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# Ti-Catalyzed Reactions of Hindered Isocyanates with Alcohols

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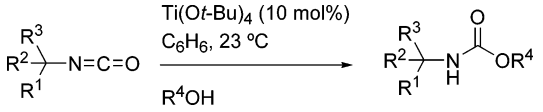


Highly hindered and sensitive isocyanates react with alcohols under mild catalysis by titanium tetra-*t*-butoxide to give high yields of the corresponding carbamates.

Isocyanates[1] are often stable intermediates in rearrangement reactions such as the Curtius or Hofmann rearrangements.[2] Such rearrangements are used to create a nitrogen−carbon bond with retention of stereochemistry at carbon, and they have been used, for instance, to make α- and *β*-amino acids[3] and 3-amino sugars.[4]

Frequently, the isocyanate is further reacted with an alcohol or an amine to produce a carbamate or a urea, respectively, with water to produce a primary amine, or with organometallics to produce amides. The carbamate or urea is normally used as a protective group for the amine. The reactions between many unhindered isocyanates and primary alcohols proceed without catalysis at temperatures ranging from 25 to 100 °C.[5] However, reactions of secondary and tertiary alcohols may require catalysis by Lewis acids,[6] Brønsted acids,[7] or conversion to the corresponding alkoxide.[1a,8] In addition, some hindered and/or sensitive isocyanates do not react readily even with primary alcohols.[9] Hydrochloric acid[7a] and copper(I) chloride[6,9b] are two frequently utilized acid catalysts for that reaction. The latter, however, is unable to catalyze the reaction between hindered isocyanates and alcohols while hydrochloric acid is not tolerant of many functional groups. Alcoholates add to isocyanates but they often give low yields of carbamate and the strongly basic conditions may also be a problem with other functional or protective groups.

We have recently developed a synthetic route to α,α-dialkylated amino acids that utilizes the Curtius rearrangement of an acyl azide to construct the pivotal nitrogen−carbon bond (cf. Scheme 1).[10] The nature of the targeted structures was such that the isocyanate intermediates **2** were highly hindered, acid-sensitive, and did not react with alcohols in the absence of a catalyst. For example, **2a** and **2b** partly decompose upon simple silica gel column chromatography. Presumably, the tertiary and allylic nature of the isocyanate leads to the facile formation of elimination products. Unfortunately, cuprous chloride was incapable of catalyzing their reaction with alcohols, and hydrochloric acid as well as many other Lewis acids, including zinc chloride, titanium tetrachloride, and tin tetrachloride, were either ineffective or led to elimination and other decomposition products.

We surmised that a catalyst that would be both mildly Lewis acidic and yet contain ligands capable of acting as a base would procure an elegant solution to this problem. In our search for a better catalyst, we initially found that titanium isopropoxide gave good results. Indeed, it was able to catalyze the reaction between isocyanates **2a** or **2b** and 9-fluorenyl methanol (9-Fm) (Scheme 1).[11]

However, varying quantities of unwanted carbamates **4a** and **4b** were formed alongside the desired ones. The source of 2-propanol was obviously the catalyst itself, the 2-propanol being released by fast ligand exchange with the surrounding alcohol molecules or by the reaction with the isocyanate.[12] The amount of **4** was indeed proportional to the amount of catalyst used in the reaction. In some cases, it was not possible to totally suppress this unwanted reaction even when a large excess of 9-Fm was used. This indicated that the addition of 2-propanol to the isocyanate was competitive with that of 9-Fm.

A quick comparison of this mildly Lewis acidic catalyst with other frequently used catalysts seemed to indicate that it was similar or better than most in terms of the

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(2) (a) Shiori, Y. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 6, p 795. (b) Smith, M. B.; March, J. In *Advanced Organic Chemistry*, 5th ed.; Wiley-Interscience: New York, 2001.

(3) See, for example: (a) Evans, D. A.; Wu, L. D.; Wiener, J. J. M.; Johnson, J. S.; Ripin, D. H. B.; Tedrow, J. *J. Org. Chem.* **1999**, *64*, 6411−6417. (b) Braibante, M. E. F.; Braibante, H. S.; Costenaro, E. R. *Synthesis* **1999**, 943−946. (c) Charette, A. B.; Côté, B. *J. Am. Chem. Soc.* **1995**, *117*, 12721−12732.

(4) Sibi, M. P.; Lu, J.; Edwards, J. *J. Org. Chem.* **1997**, *62*, 5864−5872.

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(6) Duggan, M. E.; Imagire, J. S. *Synthesis* **1989**, 131−132.

(7) (a) Benalil, A.; Roby, P.; Carboni, B.; Vaultier, M. *Synthesis* **1991**, 787−788. (b) Lammiman, S. A.; Satchell, R. S. *J. Chem. Soc., Perkin Trans. 2* **1974**, 877−883.

(8) (a) Bailey, W. J.; Griffith, J. R. *J. Org. Chem.* **1978**, *43*, 2690−2692. (b) Yu, Q.-S.; Brossi, A. *Heterocycles* **1988**, *27*, 745−750. (c) Mehrotra, R. C.; Rai, A. K.; Bohra, R. *J. Inorg. Chem.* **1974**, *36*, 1887−1888. (d) Bloodworth, A. J.; Davies, A. G. *J. Chem. Soc.* **1965**, 5238−5244.

(9) See, for example: (a) Kinsman, A. C.; Kerr, M. A. *J. Am. Chem. Soc.* **2003**, *125*, 14120−14125. (b) Miller, J. A.; Hennessy, E. J.; Marshall, W. J.; Scialdone, M. A.; Nguyen, S. T. *J. Org. Chem.* **2003**, *68*, 7884−7886.

(10) (a) Spino, C.; Godbout, C.; Beaulieu, C.; Harter, M.; Mwene-Mbega, T. M.; Boisvert, L. *J. Am. Chem. Soc.* **2004**, *126*, 13312−13319. (b) Spino, C.; Godbout, C. *J. Am. Chem. Soc.* **2003**, *125*, 12106−12107.

(11) These procedures are described in the Supporting Information accompanying ref 10b.

(12) The stoichiometric reaction between $Ti(OR)_4$ and isocyanates to form insertion products was shown to be reversible. Meth-Cohn, O.; Thorpe, D.; Twitchett, H. J. *J. Chem. Soc. C* **1970**, 132−135.

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**SCHEME 1. Ti(O*i*-Pr)$_4$ Catalyzed Reaction of 1 and 9-Fm**

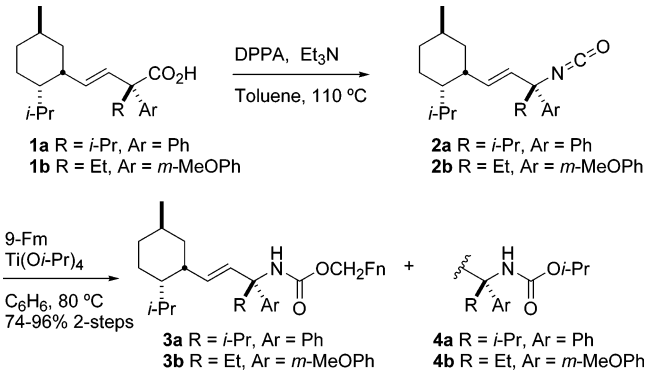



**TABLE 1. Comparison of Ti(O*i*-Pr)$_4$ with Other Lewis Acids**


| catalyst | temp (°C)[a] | Rx time (h) | conversion (%)[b] |
|---|---|---|---|
| $MgCl_2 \cdot H_2O$ | 110 | 6 | 96 |
| $ZnCl_2$ | 110 | 7 | 18 |
| CuCl | 110 | 8 | 94 |
| $CaCl_2$ | 110 | 6 | 49 |
| $Yb(OTf)_2 \cdot H_2O$ | 110 | 3 | decomp[c] |
| $Yb(OTf)_2 \cdot H_2O$ | 23 | 47 | 80 |
| Ti(*i*-OPr)$_4$ | 23 | 1.5 | 100 |
| HCl | 23 | 3 | 98 |
| $TiCl_4$ | 23 | – | decomp[c] |
| $SnCl_4$ | 23 | – | decomp[c] |

[a] Reaction conditions: 1.5 equiv of 9-Fm in toluene (0.1 M in **5**) with 10 mol % of catalyst. [b] % product as determined by HPLC, the rest is SM. [c] No product detected.

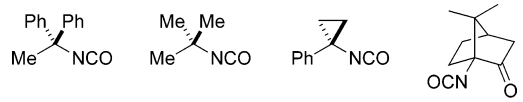


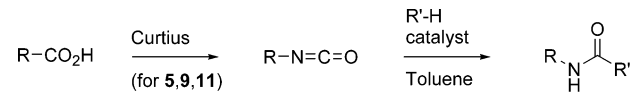

**FIGURE 1.** Isocyanates used in the Ti-catalyzed reactions with alcohols.

efficiency and rapidity with which it catalyzed the reaction between isocyanate **5** and 9-Fm (Table 1). Not apparent in Table 1 was the fact that the product mixture obtained in the reactions catalyzed by Ti(O*i*-Pr)$_4$ was much cleaner than all the other ones (vide infra). Therefore, we deemed it appropriate to evaluate the usefulness of this catalyst as part of a general method for the formation of carbamates or ureas from highly hindered isocyanates and alcohols or amines.

To do so, we purchased or prepared[13] a series of isocyanates that had in common severe steric hindrance and a relative sensitivity to acid or base (Figure 1). In fact, isocyanates **5** and **9** had to be kept in frozen benzene as they decompose upon standing. In addition, compound **9** is too unstable for chromatography and was prepared

(13) Isocyanates unavailable commercially were made from the Curtius rearrangement of the corresponding carboxylic acid obtained from commercial sources. See Supporting Information.

**TABLE 2. Efficiency of Ti(O*t*-Bu)$_4$ as Catalyst in the Reaction of Hindered Isocyanates and Alcohols**




| entry | SM | alcohol | product | R′ | *t* (h)[a] | yield (%)[b] |
|---|---|---|---|---|---|---|
| 1 | 5 | 9-Fm | **6a** | 9-Fm | 1 | 92 |
| 2 | 5 | *i*-PrOH | **6b** | *i*-PrO | 24 | 79 |
| 3 | 5 | *t*-BuOH | **6c** | *t*-BuO | 216[c] | 63 |
| 4 | 7 | *t*-BuOH | **8c** | *t*-BuO | 48[c] | 32[d] |
| 5 | 7 | *t*-$BuCH_2OH$ | **8d** | *t*-$BuCH_2O$ | 1 | 70 |
| 6 | 9 | 9-Fm | **10a** | 9-Fm | 0.6 | 81[e] |
| 7 | 9 | *i*-PrOH | **10b** | *i*-PrO | 4[f] | 58[e] |
| 8 | 9 | *i*-PrOH | **10b** | *i*-PrO | 1 | 64[e] |
| 9 | 9 | *t*-BuOH | **10c** | *t*-BuO | 48 | 60[e] |
| 10 | 9 | $Me_2NH$ | **10e** | $Me_2N$ | 1 | 81[e] |
| 11 | 11 | *i*-PrOH | **12b** | *i*-PrO | 24 | 87 |
| 12 | 11 | *t*-BuOH | **12c** | *t*-BuO | 96[c] | 56 |
| 13 | 11 | *t*-$BuCH_2OH$ | **12d** | *t*-$BuCH_2O$ | 24 | 92 |

[a] Reaction conditions: 1.5 equiv of alcohol in benzene (0.2 M in isocyanate) with 10 mol % of catalyst at 23 °C. [b] Isolated yield. [c] At 120 °C in sealed vial. [d] Volatile compound, GC yield is 83%. [e] For two steps from the carboxylic acid. [f] 2% catalyst.

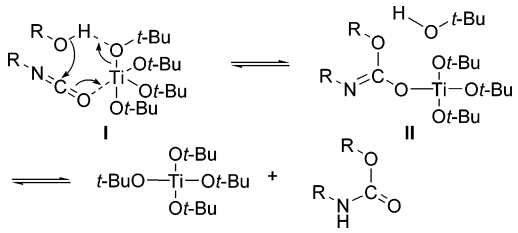
**TABLE 3. Comparison of Ti(O*t*-Bu)$_4$ with HCl and CuCl in the Reaction of Hindered Isocyanates with *t*-BuOH**

| entry | SM | product | catalyst[a] | conv (%)[b] |
|---|---|---|---|---|
| 1 | 5 | **6c** | Ti(O*t*-Bu)$_4$ | 13 |
| 2 | 5 | **6c** | none | 0 |
| 3 | 5 | **6c** | HCl | 6 |
| 4 | 5 | **6c** | CuCl | 0 |
| 5 | 7 | **8c** | Ti(O*t*-Bu)$_4$ | 92 |
| 6 | 7 | **8c** | none | 0 |
| 7 | 7 | **8c** | HCl | 0 |
| 8 | 7 | **8c** | CuCl | 11 |
| 9 | 9 | **10c** | Ti(O*t*-Bu)$_4$ | 88 |
| 10 | 9 | **10c** | none | 13 |
| 11 | 9 | **10c** | HCl | 26 |
| 12 | 9 | **10c** | CuCl | 33 |
| 13 | 11 | **12c** | Ti(O*t*-Bu)$_4$ | 67 |
| 14 | 11 | **12c** | none | 13 |
| 15 | 11 | **12c** | HCl | 26 |
| 16 | 11 | **12c** | CuCl | 33 |

[a] Reaction conditions: 1.5 equiv of *t*-BuOH in benzene (0.3 M in isocyanate) with 10 mol % of catalyst at 120 °C in sealed vial for 24 h. [b] Conversion determined by GC after 24 h.

and used in the crude form. We also chose four alcohols: two hindered primary, a secondary, and a tertiary alcohol. Preliminary results indicated clearly that Ti(O*i*-Pr)$_4$ performed much better than all of the other catalysts tried. However, the snag caused by the formation of the isopropyl carbamate remained. Noting that *tert*-butyl alcohol, as the alcohol component of the reaction, added substantially slower than the other alcohols, we decided to try Ti(O*t*-Bu)$_4$ as catalyst, hoping that the *tert*-butyl alcohol released by ligand exchange would not promptly add to the isocyanate to give a companion carbamate. We were pleased to discover the absence of any *tert*-butyl carbamate in all of the reactions that we have carried out with this catalyst (cf. Tables 2 and 3), except, of course, when *tert*-butyl alcohol was the added partner. More pleasingly, the efficiency of the catalyst did not seem altered by the larger *t*-butoxide groups. Moreover, that catalyst is more stable to air and moisture and thus is more easily handled than Ti(O*i*-Pr)$_4$.

**SCHEME 2. Hypothetical Mechanism of Action of the Ti Catalyst**



$Ti(Ot\text{-}Bu)_4$ efficiently catalyzed the reaction of alcohols with all of the isocyanates screened (Table 2). Catalyst loadings of 10% allowed for a fast reaction *at room temperature* in most cases, but catalyst loadings as low as 2% afforded a complete reaction (entry 8). As expected, *tert*-butyl alcohol underwent addition more slowly and at higher temperatures. We thus chose that alcohol to compare the efficiency of $Ti(Ot\text{-}Bu)_4$ with that of hydrochloric acid and cuprous chloride, two commonly used catalysts (Table 3).

Consumption of the starting isocyanate using $Ti(Ot\text{-}Bu)_4$ was much faster than HCl or CuCl in all cases (entries 5−16) but isocyanate **5** (entries 1−4). However, in the latter case, many decomposition products were formed with HCl or CuCl whereas $Ti(Ot\text{-}Bu)_4$ gave a very clean conversion, as judged by GC. Moreover, with $Ti(Ot\text{-}Bu)_4$, complete conversion of **5** to carbamate **6c** was obtained by stirring the reaction at 120 °C for 216 h, with a respectable isolated yield of 63% (Table 2, entry 3). The other two catalysts led only to decomposition products.

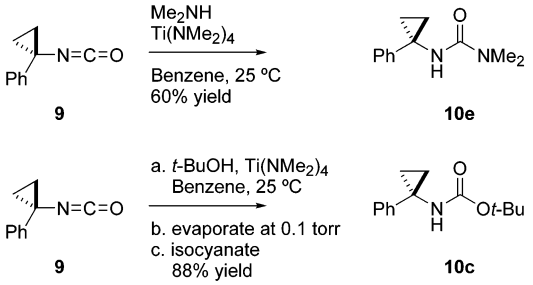
$Ti(OR)_4$ is a milder Lewis acid than other Ti(IV) species ($TiCl_4$ for example). Scheme 2 displays a possible rationale for the efficiency of this titanium catalyst. We believe that the titanium complex is activating both the isocyanate and the alcohol as shown in structure **I**. The isocyanate is activated by coordination to the Lewis acid, while the alcohol is activated through a hydrogen bond with a basic *tert*-butyl alcohol ligand. The alcohol is thus delivered through a six-membered transition state. The metalated carbamate then captures a proton from *tert*-butyl alcohol or from the added alcohol. According to the study of Meth-Cohn and co-workers, each step is reversible and the equilibrium is shifted toward product.[12] The active catalysts could consequently be a mixture of several titanium species including **II** and similar intermediates.

The reaction with dimethylamine probably follows the same pathway (Table 2, entry 10).[14] One can use $Ti(NMe_2)_4$ as catalyst for this reaction with similar success (Scheme 3). However, there is no advantage in doing so unless the isocyanate molecule is particularly sensitive to the higher Lewis acidity of $Ti(OR)_4$. Therefore, we have not investigated the use of $Ti(N(t\text{-}Bu)_2)_4$ as general catalyst for the formation of ureas from isocyanates.

$Ti(NMe_2)_4$ can also be used as precursor to form $Ti(OR)_4$ in situ, which will catalyze the formation of carbamates (Scheme 3). The requisite alcohol must be mixed in first with $Ti(NMe_2)_4$ and the dimethylamine formed, evaporated before use. Failure to do so will produce a *N*,*N*-dimethyl urea in large quantity.

(14) Chandra, G.; Jenkins, A. D.; Lappert, M. F.; Srivastava, R. C. *J. Chem. Soc. A* **1970**, 2550−2558.

**SCHEME 3. Formation of Urea 10e Using $Ti(NMe_2)_4$ as Catalyst**



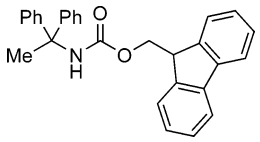
$Ti(Ot\text{-}Bu)_4$ cannot be used to hydrolyze isocyanates because of its rapid reaction with water to form titanium oxide. The hydrolysis of hindered isocyanates thus remains a challenge.

In conclusion, we have demonstrated the efficiency and usefulness of $Ti(Ot\text{-}Bu)_4$ as catalyst for the formation of carbamates and a urea from highly hindered and sensitive isocyanates. Given the growing importance of the latter intermediates in the synthesis of amino acids and other compounds containing nitrogen, the present protocol should prove useful to synthetic organic chemists.

## Experimental Section

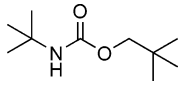
**General Procedure for the Formation of Carbamates.** To a solution of the isocyanate (1.0 equiv of 0.2 M in benzene) was added the alcohol or the amine (1.5 equiv). Titanium tetra-*t*-butoxide (0.10 equiv) was then added, and the mixture was stirred at the required temperature until completion (monitored by GC). After quenching with saturated aqueous $NH_4Cl$ and separating the two phases, we extracted the aqueous solution 3 times with $CH_2Cl_2$, dried the combined organic layers with anhydrous $MgSO_4$, and concentrated the layers in vacuo.

**(9*H*-Fluoren-9-yl)methyl 1,1-Diphenylethylcarbamate (6a).**



**6a** was prepared following the general procedure for the formation of carbamates starting with 0.444 mmol of **5**. Reaction temperature: 25 °C; Reaction time: 1 h. The crude product was purified by flash chromatography on silica gel (5−20% AcOEt in toluene) to afford **6a** as a white solid (171 mg, 92%). mp: 141−143 °C. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.77 (d, 2H, $J$ = 7.2 Hz), 7.67−7.52 (m, 2H), 7.38−7.25 (m, 14H), 5.52 (s, 1H), 4.41 (d, 2H, $J$ = 6.6 Hz), 4.28−4.11 (m, 1H), 2.17 (s, 3H); IR (neat/NaCl): 3335, 2921, 1700; LRMS (*m*/*z*, (relative intensity)): 420 (($M^+$ + H), 5), 181 (100); HRMS Calcd for $C_{29}H_{26}O_2N$: 420.1963, found: 420.1968.

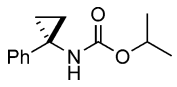
**neo-Pentyl *tert*-Butylcarbamate (8d).**



**8d** was prepared following the general procedure for the formation of carbamates starting with 0.500 mmol of *tert*-butylisocyanate. Reaction temperature: 25 °C; reaction time: 1 h. The crude product was purified by flash chromatography on silica gel (10% AcOEt in hexanes) to afford **8d** as a white solid (66 mg, 70% isolated). mp: 49−51 °C. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 4.61 (br s, 1H), 3.71 (s, 2H), 1.32 (s, 9H), 0.92 (s, 9H); IR (neat/

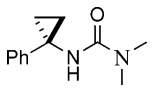
NaCl): 3347, 2961, 1708, 1525; LRMS (*m/z*, (relative intensity)): 187 ($M^+$, 1), 172 (($M^+ - CH_3$), 100), 71 (60), 57 (90); HRMS Calcd for $C_9H_{18}O_2N$: 172.1337, found: 172.1334.

***i*-Propyl 1-Phenylcyclopropylcarbamate (10b).**



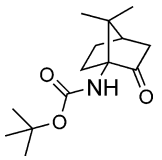
**10b** was prepared following the general procedure for the formation of carbamates starting with 0.211 mmol of **9**. Reaction temperature: 25 °C; reaction time: 1 h. The crude product was purified by flash chromatography on silica gel (10% AcOEt in hexanes) to afford **10b** as a white solid (30 mg, 64% for two steps). mp: 56−58 °C. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.32−7.16 (m, 5H), 5.39−5.18 (m, 1H), 4.91 (sept, 1H, $J$ = 6.0 Hz), 1.28−1.21 (m, 10H); IR (neat/NaCl): 3319, 2979, 1701, 1515; LRMS (*m/z*, (relative intensity)): 219 (($M^+$ + H), 9), 176 (100), 132 (80); HRMS Calcd for $C_{13}H_{17}O_2N$: 219.1259, found: 219.1255.

**1,1-Dimethyl-3-(1-phenylcyclopropyl)urea (10e).**



**10e** was prepared following the general procedure for the formation of carbamates starting with 0.421 mmol of **9**, except that the reaction mixture was concentrated in vacuo without prior workup extraction. Reaction temperature: 25 °C; reaction time: 1 h. The crude product was purified by flash chromatography on silica gel (50% AcOEt in $CH_2Cl_2$) to afford **10e** as a white solid (70 mg, 81% from **1**). mp: 146−147 °C; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.30−7.24 (m, 3H), 7.19−7.13 (m, 2H), 5.19 (br s, 1H), 2.91 (s, 6H), 1.25 (s, 4H); IR (neat/NaCl): 3308, 2917, 1637, 1521; LRMS (*m/z*, (relative intensity)): 204 ($M^+$, 12), 104 (90), 77 (100); HRMS Calcd for $C_{12}H_{16}ON_2$: 204.1263, found: 204.1270.

***t*-Butyl 7,7-Dimethyl-2-oxobicyclo[2.2.1]heptan-1-ylcarbamate (12c).**



**12c** was prepared following the general procedure for the formation of carbamates starting with 0.119 mmol of **11**. Reaction temperature: 25 °C; reaction time: 96 h. The crude product was purified by flash chromatography on silica gel (10% AcOEt in hexanes) to afford **12c** as an off-white solid (17 mg, 56%). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 5.04 (br s, 1H), 3.04 (br s, 1H), 2.39 (dm, 1H, $J$ = 18.7 Hz), 2.17−2.09 (m, 1H), 2.04−1.97 (m, 2H), 1.44 (s, 9H), 1.25−1.20 (m, 5H), 0.84 (s, 3H); IR (neat/NaCl): 3399, 2968, 2920, 1726, 1502; LRMS (*m/z*, (relative intensity)): 254 (($M^+$ + H), 60), 225 (95), 198 (78), 125 (100); HRMS Calcd for $C_{14}H_{24}O_3N$ ($M^+$ + H): 254.1756, found: 254.1761.

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**Supporting Information Available:** Experimental procedures, characterization data of all new compounds not included in the Experimental Section of this note, and $^1$H 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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