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Indium(III)-Catalyzed Addition of Diethyl Acetamidomalonate to Terminal Alkynes: An Efficient Approach to β-Branched α-Amino Acids

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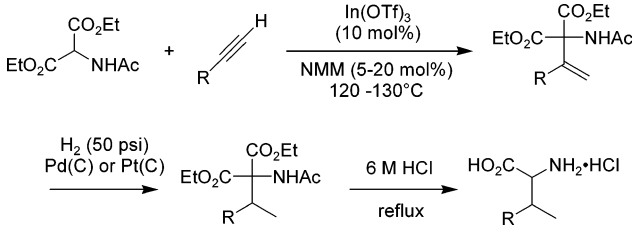
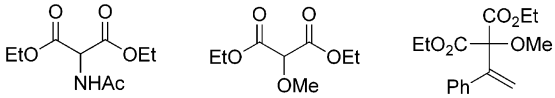


The indium(III)-catalyzed Markovnikov addition of active methylene compounds to terminal alkynes has been expanded further to include diethyl acetamidomalonate. This reaction has been studied, and a practical approach to β-branched α-amino acids was developed.

β-Branched α-amino acids are important and valuable building blocks for drug discovery since incorporation of conformationally constrained α-amino acids into peptides improves the pharmacokinetics and binding potency of drug candidates.[1] For example, L-valine was utilized successfully in the synthesis of pharmaceuticals such as Reprintrivir (AG-7088)[2] and Ritonavir (ABT-538, or Norvir),[3] as well as HIV protease inhibitors.[4] Meanwhile, the cyclic depsipeptide hormaomycin[5] is a naturally occurring product with interesting biological activities that contains two units of 3-methylphenylalanine.[6] Although there are numerous methods to prepare optically pure α-amino acids,[7] the number of highly enantioselective routes to β-branched α-amino acids is still limited.[8] The current highly efficient and practical catalytic asymmetric hydrogenation technology[9] prompted us to examine ways of making novel alkenes from which optically pure β-branched α-amino acids can be accessed expediently.[10]



1a **1b** **3**

FIGURE 1. Some useful and inexpensive starting materials (**1a**, **1b**) for the addition to 1-alkynes catalyzed by indium(III) and previously prepared adduct **3** from phenylacetylene and **1b**.

Diethyl acetamidomalonate (**1a**, DEAM) has been used for the synthesis of α-amino acids by C-alkylation via Michael addition under basic conditions.[11] It was also reported that the combination of C-alkylation and N-alkylation makes the formation of cyclic α-amino acid feasible.[12] However, to the best of our knowledge, there are no reports that employ **1a** or its

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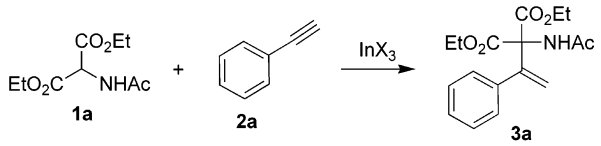
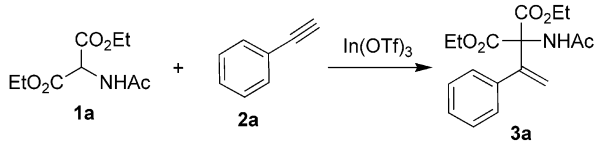
TABLE 1. Reaction Condition Screen[a]



entry	catalyst (mol %)	base	temp (°C)/time (h)	addition product area %
1	10% $In(OTf)_3$		140/3	63
2	10% $In(OTf)_3$	20% NMM	120/3	57
3	10% $In(OTf)_3$	20% NMM	120/20	83
4	10% $In(OTf)_3$	20% NMM	140/1	78
5	10% $In(OTf)_3$	20% NMM	140/3	75
6	10% $InCl_3$	20% NMM	140/1	44
7	10% $InCl_3$	20% NMM	140/3	71
8	10% $In(OTf)_3$	20% DBU	140/4	56
9	10% $In(OTf)_3$	20% *t*-BuOLi	120/4.5	62
10	10% $In(OTf)_3$	20% *t*-BuOLi	120/20	85
11	10% $In(OTf)_3$	20% *t*-BuONa	120/20	62
12	10% $In(OTf)_3$	20% *t*-BuOK	120/20	72
13	10% $In(OTf)_3$	20% LiOTf	120/4.5	75

[a] Reaction conditions: DEAM (2.0 mmol), phenylacetylene (1 mL), and InX_3 (0.2 mmol) were combined with or without base and heated as indicated.

TABLE 2. NMM Loading Study on Addition of DEAM to Phenylacetylene[a]



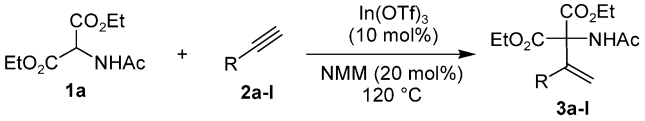
entry	NMM (mol %)	ratio of base/$In(OTf)_3$	addition product %
1	5	0.5/1	91.1 (7 h)
2	10	1/1	90.9 (7 h)
3	20	2/1	86.1 (7 h)
4	30	3/1	5.6 (7 h)
5	40	4/1	7.8 (7 h)
6	50	5/1	7.8 (7 h)

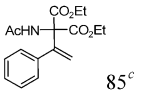
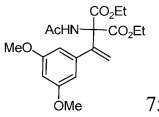
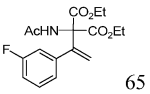
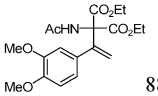
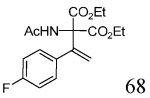
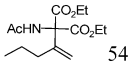
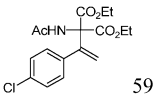
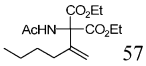
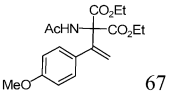
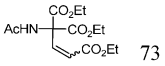
[a] Reaction conditions: DEAM (2.0 mmol), phenylacetylene (1 mL), and $In(OTf)_3$ (0.2 mmol) were combined with NMM (5−50 mol %) and heated at 120 °C for 7 h.

derivative as nucleophiles under acidic conditions to form the C−C bond. Recently, Nakamura and co-workers reported the indium triflate promoted addition of β-ketoesters and 1,3-diketones to 1-alkynes.[13] We later found that most indium(III) salts, green Lewis acids,[14] can assist this reaction and that malonates can be used as starting materials.[15] Surprisingly, when diethyl methoxymalonate (**1b**) was used under our previously published conditions ($InCl_3$, 130 °C), adduct **3** was formed in 81% isolated yield (Figure 1). This exceptional result encouraged us to further study its application. Herein we report an efficient method for the synthesis of β-branched α-amino acids with indium(III)-mediated addition of diethyl acetamidomalonate to terminal alkynes as the key step.

Unlike malonate **1b**, we expected formation of the enol−indium complex with **1a** to be difficult due to the lower acidity

TABLE 3. DEAM Addition to 1-Alkyne Catalyzed by $In(OTf)_3$[a]



entry	product / yield (%)[b]	entry	product / yield (%)[b]
3a	 85[c]	**3g**	 75
3b	 65	**3h**	 88
3c	 68	**3j**	 54
3d	 59	**3k**	 57
3f	 67	**3l**[d]	 73 (~10:1 *E*:*Z*)

[a] Reaction conditions: 1 equiv (2−20 mmol) of DEAM, 2−5 equiv of desired alkyne, 0.10 equiv of $In(OTf)_3$, 20 mol % of NMM, 16−24 h at 120−130 °C, neat conditions. The reaction time was not optimized. [b] Isolated yield after purification by silica gel chromatography. Products estimated to be >95% pure by ^{1}H NMR and elemental analysis. [c] Reaction repeated on 20 mmol (vs 2 mmol) scale with similar results. [d] Product **3l** provided the conjugate addition product (anti-Markovnikov).

of α-hydrogen. Indeed, when **1a** was combined with phenylacetylene under our previously reported conditions,[15] the desired product was not observed. When 5% DBU was added as catalyst and the mixture heated to reflux for another 20 h, only a trace amount of the desired product (<5%) was detected. Thus we decided to increase the reaction temperature to 140 °C by using xylene as solvent and 10 mol % of $InCl_3$ as Lewis acid. After 20 h, the desired product was isolated, although the yield was still poor.

After the desired conversion was achieved, further screening experiments were performed employing several In(III) salts, including $InCl_3$, $In(OTf)_3$, $In(OAc)_3$, and InF_3, and amine bases, including DIEA, *N*-methylmorpholine (NMM), DBU, DABCO, sparteine and imidazole in *o*-xylene, and mesitylene, or under neat conditions (using excess acetylene). The reaction contents were heated from 100 to 160 °C for as long as 20 h. Little or no desired product was observed using either $In(OAc)_3$ or InF_3. In contrast, a good yield (as high as 71 area % by HPLC) of the desired product was seen with $InCl_3$ in the presence of NMM (Table 1). However, even better conversion was observed using $In(OTf)_3$ in the presence of NMM (20 mol %) at 140 °C under

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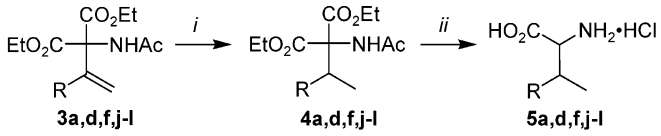
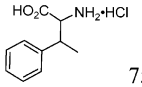
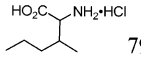
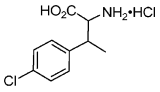
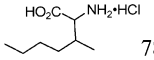
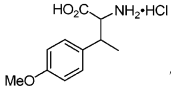
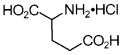
TABLE 4. Synthesis of β-Branched α-Amino Acids[a]



3a,d,f,j-l **4a,d,f,j-l** **5a,d,f,j-l**

entry	product/yield (%)[b] (*syn/anti ratio*)[c]	entry	product/yield (%)[b] (*syn/anti ratio*)[c]
5a	 75 (40/60)	**5j**	 79 (42/58)
5d	 81 (46/54)	**5k**	 78 (42/58)
5f	 79 (46/54)	**5l**	 64

[a] Reaction conditions for 1−7 mmol of substituted malonates **3a**,**d**,**f**,**j**−**l**: (i) Pd(C) or Pt(C)/H_2 50 psi, EtOH or THF, 3−16 h at 20−25 °C; (ii) 6 N aqueous HCl (w/ or w/o *p*-dioxane), 16−24 h at 90−100 °C. The reaction time was not optimized. [b] Isolated yield after purification by precipitation from acetonitrile. Products estimated to be >95% pure by ^{1}H NMR and elemental analysis. [c] Syn/anti ratio was determined by ^{1}H NMR integration; assignments of syn/anti diastereomers were based on previously published assignments for **5a**[1a] and **5f**,[8c] while the remaining β-methyl-α-amino acids were assigned by correlation.

neat conditions. The rate, purity profile, and conversion (as high as 90 area % by HPLC in 3 h) to the desired addition products were superior to all other conditions examined.

It was found that the reaction temperature must be at least 120 °C for a satisfactory reaction rate (reaction completion less than 24 h). Higher temperatures (e.g., 140 °C) increased the rate but appeared to lead to product decomposition. Interestingly, good conversion was also observed using *t*-BuOM (M = Li, Na, K) or LiOTf as bases, with yields ranging from 62 to 85% after 4.5−20 h. In the further study (Table 2) with NMM as an additive for the assistance of the deprotonation of DEAM to generate the indium enolate intermediate,[16] up to 20 mol % of base was tolerated. 5−10 mol % NMM loading gave nearly identical and optimal results, and 30−50 mol % provided very poor results. This finding clearly shows the deleterious effect for the desired addition reaction when the base/catalyst ratio approaches or exceeds 3/1.

With the success of this screening experiment, we further investigated the scope and limitation of the In(III)-catalyzed addition reaction of DEAM with various alkynes. These results are shown in Table 3.

We also found that functionalized terminal alkynes, such as 5-hexynenitrile, 6-chloro-1-hexyne, and 5-chloro-1-pentyne, provided low to moderate yields (15−35%). Unsubstituted aliphatic alkynes gave moderate yields (mid-50% range, entries 3j and 3k) and generally good yields (up to 85%, entries 3a and 3h) for aromatic alkynes. Electron-withdrawing substitution on the aromatic ring led to sub-par yield, and the electron-deficient ethyl propiolate provided a good (73%, entry 3l) yield of the expected *E*/*Z* mixture of the Michael addition product. Alcoholic alkynes or the labile acetal functional groups were unproductive. Disubstituted alkynes did not provide the desired addition product either.

With this novel application for In(III)-catalyzed addition of DEAM to alkynes available, we then developed a practical and efficient approach to prepare β-branched α-amino acids (Table 4). To that end, the addition products of DEAM and alkyne were subjected to hydrogenation using Pd(C); however, dehalogenation was avoided for **3d** → **4d** when Pt(C) was used. The hydrogenated product was treated with 6 N HCl in refluxing conditions, resulting in concomitant N-deacylation/ester hydrolysis and decarboxylation of **4** to provide the target β-methyl α-amino acid in excellent overall yield.

In conclusion, we have demonstrated the general application for the In(III)-catalyzed addition of DEAM to terminal alkynes. The addition appears to be fairly broad in scope and generally works well with phenyl acetylenes or aliphatic acetylenes. The choice and amount of base have a significant effect on the outcome of the addition reaction.

The addition products were further elaborated after hydrogenation followed by a practical one-pot concomitant N-deacylation/ester hydrolysis and decarboxylation under HCl reflux conditions to provide the target β-branched α-amino acids in excellent overall yield and purity. Further utilization of this reaction, including the synthesis of optically enriched β-branched α-amino acids via catalytic asymmetric hydrogenation, will be reported in due course.

Experimental Section

All reactions were carried out under nitrogen atmosphere unless otherwise noted.

General Method for the Preparation of Vinylmalonates 3a−l. *N*-Methylmorpholine (NMM) is added to a mixture of diethyl acetamidomalonate (**1**, DEAM) and In(OTf)$_3$ in alkyne (**2a**−**l**). The mixture is heated at 120−140 °C for 3−72 h. After cooling to rt,

(16) (a) Yang, D.; Li, J.-H.; Gao, Q.; Yan, Y.-L. *Org. Lett.* **2003**, *5*, 2869. (b) Yang, D.; Gao, Q.; Lee, C.-S.; Cheung, K.-K. *Org. Lett.* **2002**, *4*, 3271.

the reaction solution is applied directly to a column of SiO_2 and purified by flash chromatography to provide the addition product (**3a**−**l**).

General Method for the Preparation of Ethylmalonates 4a−**l.** A mixture of vinylmalonates **3a**−**l** and 10% Pd on carbon in EtOH is hydrogenated (H_2/50 psi) at rt for 1−5 h. The catalyst is removed, and the filtrate is concentrated in vacuo to provide ethylmalonates **4a**−**l**.

General Method for the Preparation of β-Methyl-α-amino acid•HCl 5a−**l.** A mixture of ethylmalonates **4a**−**l** in 6 M HCl is heated at reflux for 16−48 h. The resultant solution is concentrated in vacuo. The residue is diluted with CH_3CN and reconcentrated to effect azeotropic water removal. The concentrate is slurried in CH_3CN, collected by filtration, and dried in vacuo to provide β-methyl-α-amino acid•HCl **5a**,**d**,**f**,**j**−**l** as a mixture of diastereomers.

Supporting Information Available: Experimental procedures, spectral and analytical data for all products, and additional structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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