Nicotinoyl Azide (NCA)-Mediated Mitsunobu Reaction: An Expedient One-Pot Transformation of Alcohols into Azides

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Abstract: A practical and simple method that allows preparation of azides from alcohols is described. The process involves oxyphosphonium-type activation and it is based upon the use of nicotinoyl azide (NCA), a cheap and easily accessible azide ion source.

Key words: azides, alcohols, nicotinoyl azide (NCA)

Simple, practical and high-yielding methods that allow preparation of azides directly from alcohols are frequently required in the synthesis of N-containing compounds. Azides are useful precursors of amines through catalytic hydrogenation[1] and the Staudinger reaction.[2] Furthermore, imines[3] and nitrogen-containing heterocycles such as, for example, [3+2] cycloaddition,[4] the aza-Wittig reaction,[5] and the Aubé modification of the Schmidt rearrangement,[6] could be obtained starting from azides.

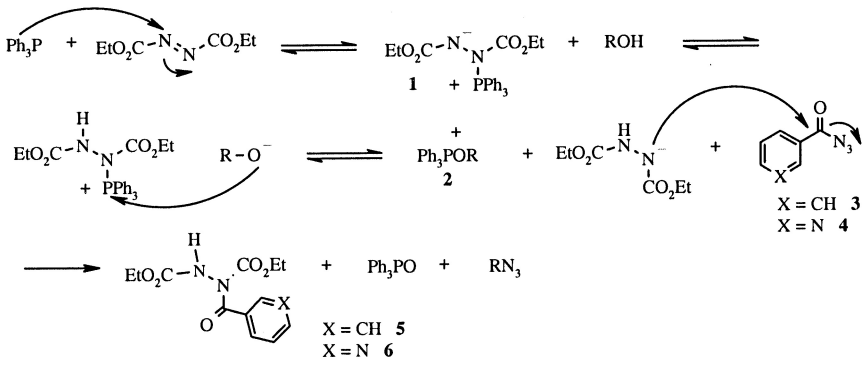
Alkyl azides are generally prepared by S_N2 displacement of halides,[7] sulfonates[8] and imidazylates.[9] Methods that employ standard Mitsunobu[10] conditions (PPh_3, dialkyl azodicarboxylate), HN_3,[11] $Zn(N_3)_2 \cdot 2Py$,[12] DPPA,[13] and Me_3SiN_3 (for 1,2-diols)[14] are also commonly used. Recent examples based on a Mitsunobu-like procedure, employ DDQ instead of DEAD and NaN_3[15] or $Bu_4N^+ N_3^-$.[16] On the other hand, sets of reagents like DPPA/DBU[17] or (*p*-NO_2)DPPA/DBU[18] exploit a different reaction mechanism, involving displacement of intermediate phosphate esters with azide ions.

Our interest in using a cheap and easily accessible source of azide ion in Mitsunobu-type reactions, prompted us to test aroyl azides as reagents. We hoped that the Morrison–Brunn–Huisgen (MBH) betaine[19] (**1**, Scheme 1) would trigger the release of the nucleophile via formation of the oxyphosphonium ion intermediate (**2**, Scheme 1) which would undergo the classical S_N2 reaction with azide ion. Generation of the oxyphosphonium ions should, in principle, avoid any competitive esterification of the aroyl azide.

To this end, we first explored benzoyl azide (**3**, Scheme 1) (mp 32 °C), prepared in nearly quantitative yield from benzoyl chloride.[20] Using the classical redox couple PPh_3/DEAD, THF as the solvent and a temperature range from 0 °C to room temperature, a nearly quantitative isolated yield was achieved in the case of 3-β-hydroxycholestane, after three hours (Table 1, entry 1).

Complete conversion and excellent yield were achieved by increasing the amount of the redox couple and the benzoyl azide in the case of axial 3-α-hydroxycholestane (Table 1, entries 2 and 3).

Having demonstrated the flexibility of the conversion of model alcohols to azides with benzoyl azide under Mitsunobu conditions, we decided to expand the scope and evaluate limitations of this procedure. However, it was soon discovered that benzoyl azide was not the reagent of choice. From a practical point of view the low melting



Scheme 1

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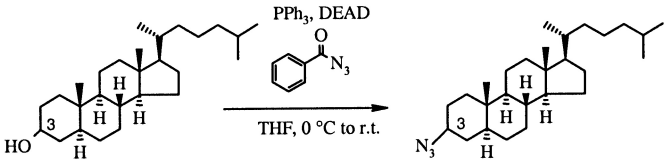
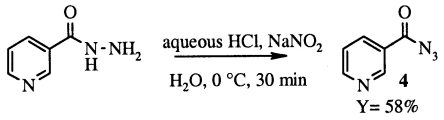
Table 1 Optimization of the Mitsunobu Displacement



Entry	Stereochemistry (substrate/product)	Stoichiometry	Equiv PPh_3, DEAD	Equiv **3**	Conversion (%)	Reaction time	Yield (%)
1	**3**-β/**3**-α	A	1.5	1.3	100	3 h	94
2	**3**-α/**3**-β	A	1.5	1.3	79	3 h	71
3	**3**-α/**3**-β	B	3	2.6	100	3 h	91

point hampers easy handling of the reagent. Moreover, problems were encountered in purifying some of the desired products either from excess benzoyl azide or from the main by-product diethyl *N*-benzoylhydrazine dicarboxylate (**5**, Scheme 1). We then turned our attention to nicotinoyl azide (NCA) **4**, as a more practical reagent. It is easily prepared on a multi-gram scale from the corresponding commercially available hydrazide[21] (Scheme 2).



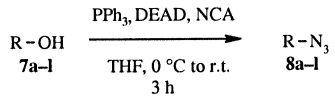
Scheme 2 Synthesis of nicotinoyl azide (NCA).

HPLC retention time and TLC retention factor were, as expected, different from the benzoyl azide. Predictably, similar carbonyl-carbon atom partial positive charge emerged from the comparative force field MMFF94[22] analysis of benzoyl azide and NCA, using the Titan® software.

Furthermore, NCA (mp 47 °C) is non-hygroscopic, with a safe DSC profile until 70 °C[23] and excellent shelf life at room temperature. NCA is completely soluble in the most frequently used organic solvents; it also shows good aqueous solubility as the free base and as its hydrochloride. It could be converted into the corresponding isocyanate through Schmidt rearrangement by refluxing in benzene,[24] or simply by heating at 80 °C in an open vessel.

We first decided to test NCA on 3-β-hydroxycholestane and 3-α-hydroxycholestane, using the same reaction conditions we found for benzoyl azide (entries 1 and 2, Table 2). As expected, NCA was found to be as effective as benzoyl azide with identical conversion and yields. Different primary, secondary and tertiary alcohols were then subjected to our azidation procedure with NCA. The results are shown in Table 2.

Table 2 Preparation of Primary, Secondary and Tertiary Aliphatic Azides Using NCA



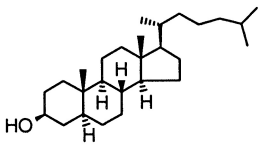
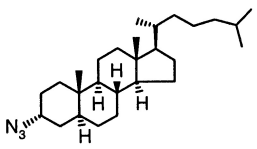
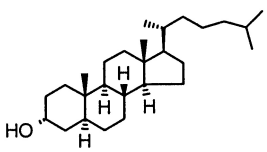
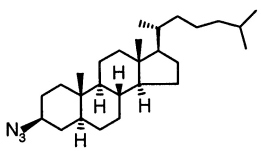
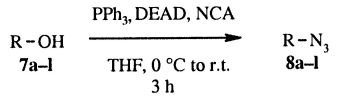
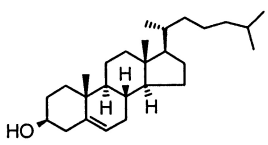
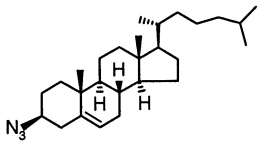
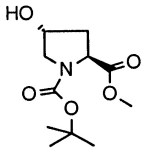
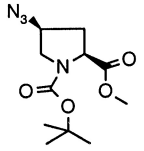
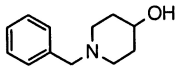
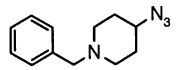
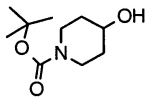
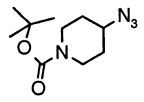
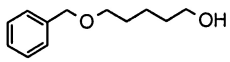
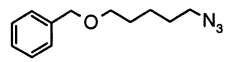
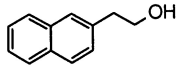
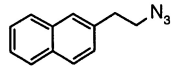
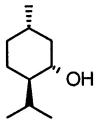
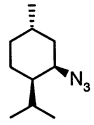
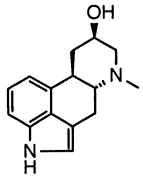
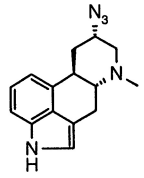
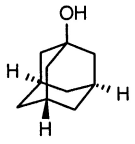
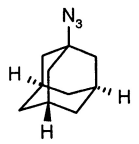
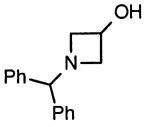
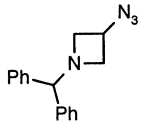
Entry	Substrate	Product	Stoichiometry (see Table 1)	Yield (%)[a,b]	Physical data
1	 **7a**	 **8a**	**A**	94	White solid[25] Mp 64–65 °C (lit. 62.5–63 °C)
2	 **7b**	 **8b**	B	96	White solid[25] Mp 71.5–72 °C (lit. 65–66 °C)

Table 2 Preparation of Primary, Secondary and Tertiary Aliphatic Azides Using NCA (continued)



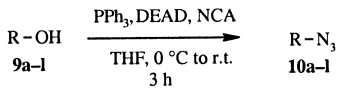
Entry	Substrate	Product	Stoichiometry (see Table 1)	Yield (%)[a,b]	Physical data
3	 **7c**	 **8c**	A	77	White solid[26] mp 119–121 °C (lit. 114–115 °C)
4	 **7d**	 **8d**	A	81	Pale yellow oil[27]
5	 **7e**	 **8e**	A	87	Pale yellow oil
6	 **7f**	 **8f**	A	81	Yellow oil[28]
7	 **7g**	 **8g**	A	84	Pale yellow oil
8	 **7h**	 **8h**	B	83	White solid Mp 57–60 °C
9	 **7i**	 **8i**	A	65	Yellow oil[29]
10	 **7j**	 **8j**	B	70	Brown solid Mp 199–200 °C. $[\alpha]^D$ –104 (c = 1, $CDCl_3$–MeOH, 1:1)
11	 **7k**	 **8k**	B	40	Pale yellow oil[30]
12	 **7l**	 **8l**	B	10	Yellow oil

[a] Isolated yields.
[b] All known compounds gave satisfactory elemental analyses (HRMS for oils) and spectral data.

All reactions were worked-up after three hours at room temperature. Good to excellent yields were achieved in most cases, with complete inversion of configuration (Table 2, entries 1–10).[10,31] Tertiary alcohols not prone to elimination in agreement with the Bredt's rule[32] (Table 2, entry 11) gave modest yields of the corresponding azide, proceeding most probably through a carbonium ion mechanism. Surprisingly, 1-benzhydryl-3-hydroxyazetidine **7l** was nicely converted into the corresponding azide **8l** using benzoyl azide (65% isolated yield), but gave a very poor yield with NCA (Table 3, entry 12).

Primary and secondary benzylic alcohols also underwent reaction with good isolated yields (Table 3, entries 1–9).

Table 3 Preparation of Primary and Secondary Benzylic Azides Using NCA



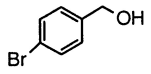
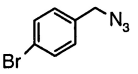
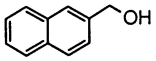
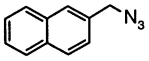
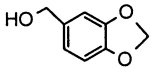
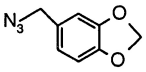
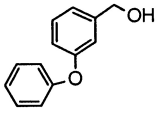
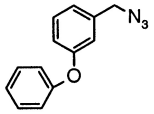
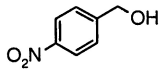
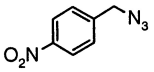
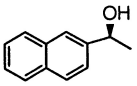
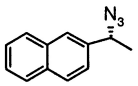
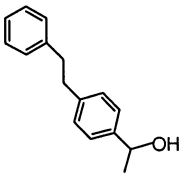
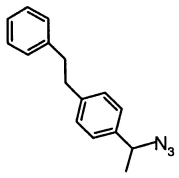
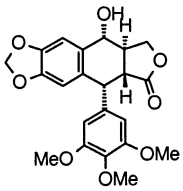
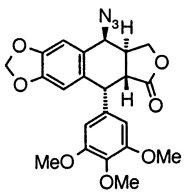
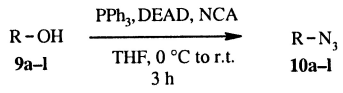
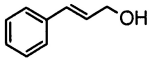
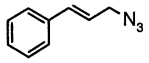
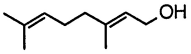
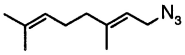
Entry	Substrate	Product	Stoichiometry (see Table 1)	Yield (%)[a,b]	Physical data
1	 **9a**	 **10a**	**A**	73	Pale yellow oil[33]
2	 **9b**	 **10b**	A	62	White solid Mp 47–49 °C
3	 **9c**	 **10c**	A	75	Pale yellow oil[34]
4	 **9d**	 **10d**	A	83	Yellow oil
5	 **9e**	 **10e**	A	64	Pale yellow oil
6	 **9f**	 **10f**	A	80	Yellow oil[35] $[\alpha]^D$ + 114 (c = 1, $CDCl_3$)
7	 **9g**	 **10g**	A	70	Yellow oil
8	 **9h**	 **10h**	A	77	Pale yellow oil
9	 **9i**	 **10i**	A	55	White solid[36] Mp 200–201 °C (lit. 202–204 °C)

Table 3 Preparation of Primary and Secondary Benzylic Azides Using NCA (continued)



Entry	Substrate	Product	Stoichiometry (see Table 1)	Yield (%)[a,b]	Physical data
10	 **9j**	 **10j**	B	52	Yellow oil[37]
11	 **9k**	 **10k**	B	55	Pale yellow oil[38]
12	 **9l**	 **10l**	B	50[c]	Yellow oil[39]

[a] Isolated yields.
[b] All known compounds gave satisfactory elemental analyses (HRMS for oils) and spectral data.
[c] Mixture of geranyl azide and linalyl azide (8:2).

The electronic nature of the substituent(s) on the phenyl ring does not seem to play a decisive role in influencing the course of the reaction (Table 3, compare entry 1 with entries 3 and 5). However, primary and secondary allylic alcohols turned out to be more difficult substrates, which required a larger excess of reagents and even then yields were not higher than 55% (Table 3, entries 10–12). Furthermore, geraniol gave an inseparable mixture of azides arising from both S_N2 and S_N2' attack.

Alkene by-products arising from potentially competitive E2 elimination, particularly in those cases in which the resulting double bonds are conjugated (Table 2, entries 3–8; Table 3, entries 6–8), were isolated only in trace amount whenever detected.

Spectral data for new compounds are listed in Table 4.

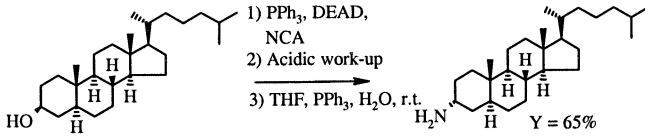
When the expected product is not a Brønsted base, NCA offers a potential advantage over, for instance, DPPA. Acidic work-up allows removal of unreacted NCA along with the main by-product, diethyl *N*-nicotinoylhydrazine dicarboxylate (**6**, Scheme 1).

Removal of those ingredients from the crude reaction mixture turned out to be beneficial both in the purification step of polar azides and in performing the Staudinger

Table 4 Spectral data for New Products

Product	IR ν (N_3) (cm^{-1})	^1H NMR ($CDCl_3$) δ (ppm), *J* (Hz)
8e	2094	1.58–1.75 (m, 2 H), 1.89 (d, *J* = 13.2 Hz, 2 H), 2.17 (t, *J* = 9.7 Hz, 2 H), 2.77 (d, *J* = 11.7 Hz, 2 H), 3.3–3.5 (m, 1 H), 3.5 (s, 2 H), 7.21–7.36 (m, 5 H)
8g	2100	1.44–1.52 (m, 2 H), 1.55–1.73 (m, 4 H), 3.27 (t, *J* = 6.9 Hz, 2 H), 3.49 (t, *J* = 6.3 Hz, 2 H), 4.51 (s, 2 H), 7.20–7.43 (m, 5 H)
8h	2098	3.07 (t, *J* = 7.3 Hz, 2 H), 3.61 (t, *J* = 7.2 Hz, 2 H), 7.35 (dd, *J* = 8.2, 1.47 Hz, 1 H), 7.42–7.53 (m, 2 H), 7.68 (s, 1 H), 7.76–7.88 (m, 3 H)
8j	2090	1.41–1.65 (m, 2 H), 2.12–2.32 (m, 2 H), 2.52 (s, 3 H), 2.6–2.72 (m, 1 H), 2.99 (d, *J* = 10.8 Hz, 2 H), 3.12–3.32 (m, 1 H), 3.41 (dd, *J* = 14.7, 4.4 Hz, 1 H), 6.8–6.98 (m, 2 H), 7.15–7.22 (m, 1 H), 7.41–7.53 (m, 1 H), 7.93 (s, 1 H)
10b	2098	4.51 (s, 2 H), 7.43 (dd, *J* = 8.5, 1.8 Hz, 1 H), 7.48–7.57 (m, 2 H), 7.78 (s, 1 H), 7.81–7.98 (m, 3 H)
10d	2100	4.31 (s, 2 H), 6.8–6.98 (m, 1 H), 7–7.08 (m, 3 H), 7.1–7.22 (m, 1 H), 7.25–7.48 (m, 4 H)
10e	2090	4.50 (s, 2 H), 7.50 (d, *J* = 9.1 Hz, 2 H), 8.24 (d, *J* = 8.8 Hz, 2 H)
10g	2088	1.76–1.88 (m, 1 H), 2.01 (d, *J* = 5 Hz, 3 H), 2.64–2.99 (m, 2 H), 4.4–4.65 (m, 1 H), 7.08–7.17 (m, 1 H), 7.20–7.43 (m, 3 H)
10h	2110	1.53 (d, *J* = 7 Hz, 3 H), 2.86–2.98 (m, 4 H), 4.60 (q, *J* = 6.7 Hz, 1 H), 7.09–7.45 (m, 9 H)

reaction[2] on the crude product (Scheme 3). The isolation of the expected amine proved to be simpler.



Scheme 3 Staudinger reaction.

Careful analysis of a model reaction mixture helped us to cast light over the reaction mechanism.[19,40,41] Thus, excess NCA was recovered after column chromatography in only trace amount because of the almost quantitative conversion into diethyl *N*-nicotinoylhydrazine dicarboxylate (**6**, Scheme 1). This latter compound, however fragile, was isolated and characterized,[42] thus demonstrating the plausibility of the proposed reaction mechanism (Scheme 1).

In conclusion, the aforementioned results clearly demonstrate that the cheap and easily accessible NCA is an effective reagent in the direct conversion of alcohols into azides.

Melting points were determined in open glass capillaries with a Büchi 535 melting point apparatus, and are uncorrected. Elemental analyses were performed on a Carlo Erba 1110 instrument. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Oxford 300 spectrometer, using the solvent as internal standard; chemical shifts are expressed in ppm (δ). Electron impact (EI) mass spectra (MS) were obtained on Finnigan-MAT TSQ 700 triple quadrupole instrument. (ESI) mass spectra were obtained on LCQ-ion trap thermo Finnigan. IR spectra were recorded on a ThermoNicolet Avatar 360 FT-IR spectrometer. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter in a 1 dm cell at ambient temperature with a sodium lamp (wavelength of 589 nm). All the reactions were performed with oven-dried glassware and under a blanket of N_2. Triphenylphosphine was recrystallized prior to use from petroleum ether–ethanol (6:4). THF was distilled under positive pressure of anhyd N_2 from sodium/benzophenone ketyl. DEAD was purchased from Lancaster and used without further purification.

CAUTION: although safe, NCA should be considered potentially dangerous like any other azido-containing compound. Precautions during its preparation and handling are thus strongly recommended (goggles, efficient hoods, protective shields, etc.).

Preparation of Nicotinoyl Azide (NCA) (4); Typical Procedure

To concd HCl acid (0.29 mol, 24 mL) stirred and chilled in an ice bath, nicotinoyl hydrazide (20 g, 0.15 mol) was added portionwise, while keeping the temperature below 10 °C. A solution of $NaNO_2$ (20.5 g, 0.29 mol) in water (34.5 mL) was added dropwise, again keeping the temperature below 10 °C. The aqueous phase was then extracted with Et_2O and the organic layer was washed with sat. aq $NaHCO_3$ solution and dried over Na_2SO_4. The solvent was removed under reduced pressure at r.t. to afford pure NCA (**4**), brown solid, mp 47–49 °C. Neutralization of the aqueous phase with $NaHCO_3$ and extraction with Et_2O yielded an additional amount of NCA. The overall yield was 12.4 g (58%).

IR: 2140–2130 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.58–7.62 (dd, J = 8.1, 4.8 Hz, 1 H), 8.27–8.31 (ddd, J = 8.1, 1.9, 1.8 Hz, 1 H), 8.85–8.88 (dd, J = 5.0, 1.8 Hz, 1 H), 9.07–9.08 (d, J = 2.3 Hz, 1 H).

^{13}C NMR (75.46 MHz, $CDCl_3$): δ = 123.68, 126.73, 136.9, 150.83, 154.77, 171.42.

MS: m/z = 149.11 [MH$^+$].

Anal. Calcd for $C_6H_4N_4O$: C, 48.65; H, 2.72; N, 37.82. Found: C, 48.35; H, 2.75; N, 37.05.

General Experimental Procedure

To an ice-cooled stirred solution of **7a** (200 mg, 0.51 mmol) and PPh_3 (203 mg, 0.77 mmol) in anhyd THF (5 mL), DEAD was slowly added dropwise (0.21 mL, 0.77 mmol), under N_2. After 15 min NCA (98 mg, 0.66 mmol) was added in one portion, the reaction mixture was allowed to warm to r.t. and then stirred until the starting material disappeared (detected by TLC). The solvent was removed under reduced pressure and the crude product was purified by flash chromatography (hexane) to give **8a** (198 mg, 94%) of the pure azide.

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References

(1) See for example: (a) Zhang, S.; Reith, M. E. A.; Dutta, A. K. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1591. (b) Deng, W.-P.; Nam, G.; Fan, J.; Kirk, K. L. *J. Org. Chem.* **2003**, *68*, 2798. (c) Jung, Y. J.; Chang, Y. M.; Lee, J. H.; Yoon, C. M. *Tetrahedron Lett.* **2002**, *38*, 8735.

(2) (a) Meyer, J. *Helv. Chim. Acta* **1919**, *2*, 635. (b) For recent examples see the following: Michellizza, S.; Al-Mourabit, A.; Gateau-Olesker, A.; Marazano, C. *J. Org. Chem.* **2002**, *67*, 6474. (c) Battaglia, A.; Barbaro, G.; Giorgianni, P.; Guerrini, A.; Pepe, A. *Tetrahedron: Asymmetry* **2001**, *12*, 1015.

(3) (a) For a treatise on azides, which includes discussion of rearrangement reactions, see: Scriven, E. F. V. *Azides and Nitrenes*; Academic Press: New York, **1984**. (b) For a review of rearrangement of alkyl and aryl azides, see: Stevens, T. S.; Watts, W. E. *Selected Molecular Rearrangements*; Van Nostrand Reinhold: London, **1973**.

(4) See for examples: (a) Katritzky, A.; Singh, S. K. *J. Org. Chem.* **2002**, *67*, 9077. (b) Trauner, D.; Porth, S.; Opatz, T.; Bats, J. W.; Geister, G.; Multzer, J. *Synthesis* **1998**, 653. (c) Schultz, A. G.; Dai, M.; Kim, S. K.; Pettus, L.; Thakhar, K. *Tetrahedron Lett.* **1998**, *39*, 4203. (d) Kolb, H. C.; Sharpless, B. *Drug Discov. Today* **2003**, *8*, 1128.

(5) Stork, G.; Niu, D.; Fujimoto, A.; Koft, E. R.; Balkovec, J. M.; Tata, J. R.; Dake, G. R. *J. Am. Chem. Soc.* **2001**, *123*, 3239.

(6) (a) Schildknegt, K.; Agrios, K. A.; Aubé, J. *Tetrahedron Lett.* **1998**, *39*, 7687. (b) Milligan, G. L.; Mossman, C. J.; Aubé, J. *J. Am. Chem. Soc.* **1995**, *117*, 10449.

(7) See for example: Ito, M.; Koyakumaru, K.-I.; Ohta, T.; Takaya, H. *Synthesis* **1995**, 376.

(8) (a) Biffin, M. E. C.; Miller, J.; Paul, D. B. In *The Chemistry of the Azido Group*; Patai, S., Ed.; Wiley Interscience: New York, **1971**, 57. (b) Alvarez, S. G.; Alvarez, M. T. *Synthesis* **1997**, 413.

(9) (a) Vatèle, J. M.; Hanessian, S. *Tetrahedron* **1996**, *52*, 10557. (b) Vatèle, J. M.; Hanessian, S. *Tetrahedron Lett.* **1981**, *22*, 3579.

(10) (a) Mitsunobu, O. *Synthesis* **1981**, 1. (b) Hughes, D. L. *Org. React.* **1992**, *42*, 335.

(11) (a) Loibner, H.; Zbiral, E. *Helv. Chim. Acta* **1976**, *59*, 2100. (b) Chen, C.-P.; Prasad, K.; Repic, O. *Tetrahedron Lett.* **1991**, *32*, 7175.
(12) Viaud, M. C.; Rollin, P. *Synthesis* **1990**, 130.
(13) Lal, B.; Pramanik, B. N.; Manhas, M. S.; Bose, A. K. *Tetrahedron Lett.* **1977**, *23*, 1977.
(14) He, L.; Wanunu, M.; Byun, H.-S.; Bittman, R. *J. Org. Chem.* **1999**, *64*, 6049.
(15) Firouzabadi, H.; Iranpoor, N.; Sobhani, S. *Tetrahedron* **2004**, *60*, 203.
(16) Iranpoor, N.; Firouzabadi, H.; Akhlaghinia, B.; Nowrouzi, N. *Tetrahedron Lett.* **2004**, *45*, 3291.
(17) Thompson, A. S.; Humphrey, G. R.; DeMarco, A. M.; Mathre, D. J.; Grabowski, E. J. J. *J. Org. Chem.* **1993**, *58*, 5886.
(18) Mizuno, M.; Shioiri, T. *Chem. Commun.* **1997**, 2165.
(19) Satish Kumar, N.; Praveen Kumar, K.; Pavan Kumar, K. V. P.; Praveen, K.; Vittal, J. J.; Swamy Kumara, K. C. *J. Org. Chem.* **2004**, *69*, 1880.
(20) Froeyen, P. *Phosphorous, Sulfur, Silicon Relat. Elem.* **1993**, *78*, 161.
(21) Breslow, D. S. *J. Am. Chem. Soc.* **1950**, *72*, 4244.
(22) Halgren, T. A. *J. Computational Chem.* **1996**, *17*, 490.
(23) DSC (Mettler-Toledo Star® System, heating rate: 10 °C min^{-1}): endothermic effect between 40 °C and 66 °C (melting of the reagent, ΔH_{endo} = 106 J g^{-1}); exothermic effect between 73 °C and 151 °C (Schmidt rearrangement plus decomposition, ΔH_{exo} = 1051 J g^{-1}).
(24) See for examples: (a) Iyengar, B. S.; Dorr, R. T.; Alberts, D. S.; Hersh, E. M.; Salmon, S. E.; Remers, W. *J. Med. Chem.* **1999**, *42*, 510. (b) L'Abbe, G. *Synthesis* **1987**, 525.
(25) Casimiro-Garcia, A.; Clercq, E. D.; Pannecoque, C.; Witvrouw, M.; Stup, T. L. *Bioorg. Med. Chem.* **2000**, *8*, 197.
(26) Freiberg, L. A. *J. Org. Chem.* **1965**, *30*, 2476.
(27) (a) Gòmez-Vidal, J. A.; Silverman, R. B. *Org. Lett.* **2001**, *3*, 2481. (b) Marusawa, H.; Setoi, H.; Sadawa, A.; Kuroda, A.; Seki, J.; Motoyama, Y.; Tanaka, H. *Bioorg. Med. Chem.* **2002**, *10*, 1399.
(28) (a) Finke, P. E.; Oates, B.; Sanders, M. G.; MacCoss, M.; Malkowitz, L.; Springer, M. S.; Gould, S. L.; DeMartino, J. A.; Carella, A.; Carver, G.; Holmes, K. *Bioorg. Med. Chem.* **2001**, *11*, 2475. (b) Moore, K. W.; Bonner, K.; Jones, E. A.; Emms, F.; Leeson, P. D. *Bioorg. Med. Chem.* **1999**, *9*, 1285.
(29) Ito, M.; Koyakumaru, K.; Otha, T.; Takaya, H. *Synthesis* **1995**, *4*, 376.
(30) (a) Kevill, D. N.; Weitl, F. L. *J. Org. Chem.* **1970**, *35*, 2526. (b) Sasaki, T.; Eguchi, S.; Katada, T.; Hiroaki, O. *J. Org. Chem.* **1977**, *42*, 3741.
(31) Mark, E.; Zbiral, E. *Monatsh. Chem.* **1981**, *112*, 215.
(32) For a review see: (a) Shea, K. J. *Tetrahedron* **1980**, *363*, 1683. (b) For a review on bridgehead alkenes, see the following: Warner, P. M. *Chem. Rev.* **1989**, *89*, 1067. (c) Billups, W. E.; Haley, M. M.; Lee, G. *Chem. Rev.* **1989**, *89*, 1147.
(33) (a) Barret, I. C.; Kerr, M. A. *Synlett* **2000**, *11*, 1673. (b) Hassner, A.; Stern, M. *Angew. Chem.* **1986**, *98*, 479.
(34) Sampath Kumar, H. M.; Reddy, B. V. S.; Anjaneyulu, S.; Yadav, J. S. *Tetrahedron Lett.* **1998**, *39*, 7385.
(35) Occhiato, E.; Jones, J. B. *Tetrahedron* **1996**, *52*, 4199.
(36) (a) Tao, L.; Wang, Y.-G.; Ma, C.; Zheng, B.; Chen, Y.-Z. *Synth. Commun.* **1999**, *29*, 2053. (b) Xu, H.; Zhang, X.; Tian, X.; Lu, M.; Wang, Y.-G. *Chem. Pharm. Bull.* **2002**, *50*, 399.
(37) Kanai, T.; Kanagawa, Y.; Ishii, Y. *J. Org. Chem.* **1990**, *55*, 3274.
(38) Malkov, A. V.; Spoor, P.; Vinader, V.; Kocovsky, P. *J. Org. Chem.* **1999**, *64*, 5308.
(39) (a) Murahashi, S.-I.; Taniguchi, Y.; Imada, Y.; Tanigawaq, Y. *J. Org. Chem.* **1989**, *54*, 3292. (b) Murahashi, S.-I.; Taniguchi, Y.; Imada, Y.; Tanigawaq, Y. *Tetrahedron Lett.* **1986**, *27*, 227. (c) Varma, R. S.; Naicker, K. P. *Tetrahedron Lett.* **1998**, *39*, 2915.
(40) Varasi, M.; Walker, K. A. M.; Maddox, M. L. *J. Org. Chem.* **1987**, *52*, 4235.
(41) Afonso, C. M.; Barros, M. T.; Godinho, L. S.; Maycock, C. D. *Tetrahedron* **1994**, *50*, 9671.
(42) ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.24–1.31 (m, 6 H), 4.15–4.27 (m, 4 H), 7.35–7.42 (m, 1 H), 7.96–7.98 (d, *J* = 7.6 Hz, 1 H), 8.71–8.73 (d, *J* = 5 Hz, 1 H), 8.86 (s, 1 H). MS *m/z* = 282.26 (MH^+).