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Synthesis of γ-Amino Esters via Mn-Mediated Radical Addition to Chiral γ-Hydrazonoesters

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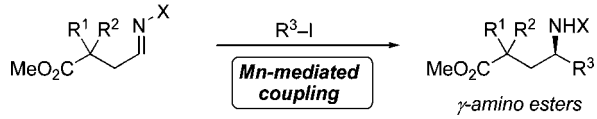
ABSTRACT



Highly stereoselective Mn-mediated couplings of alkyl iodides with chiral *N*-acylhydrazones bearing ester functionality afford a series of γ-hydrazino esters, including γ-substituted, α,γ-disubstituted, and α,α,γ-trisubstituted examples. In contrast to prior work with chiral *N*-acylhydrazones, high stereoselectivity was observed even in the absence of Lewis acid. Microwave-assisted acylation with trifluoroacetic anhydride and reductive N−N bond cleavage provided the γ-amino ester functionality in a synthetically useful *N*-TFA-protected form.

In contrast to α- and β-amino acids, general synthetic methods to supply γ-amino acids are comparatively underdeveloped.[1] Interest in biologically important γ-amino acids is expanding along with discoveries of their roles as agonists and antagonists of receptors for the neurotransmitter γ-aminobutyric acid (GABA) (Figure 1), of their presence as substructures in unusual peptide natural products,[2] and of the conformational constraints they impart to peptides.[3]

General C−C bond construction routes to γ-substituted γ-amino acids typically involve homologation of α-amino acids.[4] Alternatives to this strategy assume greater importance when uncommon γ-substituents are present or when there are substitutions at the α and β carbons, but few C−C bond construction approaches take this into account in a general way.[5]

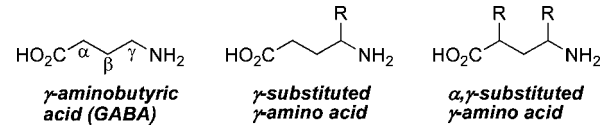


Figure 1. Structures of GABA and substituted γ-amino acids.

Our interest in γ-amino acids originated because two unique examples, tubuvaline and tubuphenylalanine (Figure 2), are prominently featured in the tubulysins, a series of extraordinarily potent tubulin-active cytotoxins.[6] We previously reported novel routes to these α-substituted γ-amino acids exploiting free radical addition[7] to chiral *N*-acylhydrazones,[8,9] in which silyl ethers at the C-termini of **1** and **2** were later oxidized to carboxylic acid functionality.[10] The Mn-mediated radical addition conditions we developed for this purpose exhibited excellent chemoselectivity and functional group tolerance,[11] and we began to question whether the efficiency and generality of this approach to γ-amino acids could be augmented if the C-terminus were to be already in the carboxylic acid oxidation state. Here we report the results of our test of this hypothesis, revealing that γ-hydrazonoesters are indeed excellent radical acceptors in Mn-mediated coupling with alkyl iodides.

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(2) Examples: (a) Matthew, S.; Schupp, P. J.; Leusch, H. *J. Nat. Prod.* **2008**, *71*, 1113–1116. (b) Kunze, B.; Bohlendorf, B.; Reichenbach, H.; Hofle, G. *J. Antibiot.* **2008**, *61*, 18–26. (c) Oh, D.-C.; Strangman, W. K.; Kauffman, C. A.; Jensen, P. R.; Fenical, W. *Org. Lett.* **2007**, *9*, 1525–1528. (d) Milanowski, D. J.; Gustafson, K. R.; Rashid, M. A.; Pannell, L. K.; McMahon, J. B.; Boyd, M. R. *J. Org. Chem.* **2004**, *69*, 3036–3042. (e) Williams, P. G.; Luesch, H.; Yoshida, W. Y.; Moore, R. E.; Paul, V. J. *J. Nat. Prod.* **2003**, *66*, 595–598. (f) Horgen, F. D.; Kazmierski, E. B.; Westenburg, H. E.; Yoshida, W. Y.; Scheuer, P. J. *J. Nat. Prod.* **2002**, *65*, 487–491.

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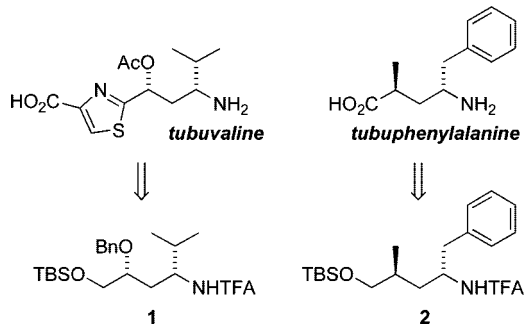
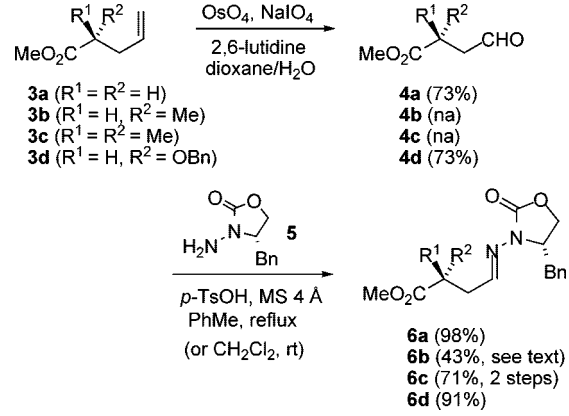


Figure 2. Precursors of tubuvaline and tubuphenylalanine, in which the C-termini required oxidation (ref 10).

The study began with series of 4-pentenoate esters **3a**−**3d** (Scheme 1) which were either commercially available or were known compounds prepared via modifications of published methods.[12] Lemieux−Johnson oxidation employing the Jin protocol[13] oxidatively cleaved alkene functionality of **3a**−**3d** to the corresponding aldehydes **4a**−**4d**,[14] and condensation with *N*-aminooxazolidinone **5**[15] provided chiral γ-hydrazonoesters **6a**−**6d**. Isolation of small quantities of aldehydes **4b**[14a] and **4c**[14c] in pure form was best avoided due to their volatility, and yields of **6b** and **6c** are reported over four-step and two-step sequences, respectively, without purification of intermediates. Specifically, the ester **3b** was obtained from the corresponding *N*-acyloxazolidinone (a known Evans allylation product,[16] not shown) by successive treatment with LiOOH and CH_2N_2, followed by oxidation and condensation as shown in Scheme 1 to furnish **6b** in 43% overall yield for the four steps.

Scheme 1



With several γ-hydrazonoesters in hand, prototypical isopropyl radical additions were examined using the Mn-mediated photolysis conditions. With $InCl_3$ as the Lewis acid, coupling of isopropyl iodide and hydrazone **6a** (Table 1, entry 1) afforded a quantitative yield of **7a** in very high diastereomeric purity.

Next, several hydrazones bearing varied substitution at the α-position of the γ-hydrazonoester were employed for addition of 2-iodopropane (Table 1, entries 2−4). Smooth Mn-mediated radical addition occurred with α-methyl, α,α-dimethyl, and α-benzyloxy-substituted γ-hydrazonoesters, all providing the isopropyl adducts with consistently high diastereoselectivities and excellent yields (91−98%). This small group of substrates **7a**−**7d** offers a brief scan of both steric and electronic effects, and within this group the reaction efficiency and selectivity appear to be largely independent of substitution at the α-position.

Analysis of the diastereomer ratios recorded in Table 1 called for a standard containing both diastereomers, so the Mn-mediated addition was attempted in the absence of $InCl_3$.

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(10) Friestad, G. K.; Deveau, A. M.; Marié, J.-C. *Org. Lett.* **2004**, *6*, 3249–3252.

(11) (a) Korapala, C. S.; Qin, J.; Friestad, G. K. *Org. Lett.* **2007**, *9*, 4243–4246. (b) Friestad, G. K.; Ji, A. *Org. Lett.* **2008**, *10*, 2311–2313.

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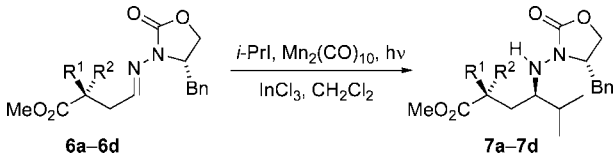
(15) Shen, Y.; Friestad, G. K. *J. Org. Chem.* **2002**, *67*, 6236–6239.

(16) (a) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737–1739. (b) Williams, D. R.; Cortez, G. S. *Tetrahedron Lett.* **1998**, *39*, 2675–2678. (c) See Supporting Information for details.

The purpose of the $InCl_3$ in these reactions is 2-fold: the chelation of bidentate *N*-acylhydrazones with the Lewis acid (a) activates the C═N bond toward radical addition by lowering its LUMO energy and (b) assists in discriminating the *re* and *si* faces at the prochiral imino carbon by restricting rotamer populations.[8,9] Thus, Mn-mediated radical additions in the absence of $InCl_3$ would be expected to furnish low diastereoselectivity. Surprisingly, the selectivity was only slightly diminished (dr 91:9) for isopropyl addition to **6a** (Table 1, entry 5); the yield was modest, as expected. For hydrazone **6d**, the diminished selectivity in the absence of $InCl_3$ was also observed, and the yield was maintained at a synthetically useful level (entry 6).

Table 1. Mn-Mediated Addition of *i*-PrI to γ-Hydrazonoesters[a]

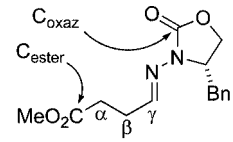


entry	γ-hydrazonoester	$InCl_3$	yield	dr[b]
1	**6a**	2.2 equiv	>99%	94:6
2	**6b**	2.2 equiv	98%	95:5
3	**6c**	2.2 equiv	96%	99:1
4	**6d**	2.2 equiv	96%	90:10[c]
5	**6a**	0 equiv	32%	91:9
6	**6d**	0 equiv	75%	85:15[c]

[a] Conditions: $InCl_3$ (2.2 equiv) and γ-hydrazonoester in CH_2Cl_2 (0.02 M), 2 h, then $Mn_2(CO)_{10}$ (1.1 equiv) and alkyl iodide (8 equiv), irradiation (300 nm, Pyrex) for 18 h at ca. 35 °C under Ar. [b] Ratio by GC and GC-MS unless noted. [c] Ratio by HPLC (Chirex 3014; 6% *i*-PrOH, 0.5% HCO_2H, hexane).

The presence of a Lewis basic ester could potentially alter the normal two-point binding of $InCl_3$ by *N*-acylhydrazones,[8,9] and this consideration prompted NMR experiments to substantiate the chelation model with substrates of this new type. Admixture of γ-hydrazonoester **6a** with $InCl_3$ in CD_2Cl_2[17] caused the characteristic H−C═N absorbance of the γ-hydrazonoester to shift from 8.04 to 7.74 ppm (Figure 3), an upfield shift precedented in similar cases.[18] Downfield shifts were observed for the α- and β-protons, as well as those of the oxazolidinone. Similar downfield shifts were noted throughout the ^{13}C NMR spectra, and of particular note, the carbons of the oxazolidinone C═O and the hydrazone C═N exhibited downfield shifts of 8 and 5 ppm in the complex compared to the starting γ-hydrazonoester. In contrast, the C═O carbon of the ester showed minimal change (<1 ppm). This suggests that the $InCl_3$ is chelated by the imino nitrogen and the oxazolidinone carbonyl in the usual way, without significant interference by the ester function.

A range of iodides were next examined in reactions with and without $InCl_3$, starting with a comparison of secondary

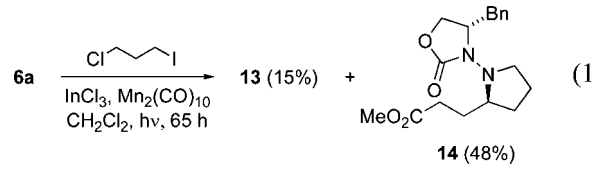


	δ (ppm), ^1H NMR			δ (ppm), ^{13}C NMR		
	H_α	H_β	H_γ	C_γ	C_{oxaz}	C_{ester}
without $InCl_3$	2.67	2.67	8.04	153.1	154.3	173.2
with $InCl_3$	2.76	3.09	7.74	161.0	159.7	174.0

Figure 3. Affects of $InCl_3$ on ^1H and ^{13}C chemical shifts of γ-hydrazonoester **6a**.

and primary iodides (Table 2). Both isopropyl and *sec*-butyl groups added more efficiently in the presence of $InCl_3$, as previously observed in Table 1. Analysis of diastereomerism in the *sec*-butyl addition, where an additional new stereocenter is formed, has not yet been addressed.

Previously, we have shown that the Mn-mediated photolysis conditions enable challenging radical additions of primary iodides.[9−11] This class of radical precursor generally gives low yields or mixtures of products in Et_3B- or tin-mediated additions. When primary iodides were subjected to coupling with γ-hydrazonoester **6a**, the desired adducts were obtained in moderate yields (33−66%, Table 2, entries 3−8) and excellent diastereoselectivity. Silyl ether and alcohol functionality were accommodated. Upon repeating these reactions under In-free conditions, there was no clear trend of diminished yields, in contrast to the observations with secondary iodides. Interestingly, the additions of homologous alcohols (entries 5 and 6) showed opposite effects of the $InCl_3$ on the yield. In most cases, the additions of primary iodides showed an erosion of diastereoselectivity when carried out in the absence of $InCl_3$.

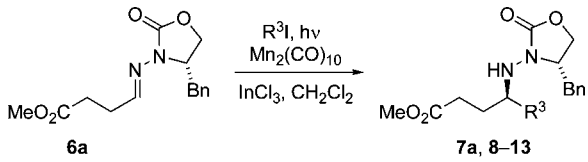


The reaction of 3-chloropropyl iodide with γ-hydrazonoester **6a** in the presence of $InCl_3$ afforded a mixture of alkyl chloride **13** in quantities which were dependent on the duration of photolysis. Acyclic chloropropyl adduct **13** was the major product when the irradiation time was 15 h (Table 2, entry 7). A longer irradiation time of 65 h afforded pyrrolidine **14** (dr >98:2) as a major product (eq 1), presumably via a radical addition followed by in situ S_N2-type polar cyclization. Such radical−polar crossover reactions have attracted considerable interest.[9,19] Interestingly, in this instance, operation in the absence of $InCl_3$ seems to be advantageous for the polar cyclization stage; under In-free conditions, pyrrolidine **14** was the exclusive isolated product, even without extended reaction time (Table 2, entry 8).

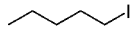
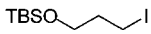
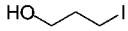
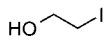
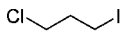
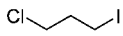
Lastly, removal of chiral auxiliary from the γ-hydrazinoester was examined. Our preferred general method in-

(17) See Supporting Information for details.
(18) Lin, C. H. *Synth. React. Inorg. Met.-Org. Chem.* **1993**, *23*, 1097–1106.

Table 2. Mn-Mediated Addition of Various Iodides to **6a**[a]



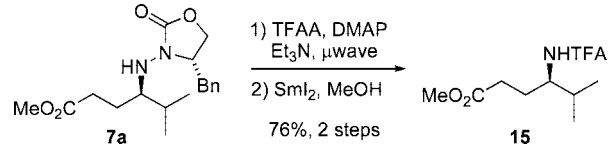
6a **7a**, **8**–**13**

entry	R^3I	product, yield[a,b]	dr[a,c]
1	*i*-PrI	**7a**, >99% (32%)	94:6 (91:9)
2	*s*-BuI	**8**, 82% (46%)	nd[d]
3		**9**, 66% (78%)	94:6 (>98:2)
4		**10**, 37% (44%)	96:4 (88:12)
5		**11**, 61% (30%)	97:3 (94:6)
6		**12**, 33% (51%)	96:4 (91:9)
7[e]		**13**, 45%	85:15
8[f]		(**14**[g], 56%)	(88:12)

[a] Conditions: see Table 1. Data in parentheses are for reactions without $InCl_3$. [b] Isolated yield. [c] Ratios by GC-MS or HPLC (Chiralcel OD-H; *i*-PrOH/hexane). [d] Due to complications from the additional stereocenter in the *s*-Bu group, the dr was not determined. [e] Irradiated for 15 h. [f] Compound **13** was not observed in chloropropyl addition without $InCl_3$. [g] For the structure of **14**, see eq 1.

volves acylation with trifluoroacetic anhydride (TFAA) to activate the N−N bond toward SmI_2-mediated reductive cleavage.[20] Hydrazines of the *N*-aminooxazolidinone type are somewhat recalcitrant toward acylation, which often requires sequential treatment with *n*-BuLi and TFAA. However, such conditions are incompatible with the ester functionality of **7a**. An effective alternative procedure was discovered; this entailed trifluoroacetylation under microwave irradiation[21] in the presence of Et_3N and DMAP (Scheme 2). The *N*-TFA derivative of **7a** obtained in this manner was exposed to SmI_2, smoothly furnishing known γ-aminoester **15** and proof of absolute configuration.[22,23] This microwave-enhanced *N*-acylhydrazine acylation is an important practical advance, extending the Mn-mediated coupling to chiral amines which bear ester functionality.

Scheme 2



In summary, we have developed a new entry to γ-amino acids via Mn-mediated coupling of alkyl iodides and γ-hydrazinoesters. This study exhibits additional elements of novelty in surprisingly high diastereomer ratios in the absence of $InCl_3$, NMR evidence regarding Lewis acid binding to γ-*N*-acylhydrazonoesters, facile radical−polar crossover annulation in the absence of $InCl_3$, and a new microwave-enhanced procedure for release of *N*-TFA-protected amines from the hydrazines formed in Mn-mediated radical addition.

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Supporting Information Available: Preparative details and characterization data for **6**−**15**. This material is available free of charge via the Internet at http://pubs.acs.org.

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