. L.; Lenicek, S.; Mewshaw, R. E.; Saab, A.; Shah, U.; Sze, J.; Zhang, M.; Zhou, D.; Chlenov, M.; Kagan, M.; Golembieski, J.; Hornby, G.; Lai, M.; Smith, D. L.; Sullivan, K. M.; Schechter, L. E.; Andree, T. H. *J. Med. Chem.* **2008**, *51*, 6980. (h) Biswas, S.; Zhang, S.; Fernandez, F.; Ghosh, B.; Zhen, J.; Kuzhikandathil, E.; Reith, M. E. A. K.; Dutta, A. K. *J. Med. Chem.* **2008**, *51*, 101. (i) Liu, D.; Wikström, H. V.; Dijkstra, D.; de Vries, J. B.; Venhuis, B. J. *J. Med. Chem.* **2006**, *49*, 1494.