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Radical Fixation of Functionalized Carbon Resources: α-sp^{3}C–H Carbamoylation of Tertiary Amines with Aryl Isocyanates

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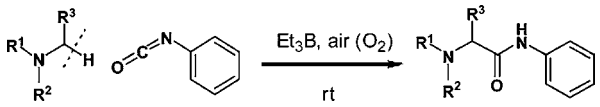
ABSTRACT

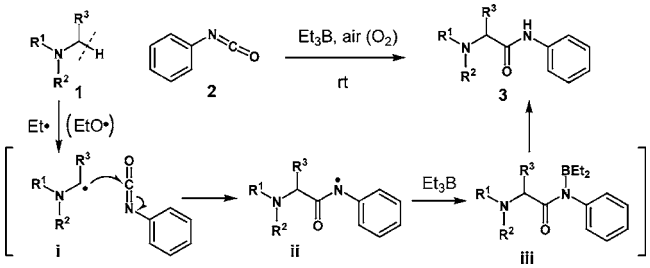


A new carbamoylation of tertiary amines is reported. This rare C–H transformation features the direct generation of α-aminoalkyl radicals from tertiary amines, followed by the addition of the resultant nucleophilic radicals to isocyanates, enabling unique access to *N,N*-dialkylated amino acid derivatives. The authors put forward a mechanistic proposal that is based on the isolation of borinamides produced by capturing nitrogen radical intermediates with Et_3B. The present transformation provides a novel one-step process for producing mepivacaine, a clinically important local anesthetic, from readily available materials.

Intensive efforts aimed at the development of new methods for the transformation of α-nitrogen-substituted sp^{3}C−H bonds into C−C bonds have led to the emergence of novel approaches to nitrogen-containing molecular frameworks.[1,2] In this context, we recently reported the discovery of radical reactions that enabled α-sp^{3}C−H hydroxyalkylation of various nitrogen compounds with aldehydes, using Et_3B/air as the radical source.[3,4]

In the present study, we show that aryl isocyanates serve as radical acceptors[5] in the presence of Et_3B and that the α-sp^{3}C−H bonds of tertiary amines are directly carbamoylated under Et_3B/air or Et_3B/O_2 conditions to provide biologically important *N,N*-dialkylated amino acid derivatives (Scheme 1).[6,7] We also put forward in this Letter a

Scheme 1. α-C−H Carbamoylation of Tertiary Amines



mechanistic proposal that is based on the isolation of borinamide **iii** produced by capturing nitrogen radical intermediate **ii** with Et_3B.[8]

Table 1 shows α-amino anilides obtained by the carbamoylation of tertiary aliphatic amines with phenyl isocyanate

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(1) Recent reviews of α-amino sp^{3}C−H functionalization: (a) Campos, K. R. *Chem. Soc. Rev.* **2007**, *36*, 1069. (b) Griesbeck, A. G.; Hoffmann, N.; Warzecha, K.-d. *Acc. Chem. Res.* **2007**, *40*, 128−140. (c) Hoffmann, N.; Bertrand, S.; Marinkovic, S.; Pesch, J. *Pure Appl. Chem.* **2006**, *78*, 2227−2246. (d) Ishii, Y.; Sakaguchi, S. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 909−920. (e) Beak, P.; Johnson, T. A.; Kim, D. D.; Lim, S. H. *Top. Organomet. Chem.* **2003**, *5*, 139. (f) Doye, S. *Angew. Chem., Int. Ed* **2001**, *40*, 3351.

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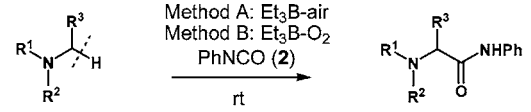
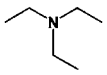
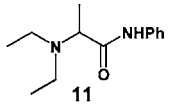
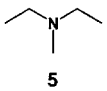
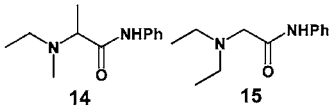
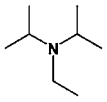
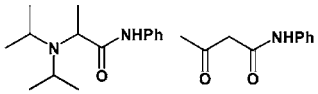
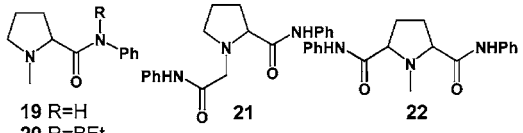
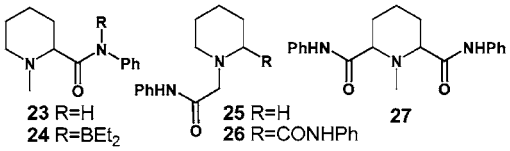
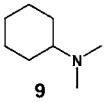
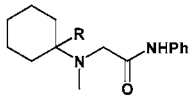
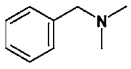
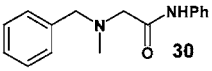
Table 1. α-C−H Carbamoylation of Tertiary Aliphatic Amines



entry	substrate	time (h)	α-amino anilide (%)[a,b,c]
1	 **4**	A: 7 B: 6	 **11** A: **11** (82) B: **11** (86)
2	 **5**	A: 13 B: 10	 **14** **15** A: **14** (60), **15** (12) B: **14** (63), **15** (13)
3	 **6**	A: 14 B: 11	 **16** **17** A: **16** (43), **17** (23)[d] B: **16** (38), **17** (16)[d]
4	 **7**	A: 13 B: 10	 **19** R=H **20** R=BEt_2 **21** **22** A: **19** (17), **20** (4), **21** (42), **22** (9) B: **19** (17), **20** (5), **21** (37), **22** (6)
5	 **8**	A: 12 B: 10	 **23** R=H **24** R=BEt_2 **25** R=H **26** R=CONHPh **27** A: **23** (trace), **24** (34), **25** (5), **26** (7) , **27** (35)[e] B: **23** (2), **24** (34), **25** (6), **26** (5), **27** (28)[f]
6	 **9**	A: 13 B: 12	 **28** R=H **29** R=CONHPh A: **28** (42), **29** (14) B: **28** (41), **29** (16)
7	 **10**	A: 24 B: 24	 **30** A: **30** (20)[g] B: **30** (22)[h]

[a] The reaction was carried out using amine (35 equiv relative to PhNCO) and Et_3B (6 equiv) with continuous dry air admission (10−20 mL/h·mmol PhNCO) (Method A) or dry O_2 admission (2−4 mL/h·mmol PhNCO) (Method B). [b] Yield based on PhNCO. [c] Accompanied by ethyl phenylcarbamate (EtOCONHPh) (**12**) and 1,3-diphenylurea (PhNHCONHPh) (**13**). For details about each entry, see Supporting Information. [d] 1-Ethyl-1-isopropyl-3-phenylurea (PhNHCON(*i*Pr)Et) (**18**) was also formed via dealkylative carbamoylation (4−6%). [e] *cis*:*trans* = 1.3:1. [f] *cis*:*trans* = 2:1. [g] 1,1-Dimethyl-3-phenylurea ($Me_2NCONHPh$) (**31**) (2%) and *N*,*N*,*N*′,*N*′-tetramethyl-1,2-diphenyl-1,2-ethanediamine (**32**) (14% based on PhNCO) were also formed. [h] **31** (2%) and **32** (17% based on PhNCO) were formed.

(**2**) under Et_3B/air or Et_3B/O_2 conditions. Triethylamine (**4**) was transformed into α-*N*,*N*-diethyl alaninanilide (**11**) in high yield along with small amounts of ethyl phenylcarbamate (**12**) (EtOCONHPh) and 1,3-diphenylurea (**13**) (PhNHCONHPh) (Table 1, entry 1). Byproduct **12** may have been formed by the ethoxylation of isocyanate **2** with ethoxyl radical produced by the oxidation of Et_3B, or with EtOH that was possibly generated by hydrogen abstraction of the C−H substrate with ethoxyl radical.[9] 1,3-Diphenylurea (**13**) was probably produced by the hydrolysis of moisture-sensitive isocyanate **2**, followed by carbamoylation of the resultant aniline. *N*,*N*-Diethylmethylamine (**5**) was also carbamoylated in good yield to provide **14** and its regioisomer **15** in the ratio of ca. 5:1 (entry 2). In contrast, *N*,*N*-diisopropylethylamine (**6**) was found to be a somewhat poor substrate (entry 3): its use resulted in the formation of α-amino anilide **16** in moderate yield. *β*-Ketoanilide **17** was also formed, suggesting that abstraction of the methine hydrogen in amine **6** followed by oxidative decomposition of the α-aminoalkyl radical occurred to give an enamine that underwent addition reaction with isocyanate **2**.

When five- and six-membered cyclic amines **7** and **8** were used as substrate, we discovered several compounds that provided insights into the reaction mechanisms (entries 4

and 5). Borinamide **24**, whose structure was unambiguously confirmed by X-ray crystallographic analysis, indicates an intermediacy of amidyl radical **ii** that is captured by Et_3B (Figure 1).[10−12] The reason why borinamide **24** was produced

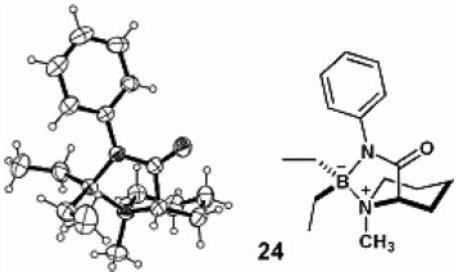
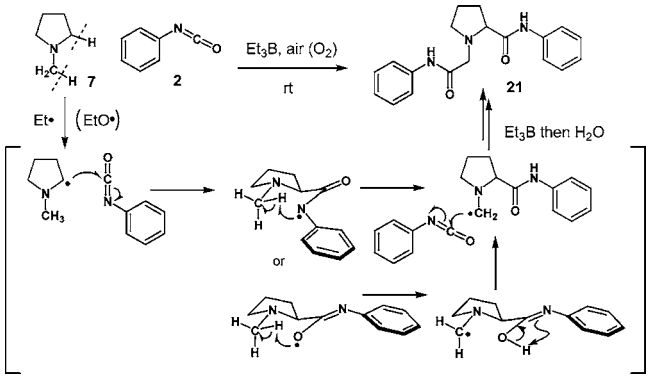


Figure 1. ORTEP diagram of borinamide **24**.

in this particular case is unclear, although it is likely that the stability against hydrolysis owing to its structural rigidity enabled the successful isolation.[13] Interestingly, contrary to the previously reported hydroxyalkylation reaction in which only one α-hydrogen was selectively substituted with a carbon atom,[3a] the present reaction gave not only expected monoanilide but also biscarbamoylated products such as **21**. This may be rationalized by the intramolecular 1,5-hydrogen transfer of amidyl or oxyradical intermediate (Scheme 2).[14]

Scheme 2. Plausible Mechanism of Double α-C−H Carbamoylation of *N*-Methylpyrrolidine (**7**)



A similar rationale may be applicable to the formation of bisanilides **22**, **26**, **27**, and **29**;[15] the 1,5-radical transposition took place between the heteroradical center generated on the carbamoyl substituent and the hydrogens located at the *δ*-position from the radical center.[16] *N*,*N*-Dimethylcyclohexylamine (**9**) was also moderately converted into anilides

(2) For recent exmaples of C−C bond formations via α-amino sp^3C−H functionalization, see: (a) Hartwig, J. F.; Seth, B. H. *J. Am. Chem. Soc.* **2007**, *129*, 6690−6690. (b) Li, Z.; Bohle, D. S.; Li, C.-J. *Proc. Natl. Acad. Sci. U.S.A.* **2006**, *103*, 8928. (c) Campos, K. R.; Klapars, A.; Waldman, J. H.; Dormer, P. G.; Chen, C.-y. *J. Am. Chem. Soc.* **2006**, *128*, 3538−3539. (d) Pastine, S. J.; Gribkov, D. V.; Sames, D. *Am. Chem. Soc.* **2006**, *128*, 14220−14221. (e) Catino, A. J.; Nichols, J. M.; Nettles, B. J.; Doyle, M. P. *J. Am. Chem. Soc.* **2006**, *128*, 5648−5649. (f) Matsuo, J.; Tanaki, Y.; Ishibashi, H. *Org. Lett.* **2006**, *8*, 4371−4374. (g) Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2005**, *127*, 3672−3673. (h) Li, Z.; Li, C.-J. *Eur. J. Org. Chem.* **2005**, *15*, 3173−3176. (i) Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2004**, *126*, 11810−11811. (j) Li, Z.; Li, C.-J. *Org. Lett.* **2004**, *6*, 4997−4999. (k) DeBoef, B.; Pastine, S. J.; Sames, D. *J. Am. Chem. Soc.* **2004**, *126*, 6556−6557. (l) Murahashi, S.-i.; Komiya, N.; Terai, H.; Nakase, T. *J. Am. Chem. Soc.* **2003**, *125*, 15312−15313. (m) Davies, H. M. L.; Venkataramani, C.; Hansen, T.; Hopper, D. W. *J. Am. Chem. Soc.* **2003**, *125*, 6462−6468. (n) Davies, H. M. L.; Venkataramani, C. *Angew. Chem., Int. Ed.* **2002**, *41*, 2197−2199. (o) Suga, S.; Suzuki, S.; Yoshida, J. *J. Am. Chem. Soc.* **2002**, *124*, 30−31. (p) Yoshida, J.; Suga, S.; Suzuki, S.; Kinomura, N.; Yamamoto, A.; Fujiwara, K. *J. Am. Chem. Soc.* **1999**, *121*, 9546−9549. (q) Chatani, N.; Asaumi, T.; Yorimitsu, S.; Ikeda, T.; Kakiuchi, F.; Murai, S. *J. Am. Chem. Soc.* **2001**, *123*, 10935−10941. (r) Chatani, N.; Fukuyama, T.; Tatamidani, H.; Kakiuchi, F.; Murai, S. *J. Org. Chem.* **2000**, *65*, 4039−4047. (s) Marinkovic, S.; Hoffmann, N. *Chem. Commun.* **2001**, 1576−1578.

(3) (a) Yoshimitsu, T.; Arano, Y.; Nagaoka, H. *J. Am. Chem. Soc.* **2005**, *127*, 11610−11611. (b) Yoshimitsu, T.; Nagaoka, H.; Tanaka, T. *J. Synth. Org. Chem., Jpn.* **2007**, *65*, 665−675. (c) Yoshimitsu, T. *Farumashia* **2007**, *43*, 219−223.

(4) Reviews of Et_3B as radical source: (a) Ollivier, C.; Renaud, P. *Chem. Rev.* **2001**, *101*, 3415−3434. (b) Yorimitsu, H.; Oshima, K. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, Germany, 2001; Vol. 1, pp 11−27. (c) O'Mahony, G. *Synlett* **2004**, 572−573. Also see: (d) Yoshimitsu, T. Et_3B+O_2 (first update). In *Handbook of Reagents for Organic Synthesis: Reagents for Direct Functionalization of C−H Bonds*; Fuchs, P. L., Ed.; Wiley-VCH: Weinheim, Germany, 2006; pp 351−356.

(5) Alkyl radical addition reaction with isocyanates has met with limited success: (a) Minin, P. L.; Walton, J. C. *J. Org. Chem.* **2003**, *68*, 2960−2963. (b) Heinrich, M. R.; Pérez-Martin, I.; Zard, S. Z. *Chem. Commun.* **2005**, 5928−5930. Also see: (c) Tlumak, R. L.; Day, J. C.; Slanga, J. P.; Skell, P. S. *J. Am. Chem. Soc.* **1982**, *104*, 7257−7267.

(6) Another approach to radical carbamoylation: Cannella, R.; Clerici, A.; Panzeri, W.; Pastori, N.; Punta, C.; Porta, O. *J. Am. Chem. Soc.* **2006**, *128*, 5358−5359.

(7) Reviews of α-aminoalkyl radical chemistry: (a) Aurrecoechea, J. M.; Suero, R. *ARKIVOC* **2004**, 10−35. (b) Hart, D. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, Germany, 2001; Vol. 2, pp 279−302. (c) Renaud, P.; Giraud, L. *Synthesis* **1996**, 913−926.

(8) Nakakoshi, M.; Ueda, M.; Sakurai, S.; Miyata, O.; Sugiura, M.; Naito, T. *Magn. Reson. Chem.* **2006**, *44*, 807−812.

(9) Intermediacy of ethoxyl radical in Et_3B/air system: (a) Sonnenschein, M. F.; Webb, S. P.; Kastl, P. E.; Arriola, D. J.; Wendt, B. L.; Harrington, D. R. *Macromolecules* **2004**, *37*, 7974−7978. (b) Sato, T.; Hibino, K.; Otsu, T. *Nippon Kagakukai Shi* **1975**, 1080−1084. We have also found that PhNCO reacts slowly with $(EtO)_3B$, an oxidation product of Et_3B possibly generated in situ, giving ethyl carbamate **12**.

(10) Borinamide **24** was not produced by reacting isolated anilide **23** with Et_3B, suggesting that **24** was directly generated by capturing radical intermediate **ii**. For details, see Supporting Information.

(11) Isomerization of *O*-borinate that was possibly produced by capturing the oxyradical intermediate with Et_3B into borinamide **24** may also be assumed.

(12) Et_3B and amines probably form Lewis acid/base adducts (ate complexes), and there may be a small amount of the free Et_3B present at equilibrium that is responsible for the successful radical processes. Similar observations have been made in the Pd/Et_3B-catalyzed allylic amination reactions reported by Kimura and Tamaru et al.; see: Kimura, M.; Futamata, M.; Shibata, K.; Tamaru, Y. *Chem. Commun.* **2003**, 234.

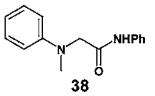
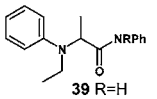
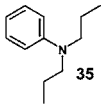
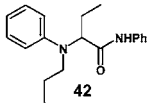
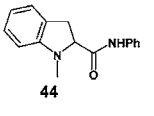
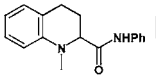
(13) As shown in Table 1, entry 4, borinamide **20** was obtained from *N*-methylpyrrolidine (**7**) by either method A or B, albeit in low yield (4−5%). The structure was elucidated by NMR, IR, and HRMS analysis.

(14) If amidyl radicals **ii** abstract hydrogens from amines *intermolecularly* to generate α-aminoalkyl radicals via radical chain processes, then a relatively small or even a catalytic amount of Et_3B/air (O_2) would be sufficient enough to promote the carbamoylation reactions. However, we have not yet succeeded in such catalytic chain transformations under the Et_3B/air conditions, indicating that the above-hypothesized chain process may not be involved in the present transformations.

(15) Stereochemistry of **27** was established by both X-ray analysis and chemical correlations (see Supporting Information). Bisanilide **22** is a single isomer, and its stereochemistry has yet to be determined.

(16) It is unlikely that the direct C−H carbamoylation of borinamide intermediate **20** (or **24**) takes place to give bisanilides **21** and **22** (or **26** and **27**) because, under the present conditions, monoanilide **20** (or **24**) is present in a much smaller amount than its C−H substrate **7** (or **8**) that is susceptible to hydrogen abstraction.

Table 2. α-C−H Carbamoylation of Tertiary Aromatic Amines

entry	substrate	time (h)	α-amino anilide(%)[a,b,c]
1	 **33**	A: 14 B: 12	 **38** A: **38** (85) B: **38** (86)
2	 **34**	A: 23 B: 20	 **39** R=H **40** R=CONHPh A: **39** (53), **40** (10)[d] B: **39** (52), **40** (8)[d]
3	 **35**	A: 25 B: 22	 **42** A: **42** (33)[e] B: **42** (35)[e]
4	 **36**	A: 22 B: 19	 **44** **45** A: **44** (51), **45** (9) B: **44** (45), **45** (10)
5	 **37**	A: 20 B: 19	 **46** **47** A: **46** (45), **47** (15) B: **46** (42), **47** (15)

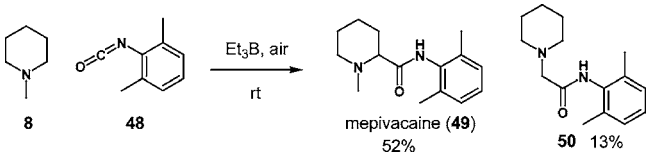
[a] The reaction was carried out using amine (35 equiv relative to PhNCO) and Et_3B (6 equiv) with continuous dry air admission (10−20 mL/h·mmol PhNCO) (Method A) or dry O_2 admission (2−4 mL/h·mmol PhNCO) (Method B). [b] Yield based on PhNCO. [c] Accompanied by ethyl phenylcarbamate (EtOCONHPh) (**12**) and 1,3-diphenylurea (PhNHCONHPh) (**13**). For details about each entry, see Supporting Information. [d] 1-Ethyl-1,3-diphenylurea (PhNHCON(Et)Ph) (**41**) (3−7%) was also formed via dealkylative carbamoylation. [e] 1,3-Diphenyl-1-propylurea (PhNHCON(Pr)Ph) (**43**) (7%) was also formed.

28 and **29** (entry 6). *N*,*N*-Dimethylbenzylamine (**10**) afforded not the phenylglycine derivative but regioisomer **30** in low yield (entry 7); the benzylic radical did not undergo an addition reaction with isocyanate **2**, probably due to its stability or low nucleophilicity, preferentially giving *N*,*N*,*N*′,*N*′-tetramethyl-1,2-diphenyl-1,2-ethanediamine (**32**), a self-coupling product.[17]

N,*N*-Disubstituted anilines were also examined (Table 2). The α-C−H carbamoylation of dimethylaniline (**33**) provided glycinanilide **38** in good yield (entry 1). The yields decreased when substrates possessing long *N*-alkyl substituents were used, due to an increase in the amounts of byproducts formed (entries 2 and 3).[18] *N*-Methylindoline (**36**) and *N*-methyltetrahydroquinoline (**37**) were transformed into anilides **44**/**45** and **46**/**47** in acceptable yields (ca. 60%), respectively (entries 4 and 5). In general, the regioselectivity of the carbamoylation of aliphatic and aromatic amines indicates preferential abstraction of methylene hydrogen over methyl hydrogen, reflecting thermochemical factors involved in the C−H bond cleavage. It was also revealed that the two conditions, Et_3B/air (A) and Et_3B/O_2 (B), for the carbamoylation provided similar yields and selectivities in all cases.

The C−H carbamoylation of amines has provided a new approach to mepivacaine (**49**), a clinically important local anesthetic, from readily available materials (Scheme 3). A mixture of *N*-methylpiperidine (**8**), 2,6-dimethylphenylisocyanate (**48**), and Et_3B was stirred at room temperature with continuous admission of dry air to furnish compound **49** (52%) and its regioisomer **50** (13%).[19]

Scheme 3. One-Step Synthesis of Mepivacaine (**49**) via α-C−H Carbamoylation of *N*-Methylpiperidine (**8**)



In conclusion, the present study has uncovered novel aspects in the radical chemistry of isocyanates, which have broad applications in organic synthesis and provide the basis for the development of new radical sp^3C-H transformation chemistry. Further refinement of this rare chemical transformation is being undertaken to improve yields and selectivities and to expand substrate scope.

Supporting Information Available: Experimental procedures, characterization data including CIF, and $^1H/^{13}C$ NMR spectra of products. This material is available free of charge via the Internet at http://pubs.acs.org.

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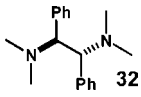
(17) The identity of compound **32** was confirmed by comparison with reported analytical data. See Supporting Information.



(18) When amine **34** was subjected to the radical carbamoylation under Et_3B/air conditions (Method A), 23% of ethyl phenylcarbamate (**12**), 2% of 1,3-diphenylurea (**13**), and 7% of 1,3-diphenyl-1-ethylurea (**41**) were obtained as byproducts (determined by ^1H NMR). Method B gave similar results. For more details, see Supporting Information.

(19) Biscarbamoylated isomers were also produced in 26% combined yield. Similar yields and ratios of the products were obtained under Et_3B/O_2 conditions (**49**, 53%; **50**, 14%; and other isomers, 26%). Presumably, the bulkiness of the methyl substituents of isocyanate **48** retarded the 1,5-hydrogen transfer, thereby allowing the selective production of monocarbamoylated amines **49**/**50** rather than bisisomers, in marked contrast to the reactions of phenyl isocyanate **2**.