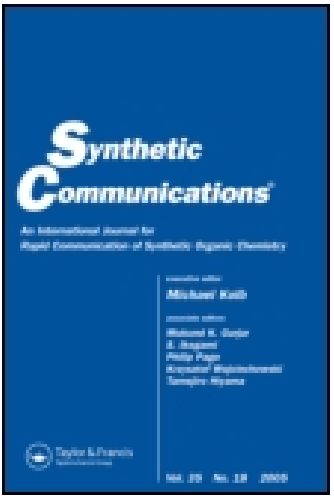


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Studies on the Transformation of Azido-Group to N-(t-Butoxycarbonyl)amino Group via Staudinger Reaction

Carlos A. M. Afonso [a]
[a] Faculdade de Ciências e Tecnologia da Universidade Nova de Lisboa, Departamento de Química, Quinta da Torre , P-2825 , Monte de Caparica , Portugal
Published online: 21 Aug 2006.

To cite this article: Carlos A. M. Afonso (1998) Studies on the Transformation of Azido-Group to N-(t-Butoxycarbonyl)amino Group via Staudinger Reaction, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 28:2, 261-276, DOI: 10.1080/00397919808005719

To link to this article: http://dx.doi.org/10.1080/00397919808005719

SYNTHETIC COMMUNICATIONS, 28(2), 261-276 (1998)

Studies on the Transformation of Azido-Group to N-(t-Butoxycarbonyl)amino Group *via* Staudinger Reaction

Carlos A. M. Afonso

Faculdade de Ciências e Tecnologia da Universidade Nova de Lisboa, Departamento de Química, Quinta da Torre; P-2825 Monte de Caparica, Portugal

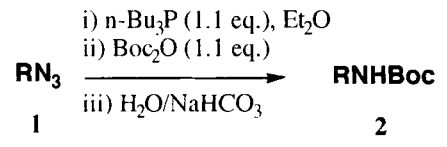
Abstract: By a simple and direct sequence, treatment of primary azides with tri-*n*-butylphosphine, followed by addition of di-*t*-butyl dicarbonate (Boc_2O) affords, N-(t-Butoxycarbonyl)amines **2** in moderate to good overall yields. For secondary azides the formation of symmetrical disubstituted ureas is a competitive process. Conditions were found which, in the presence of a primary amine, allow for moderate selectivity for the reaction with Boc_2O.

Conversion of azides into amines is of considerable importance in organic synthesis[1]. When protection of the amino group is required and in order to avoid the manipulation of the very polar amino group[2], a protecting group can be introduced simultaneously, using di-t-butyl dicarbonate (Boc_2O) under catalytic hydrogenation conditions (H_2, Pd/C)[3a] or using recently reported strategy by azide reduction with triethylsilane in the presence of catalytic amount of 20% Degussa $Pd(OH)_2/C$[3b]. The reduction of azides to amines *via* hydrolysis of corresponding iminophosphoranes is a very common method[4,5] but sometimes requires basic[4,6] or acidic conditions[4,6a,7]. In a preliminary communication we reported a convenient method for the conversion of azides into N-Boc-amines *via* reaction of iminophosphoranes with Boc_2O at low temperature[8] (scheme 1). Here this transformation will be described in more detail.

The transformation of benzyl azide **1b** to the corresponding N-Boc-amine **2b** was studied (table 1). The results obtained under different experimental

conditions suggest that the solvent has little effect on the yield of **2b** (entries 1-4). The importance of the order of addition of the reagents was also noticed, (entries 3, 7, 10-11) and the best results were obtained when the iminophosphorane was prepared before the Boc_2O addition. A sign that dependence on temperature and reaction time was found for step ii, thus better results were obtained at low temperature (-50 to -60 °C), while no significant effect was observed when the reaction time was increased (entries 2 and 3). When a large excess of Boc_2O (2.2 eq) was used only a moderate increase on the yield was observed (entries 9-10).

Scheme 1



The optimized conditions found for azide **1b** were used for other azides (table 2). It was observed that primary azides gave the expected product in good yield at -50 °C (step ii)[9], while more hindered azides required higher temperature to occur in moderate to low yield.

Azide **1h** was selected to study the reaction of the corresponding iminophosphorane with Boc_2O, in the presence of benzylamine (1 eq.). Some of the experimental conditions that were evaluated, are summarised in table 3. A large excess of ethylamine was added before the workup, to trap the remaining Boc_2O. The selectivity observed is strongly influenced by the reaction conditions and should not be due to amine-iminophosphorane exchange[10]. When the temperature was lowered until - 50°C an increase on the ratio **2h/2b** was observed (entries 1-3). However, at -95°C the ratio **2h/2b** decreased becoming similar to that observed when the reaction was carried out at room temperature. The reaction solvent has also a remarkable effect on the selectivity (entries 3, 5-7) with an inversion observed when changing solvent from diethyl ether to dimethylformamide. The use of a Lewis acid, was also tried in the expectation that there would be an inhibition of the amine reaction resulting from preferential complexation with the more basic amine site[11]. In fact, using BF_3OEt_2 the best selectivity (8.4:1) was observed but with a considerable reduction in the overall yield[12].

The selectivity of the reaction of Boc_2O with primary and secondary iminophosphoranes was also examined (table 4). Starting from a mixture of **1h** and **1i** (1.3 : 1) only the primary N-Boc-amine **2h** was isolated from polar

Table 1. Influence of Experimental Conditions on the Transformation of **1b** to **2b**.

Entry	Method[a]	Phosphine	Solvent	Step i temp. °C	time	Step ii Boc_2O	temp. °C	time	**2a** Yield[b]
1	A	*n*-Bu_3P	DCM	rt	2.5 h	1.1 eq.	rt	18 h	49 %
2	A	*n*-Bu_3P	Et_2O	rt	2.5 h	1.1 eq	rt	18 h	56 %
3	A	*n*-Bu_3P	Et_2O	rt	2.5 h	1.1 eq	rt	15 min.	67 %
4	A	*n*-Bu_3P	THF	rt	2.5 h	1.1 eq	rt	22 h	55 %
5	A	*n*-Bu_3P	THF	reflux	35 min.	2.2 eq	reflux	30 min.	32 %
6	A	Ph_3P	THF	reflux	3 h	2.2 eq	0 °C	4 h	26 %
7	B	*n*-Bu_3P	Et_2O	rt	25 min	1.1 eq			39 %
8	A	*n*-Bu_3P	Et_2O	rt	1.5 h	1.1 eq	-12 °C	1 h	76 %
9	A	*n*-Bu_3P	Et_2O	rt	1.5 h	1.1 eq	-60 °C	1 h	78 %
10	A	*n*-Bu_3P	Et_2O	rt	1.5 h	2.2 eq	-60 °C	15 min	86 %
11	B	*n*-Bu_3P	Et_2O	-50 °C	2.5 days	2.2 eq			38 %
12	A	*n*-Bu_3P	Et_2O	rt	1.5 h	2.2 eq	-85 °C	1.5 h	85 %
13	A	*n*-Bu_3P	Et_2O	rt	1.5 h	1.1 eq	-85 °C	1.5 h	57 %
14	A	*n*-Bu_3P	Et_2O	rt	1.5 h	2.2 eq	-100 °C	1 h	28 %

a) **Method A**: Phosphine (1.1 eq) was added to a solution of azide **2b** in the solvent (step i) followed by the addition of Boc_2O (step ii) and aqueous work-up. **Method B**: Phosphine (1.1 eq) was added to a solution of azide **2b** and Boc_2O in the solvent followed by aqueous work-up. b) yield of pure product isolated by flash chromatography.

mixture (entry 1). However, reaction of the diazide **4** gave the N-Boc-amine **5** and the symmetric urea **6**[13] both in very low overall yields (entry 2)[14]. Using 2.2 mol. eq. of Boc_2O only a slight increase in the formation of the urea **6** was observed (entry 2). The best yield (29 %) was obtained at 0 °C using a catalytic amount of DMAP (entry 4). For the diazides **7** and **9** the corresponding ureas **8** and **10** were also isolated (entries 5 and 6).

The formation of aromatic cyclic carbodiimides from *bis*(iminophosphoranes) by reaction with Boc_2O/DMAP, *via* the corresponding isocyanate through DMAP catalysis has been reported[15]. They also observed that iminophosphoranes, from aromatic azides and triphenylphosphine (TPP), were

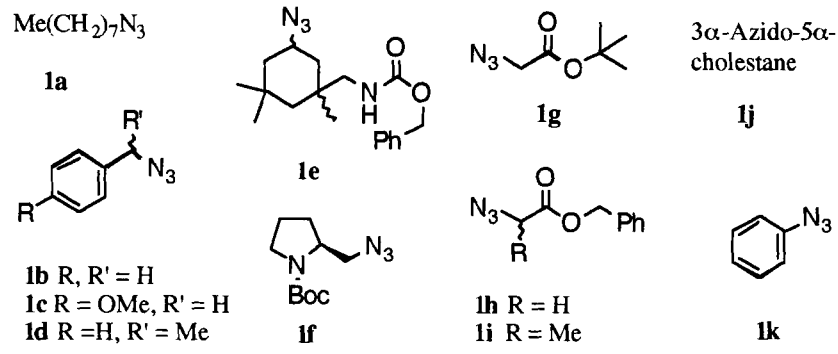


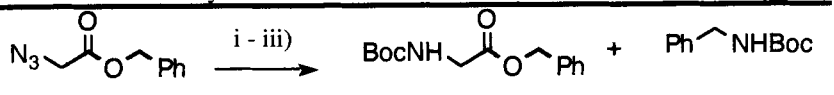
Table 2. Representative Examples for the Conversion of Azides into N-Boc-amines.

Azide **1**	Step i temp.; time	Step ii temp.; time	RNHBoc **2** Yield[a]	Azide **1**	Step i temp.; time	Step ii temp.; time	RNHBoc **2** Yield[a]
a	rt; 1.5 h	-50 °C; 1.5 h	79 %	**f**	rt; 2 h	-50 °C; 12 h	69 %
b	rt; 1.2 h	-50 °C; 1.5 h	78 %	**g**	rt; 1 h	-50 °C; 1.5 h	80 %
c	rt; 1 h 35 °C; 10 min.	-50 °C; 1.5 h	81 %	**h**	rt; 45 min.	-50 °C; 1 h	81 %
d	rt; 35 min.	-60 °C; 1 h	traces	**i**	rt; 2.3 h	0 °C; 4 h	18 %
d	rt; 35 min.	0 °C; 6 h	31 %	**j**	rt; 12 h	-30 °C; 3 h	56 %
d	rt; 35 min.	0 °C[b]; 6 h	10% + **3**[c] (77 %)	**j**	reflux[d] 20 h	-50 °C; 1.5 h	41 %
e	rt; 21 h	-50 °C; 1 h	56 %	**k**	rt; 1.5 h	-50 °C; 1 h	32 %

a) Yield of pure product isolated by flash chromatography. b) DMAP (catalytic amount) was added before Boc_2O. c) The carbodiimide PhCH(Me)N=C=NCH(Me)Ph **3** was also isolated. d) Triphenylphosphine (1.1 eq) was used and a solution of azide **1j** in benzene (42 mM) which was further diluted in diethyl ether (13 mM) before Boc_2O addition.

unreactive to Boc_2O at room temperature in the absence of DMAP[15a]. However, reaction of phenyl azide **1k** and tributylphosphine (TBP) at -50 °C gave the corresponding N-Boc-amine **2k** in 32 % yield. We also observed that TPP was less effective than TBP for non-aromatic azides (table 1, entry 6 and table 2 for

Table 3. Competitive Reaction of Iminophosphorane of Azide **1h** with Boc_2O in the Presence of Benzylamine.



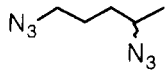
1h **2h** **2b**

Entry	Step ii temp.; time	Solvent	Yield **2h**[a]	Yield **2b**[a]	**2h:2b**	**2h+2b**
1	rt; 40 min.	Et_2O	64 %	35 %	1.8:1	99 %
2	-20 °C 14 h	Et_2O	64 %	25 %	2.6:1	89 %
3	-50 °C 1.5 h	Et_2O	78 %	18 %	4.4:1	96 %
4	-95 °C 3 h	Et_2O	51 %	29 %	1.8:1	80 %
5	-50 °C 1 h	CH_2Cl_2	30 %	43 %	1:1.4	73 %
6	-40 °C 3 h	CH_3CN	28 %	67 %	1:2.4	95 %
7	-40 °C 24 h	DMF	17 %	75 %	1:4.3	92 %
8	-50 °C 1.5 h	Et_2O[b]	51 %	6 %	8.4:1	57 %

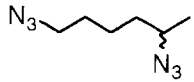
i) Bu_3P (1.1 eq.), rt, 1 h; ii) benzylamine (1 eq.), followed by Boc_2O (0.8 eq.); iii) ethylamine (10 eq.) followed by $H_2O/NaHCO_3$. a) Yield of pure product isolated by flash chromatography. b) BF_3OEt_2 (1.2 eq) was added before Boc_2O adition

1j) and that the use of DMAP changed the reactivity of azide **1d** to the formation of carbodiimide **3** (77 %) instead of **2d** (see table 2). Thus, the use of TBP instead of TPP or the combination of TPP/DMAP, seems to have a remarkable influence upon the products which are obtained.

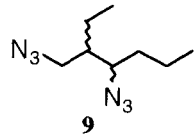
A possible explanation is that the iminophosphorane resulting from TBP, is more reactive with Boc_2O or, the presence of TBP in solution increases the reactivity of Boc_2O, as has been reported for anhydrides[16]. Following the reaction by ^{31}P NMR, after addition of Boc_2O (1.2 eq.) to the iminophosphorane of **1b** (0.17 mmol in 0.4 ml $CDCl_3$) at -50 °C a shift of the signal of iminophosphorane from +27.1 ppm to +73.4 ppm was observed. Addition of D_2O, shifted the signal to +49.7 ppm (tributylphosphine oxide; lit[17]. + 49.4 ppm). The signal at +73.4



4

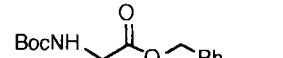
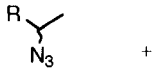
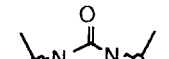
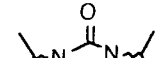
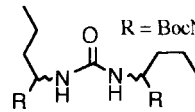


7



9

Table 4. Reaction of Boc_2O with Primary and Secundary Iminophosphoranes.

Entry	Azide[a]	Step i temp.; time	Boc_2O (eq.)	Step ii temp.; time	Isolated Products
1	**1h** and **1i** (1.3:1)	rt; 2 h	1.1 eq. (in relation to **1h**)	-50 °C; 1 h	 **2h** 79 % (none of **2i** was detected by TLC)
2	**4**	rt; 1 h	2.2 mol. eq.	-60 °C; 1.3 h	 R = $BocNH(CH_2)_3$ **5** 15 % +  **6** 25 %
3	**4**	rt; 1 h	1.0 mol. eq.	-60 °C; 1.3 h	**5** 11 %; **6** 20 %
4	**4**	rt; 1 h	2.2 mol. eq.[b]	0 °C; 1 h	**5** 9 %; **6** 29 %
5	**7**	rt; 2.5 h	2.2 mol. eq.	-60 °C; 1 h	 R = $BocNH(CH_2)_4$ **8** 32 %
6	**9**	rt; 1.5 h reflux; 1 h	2.2 mol. eq.	-60 °C; 1.5 h	 R = $BocNHCH_2CH(Et)$ **10** 34 %

a) All reactions were performed in diethyl ether using tributylphosphine (1.1 eq./ azide group). b) DMAP (catalytic amount) was added to the reaction mixture, followed by Boc_2O addition.

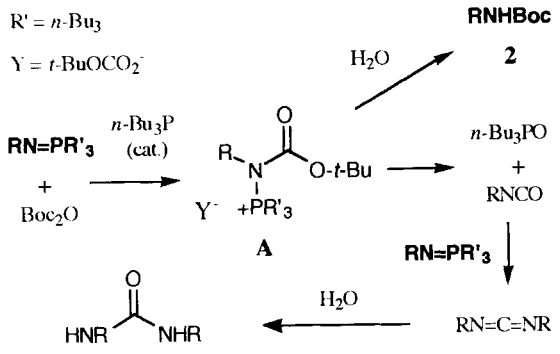
ppm is typical of a phosphonium species[17,18] which could be atributed to the structure **A** in accordance to recent observations[19] (scheme 2).

The lower reactivity observed for secondary azides could be a result of steric hinderance on the nucleophilic attack of the iminophosphorane on the anhydride. The formation of ureas **6**, **8** and **10** on the reaction of diazides **4**, **7** and **9** was curious, and it could eventually result from a faster formation of intermediate **A** of the primary azide than from secondary azide. As a result of steric hinderance, this intermediate could be transformed on the isocyanate which

by reaction with another unreacted more hindered secundary iminophosphorane group gives the symmetrical carbodiimide[15a,20] (scheme 2).

From the synthetic point of view, the procedure here described is a simple alternative for the preparation of N-Boc-amines from azides under mild conditions. This procedure seems specially appropriate for the conversion of less hindered azides incorporating functional groups which are non compatible (e.g. **1b**, **1e** and **1h**) with the reported methods[3]. Moderate selectivity were also observed for reaction of iminophosphorane in the presence of primary amine.

Scheme 2



Experimental

Reagent quality solvents were distilled prior to use. Diethyl azodicarboxylate was dried by standing over molecular sieves. Anhydrous dimethylformamide (BaO), triethylamine (NaOH), pyridine (NaOH) and dichloromethane (P_2O_5) were distilled. Anhydrous benzene, tetrahydrofuran and diethyl ether were prepared by distillation from sodium/benzophenone ketyl under argon. Tributylphosphine and benzylamine were distilled under argon prior to use. Triphenylphosphine was recrystalized successively from ethanol and petroleum ether 40/60. Column chromatography was performed using Silica gel Merck 60 H (Art. 7736) and aluminum-backed silica gel Merck 60 F_{254} plates was used for analytical TLC. Melting points (uncorrected) were determined on a Electrothermal Mod. IA 6304 capillary melting point apparatus. Microanalyses were carried out at ITQB using a Carlo Erba analyser. Mass spectra (MS) and accurate masses (HRMS) were obtained from the Mass Spectrometry Service, School of Pharmacy, University of London. Infrared spectra (IR) were recorded

on a Buck Scientific Mod. 500 spectrophotometer. ^{1}H, ^{13}C and ^{31}P NMR were recorded on a Bruker ARX 400 spectrometer. Chemical shifts are reported as δ values relative to tetramethylsilane (δ_H = 0 ppm), $\underline{C}DCl_3$ (δ_C = 77.0) or external phosphoric acid (δ_P = 0). All coupling constants are given in Hz. Observed rotations at the Na-D line were measured at 25°C using a Optical Activity polarimeter Mod. AA-1000.

Preparation of azides: Azides **1a** to **1d**, **1g** to **1i** and **4** were prepared following reported method[21]:

1a: clear colourless oil; b.p. 46 - 48 °C / 0.2 mmHg; lit.[22] 105 °C / 22 torr; lit.[23] 62 °C / 3.3 torr; lit.[24] 73 - 75 °C / 3 mmHg; spectral data identical to those reported[25].

1b: purified by flash chromatography (hexane) followed by distillation b.p. 58 - 60 °C/ 5 mmHg; lit.[26] 71 - 71.5 °C / 13 mmHg; clear colourless oil; spectral data identical to those reported[24,27, 25]; m/z (EI) 133, 105, 104, 91, 77, 65.

1c: purified by flash chromatography (7:3 hexane / dichloromethane), clear colourless oil; IR spectral data identical to those reported[27]; ^{1}H δ(400 MHz, $CDCl_3$) 3.81 (3H, s, OMe), 4.26 (2H, s, CH_2), 6.90 (2H, d J 7.7, Ar), 7.24 (2H, d J 7.7, Ar); m/z (EI) 163 (M^+), 135 (M^+-N_2), 121 (M^+-N_3), 91, 77, 65.

1d: purified by flash chromatography (hexane), spectral data identical to those reported[25, 28-30].

1g: purified by distillation; b.p. 70 °C/ 0.9 mmHg (Kugelrohr); lit.[31] 33 - 41 °C / 1 mmHg; clear colourless oil; ν_{max} (film) 2130, 1748 cm^{-1}; ^{1}H δ(400 MHz, $CDCl_3$) 1.51 (9H, s, *t*-Bu), 3.74 (2H, s, H-2); m/z (EI) 142 (M^+-Me), 124, 114, 84, 70, 59.

1h: purified by distillation; b.p. 110 °C/ 0.02 mmHg (Kugelrohr), clear colourless oil; ν_{max} (film) 2116, 1753 cm^{-1}; ^{1}H δ(400 MHz, $CDCl_3$) 3.92 (2H, s, H-2), 5.25 (2H, s, $C\underline{H}_2Ph$), 7.37 (5H, s, Ph); ^{13}C δ(100.61 MHz, $CDCl_3$) 50.3 (C2), 67.5 ($\underline{C}H_2Ph$), 128.5, 128.7, 134.8 (Ar), 168.1 (C1); m/z (EI) 191 (M^+), 144, 119, 108, 91, 77, 65.

1i: purified by distillation; b.p. 135 °C/ 0.5 mmHg (Kugelrohr), followed by flash chromatography (9:1 hexane / diethyl ether), clear colourless oil; ν_{max} (film) 2122, 1747 cm^{-1}; ^{1}H δ(400 MHz, $CDCl_3$) 1.49 (3H, d J 7.2, H-3), 3.98 (1H, q J 7.2, H-2), 5.22 (2H, s, $C\underline{H}_2Ph$), 7.37 (5H, s, Ph); m/z (EI) 132, 105, 91 (base), 77, 65.

1j: prepared as described[32]: m.p. 58-61 °C (from hexane/ ethanol); lit.[32] m.p. 61-62°C (diethyl ether/ ethanol); $[\alpha]^{25}_D$ = +18.0 (c 0.9, $CHCl_3$); lit.[32] $[\alpha]^{25}_D$ = +18.2

(c 0.9, $CHCl_3$); lit.[28] $[\alpha]^{25}_D$ = +19 (c 0.7, $CHCl_3$); IR spectra data identical to those reported[32]; ^1H δ(400 MHz, $CDCl_3$) 0.66 (3H, s, Me), 0.79 (3H, s, Me), 0.872 (3H, d J 6.6, $CHMe_2$), 0.877 (3H, d J 6.6, $CHMe_2$), 0.91 (3H, d J 6.5 CHMe), 0.7-1.8 (31 H, m), 1.97 (1H, dt J 12.2, 3.2), 3.89 (1H, $W_{1/2}$= 6 Hz, H-3).

1e: *cis* and *trans* 3-aminomethyl-3,5,5-trimethyl-cyclohexanol (1.410 g, 8.23 mmol) reacted with benzyl chloroformate following literature procedure[33]: Purification by flash chromatography (7:3 to 1:1 dichloromethane / ethyl acetate) gave *cis* and *trans* (N-benzyloxycarbonyl)-3-aminomethyl-3,5,5-trimethyl-cyclohexanol **11** (2.246 g, 89 %) as a clear colourless viscous oil, ν_{max} (film) 3360 1719 cm^{-1}; ^1H δ(400 MHz, $CDCl_3$) 0.91, 0.96 (3H, s, Me), 1.03 (6H, s, Me), 1.0-1.9 (6H, m, H-2, H-4, H-6), 2.99 (2H, m, CH_2NH), 3.95 (1H, m, H-1), 4.78 (1H, br), 4.87 (1H, br), 5.11 (2H, s, CH_2PH), 7.38 (5H, s, Ph); m/z (EI) 305 (M^+), 123, 104, 91; HRMS calcd. for $C_{18}H_{27}NO_3$: 305.1999 found: 304.9824. Diethyl azodicarboxylate (0.93 ml, 5.93 mmol) was added dropwise (3 min) to a stirred solution of **11** (1.647 g, 5.39 mmol) and triphenylphosphine (1.56 g, 5.93 mmol) in anhydrous benzene (30 ml) and hydrazoic acid (4.98 ml of 1.3 M solution in benzene, 6.47 mmol) under argon at room temperature (water bath). After being stirred for 24 h the reaction mixture was evaporated and the crude product was chromatographed on silica gel column (6:4 to 1:1 hexane / dichloromethane) to afford **1e** (0.765 g, 43%) as a clear colourless viscous oil; ν_{max} (film) 3349 (br), 2099, 1730 cm^{-1}; ^1H δ(400 MHz, $CDCl_3$) 0.92 (3H, s, Me), 0.98 (3H, s, Me), 1.03 (3H, s, Me), 1.1-1.8 (6H, m, H-2, H-4, H-6), (2.91 (dd J 14.0, 5.2), 2.99 (d J 6.7) and 3.71 (m), (2H, CH_2NH)), 3.55 (1H, dd J 13.8, 7.9, H-1), 4.78, 4.85 (1H, br, NH), 5.12 (2H, s, CH_2Ph), 7.38 (5H, s, Ph); m/z (EI) 302 (M^+-N_2), 287, 231, 172, 91.

1f: A mixture of (S)-N-*tert*-butoxycarbonylprolinol methanesulfonate, (prepared according to literature method[34], 0.227 g, 0.81 mmol), sodium azide (0.108 g, 2 eq.) and tetrabutylammonium bromide (0.013 g, 5 mmol%) in anhydrous dimethylformamide (2 ml) was stirred at 80 °C under argon, for 16 h. The solvent was removed *in vacuo* and diethyl ether (20 ml) was added. The mixture was filtered, evaporated to dryness, and chromatographed on a silica gel column (9:1 hexane / diethyl ether) to afford **1f** (0.142 g, 77%) as a clear colourless oil; $[\alpha]^{25}_D$ = -49.5 (c 1.16, $CHCl_3$); ν_{max} (film) 2111 1696 cm^{-1}; ^1H δ(400 MHz, $CDCl_3$) 1.47 (9H, s, *t*-Bu), 1.81-1.99 (4H, m), 3.37 (3H, $W_{1/2}$ = 15 Hz), 3.57 (1H, m), 3.94 (1H, m); m/z (FAB) 227 (MH^+), 171, 153, 127, 125, 114.

1k: prepared as described in the literature[15a].

4 : purified by distillation; b.p. 98 °C/ 20 mmHg; clear colourless oil; ν_{max} (film) 2099 cm^{-1}; ^1H δ(400 MHz, $CDCl_3$) 1.29 (3H, d J 6.5, H-5), 1.52-1.79 (4H, m, H-2, H-3), 3.31 (2H, t J 6.6, H-1), 3.48 (1H, sextet, J 6.4, H-4); ^{13}C δ(100.61 MHz, $CDCl_3$) 19.32 (C5), 25.45 (C2 or C3), 33.24 (C2 or C3), 51.04 (C1), 57.37 (C4); m/z (EI) 100, 98, 97, 84, 83, 70, 57.

7: diisopropyl azodicarboxylate (0.87 ml, 4.39 mmol) was added dropwise (5 min) to a stirred solution of 1,5-hexanediol (0.247 g, 2.09 mmol) and triphenylphosphine (1.15 g, 4.39 mmol) in anhydrous diethyl ether (20 ml) and hydrazoic acid (3.5 ml of 1.3 M solution in benzene, 4.6 mmol) under argon at room temperature (water bath). After being stirred for 14 h the reaction mixture was evaporated and the crude product was chromatographed on a silica gel column (hexane) to afford **7** (0.204 g, 58%) as a clear colourless oil; ν_{max} (film) 2105 cm^{-1}; ^1H δ(400 MHz, $CDCl_3$) 1.27 (3H, d J 6.6, H-6), 1.43-1.64 (6H, m, H-2, H-3, H-4), 3.29 (2H, t J 6.8, H-1), 3.45 (1H, sextet J 6.6, H-5); ^{13}C δ(100.61 MHz, $CDCl_3$) 19.29 (C6), 23.22 ($\underline{C}H_2$), 28.54 ($\underline{C}H_2$), 35.63 ($\underline{C}H_2$), 51.17 (C1), 57.67 (C5); m/z (EI) 111, 96, 82, 70, 57.

9: was prepared from 2-ethyl-1,3-hexanediol (0.412 g, 2.82 mmol, mixture of isomers) using the procedure reported earlier for **7**. The mixed isomers of diazide **9** (0.262 g, 51%) were obtained as a clear colourless oil; ν_{max} (film) 2105 cm^{-1}; ^1H δ(400 MHz, $CDCl_3$) 0.93-0.98 (6H, m), 1.26-1.62 (7H, m), 3.32-3.53 (3H, m, H-1 and H-3); ^{13}C δ(100.61 MHz, $CDCl_3$) 11.33, 11.82 (Me), 13.76, 14.03 (Me), 19.63, 20.06 ($\underline{C}H_2$), 21.78 ($\underline{C}H_2$), 33.66, 33.96 ($\underline{C}H_2$), 43.83, 43.94 (C2), 51.34, 52.04 (C3), 63.39, 63.70 (C1); m/z (EI) 127, 113, 97, 70.

Conversion of azides 1 into N-Boc-amines 2.

General procedure (for specific conditions of each example see table 2): To a stirred solution of **1h** (114.5 mg, 0.60 mmol) in anhydrous diethyl ether (4 ml) at room temperature under argon was added dropwise tri-*n*-butylphosphine (157 μl, 1.1 eq). After 1h (gas liberation has ceased) the reaction mixture was cooled to -50 °C and a solution of di-t-butyl dicarbonate (144.0 mg, 1.1 eq) in anhydrous diethyl ether (2 ml) was added dropwise *via* canula. The mixture was stirred for another hour at -50 °C. Saturated aqueous sodium bicarbonate (2 ml) was added, the cooling bath was removed, the reaction mixture was allowed to warm to room temperature and was partitioned between diethyl ether (20 ml) and saturated aqueous sodium bicarbonate (20 ml). The aqueous phase was extracted with

diethyl ether (2 x 20 ml), the combined organic layers were dried ($MgSO_4$), filtered, evaporated to dryness and chromatographed on a silica gel column (7:3 hexane: diethyl ether) to afford **2h** (128.6 mg, 81 %) as a white solid; m.p. 72.5-73.5 °C (hexane); reported[35] m.p. 72-73 °C and 74-75 °C (light petroleum).

2a: purified by flash chromatography (9.5 / 0.5 hexane / diethyl ether); yield 79%; clear colourless oil, ν_{max} (film) 3360, 1696 cm^{-1}; ^1H δ(400 MHz, $CDCl_3$) 0.88 (3H, t J 5.7, H-8), 1.27 (12H, m, H-2 to H-7), 1.44 (9H, s, *t*-Bu), 3.10 (2H, m, H-1), 4.46 (1H, br, NH); m/z (FAB) 231, 174, 154, 128, 107, 89; HRMS calcd. for $C_{13}H_{28}NO_2$: 230.2120 , found: 230.2124.

2b: purified by flash chromatography (9:1 hexane / diethyl ether); yield 78%; as white needles, m.p. 55.5-56 °C (hexane); lit.[36] m.p. 54-55 °C; lit.[3b] m.p. 56-57 °C; identical spectral data to those reported[36,37]; m/z (FAB) 176, 152, 137, 127, 106; HRMS calcd. for $C_{12}H_{19}NO_2$: 209.1416, found: 209.1433.

2c: purified by flash chromatography (9:1 hexane / diethyl ether); yield 81%; white needles, m.p. 50-50.5 °C (hexane); identical spectral data to those reported[37]; Anal. calcd. for $C_{13}H_{19}NO_3$: C 65.80, H 5.90, N 8.07%. Found:C 66.27, H 6.01, N 8.31%.

2d: purified by flash chromatography (8 / 2 hexane / diethyl ether); yield 31%; white needles, m.p. 76 - 77 °C (hexane); lit.[20] m.p. 88 °C; identical spectral data to those reported[20]; Anal. calcd. for $C_{13}H_{19}NO_2$: C 70.56, H 8.65, N 6.33%. Found:C ,70.29 H 8.61, N 6.37%. Starting from **1d** (0.085 g, 0.58 mmol), when the reaction was performed by adding 4-dimethylaminopyridine (one crystal) before Boc_2O addition, the products isolated by flash chromatography (9:1 hexane / diethyl ether) were in order of elution; di-(1-penyl-ethyl)carbodiimide **3** (0.056 g, 77%) as a clear colourless oil; mixture of two isomers; ν_{max} (film) 2122 cm^{-1}; ^1H δ(400 MHz, $CDCl_3$) 1.45 (3H, d J 6.7, $CHC\underline{H}_3$), 1.46 (3H, d J 6.7, $CHC\underline{H}_3$), 4.54 (1H, q J 6.7, C<u>H</u>Me), 4.55 (1H, q J 6.7, C<u>H</u>Me), 7.23-7.33 (10H, m, Ar); ^{13}C δ(100.61 MHz, $CDCl_3$) 24.6 ($\underline{C}H_3$), 56.7 (<u>C</u>HMe), 125.9, 127.3, 128.5, 140.4, 143.6; m/z (EI) 250 (M^+), 235, 191, 145, 131, 105; HRMS calcd for $C_{17}H_{18}N_2$: 250.1470, found: 250.1468 and **2d** (0.013 g, 10%).

2e: purified by flash chromatography (6:4 hexane / diethyl ether); yield 56%; clear colourless viscous oil, ν_{max} (film) 3417 1730 cm^{-1}; ^1H δ(400 MHz, $CDCl_3$) 0.89 (3H, s, Me), 0.96 (3H, s, Me), 1.02 (3H, s, Me), 1.1-1.9 (6H, m, H-2, H-4, H-6), (2.89 (dd J 14.0, 5.1), 2.97 (d J 6.7) and 3.75 (m), (2H, $C\underline{H}_2NH$)), 3.53 (1H, dd J 13.9, 7.9, H-1), 4.75, 4.83 (1H, br, NH), 5.11 (2H, s, $C\underline{H}_2Ph$), 7.37 (5H, s, Ph);

m/z (FAB) 405 (MH^+), 349, 305, 288, 241, 215; HRMS calcd for $C_{23}H_{37}N_2O_4$: 405.2753 found: 405.2755.

2f: purified by flash chromatography (7:3 hexane / diethyl ether); yield 69%; white plates; m.p. 101-102°C (hexane); $[\alpha]^{25}_D$ = -44.3 (c 1.0, $CHCl_3$); ν_{max} (film) 3360 1690 cm^{-1}; ^1H δ(400 MHz, $CDCl_3$) 1.43 (9H, s, *t*-Bu), 1.47 (9H, s, *t*-Bu), 1.79-1.91 (4H, m), 3.20 (2H, $W_{1/2}$=28 Hz), 3.33 (2H, $W_{1/2}$=19 Hz), 3.44 (1H, br), 3.88 (1H, m), 4.95 (1H, $W_{1/2}$=26 Hz, NH); m/z (EI) 183, 170, 127, 114, 70, 57; Anal. calcd. for $C_{15}H_{28}N_2O_4$: C ,59.98 H ,9.40 N 9.33%. Found:C 59.58, H ,9.56 N 9.17%.

2g: purified by flash chromatography (9:1 hexane / diethyl ether); yield 80%; white needles; m.p. 65.5-66°C (hexane); lit.[38] 64°C; ν_{max} (film) 3372, 1753 1719 cm^{-1}; spectral data identical to those reported[38];Anal. calcd. for $C_{11}H_{21}NO_4$: C 57.12, H 6.06, N 9.15%. Found:C 57.14, H 6.09, N 9.39%.

2i: purified by flash chromatography (8:2 hexane / diethyl ether); yield 18%; white plates, m.p. 29.5-30 °C (hexane); lit.[35] m.p. 25.5-26 °C (light petroleum); ν_{max} (film) 3372, 1747, 1713 cm^{-1}; ^1H δ(400 MHz, $CDCl_3$) 1.39 (3H, d J 7.2, H-3), 1.43 (9H, s, *t*-Bu), 4.36 (1H, br, H-2), 5.05 (1H, br, NH), 5.14 (1H, d J 12, C<u>H</u>$_2$Ph), 5.20 (1H, d J 12, C<u>H</u>$_2$Ph), 7.38 (5H, s, Ph).

2j: purified by flash chromatography (1:1 hexane / dichloromethane); yield 56%; white needles, m.p. 147-148°C (hexane); $[\alpha]^{25}_D$ = +25.4 (c 0.45, $CHCl_3$); ν_{max} (film) 3349, 1713 cm^{-1}; ^1H δ(400 MHz, $CDCl_3$) 0.65 (3H, s, Me), 0.79 (3H, s, Me), 0.869 (3H, d J 6.6, CHC<u>H</u>$_3$), 0.873 (3H, d J 6.6, CHC<u>H</u>$_3$), 0.91 (3H, d J 6.4, CHC<u>H</u>$_3$), 1.46 (3H, s, *t*-Bu), 0.7-1.8 (31H, m), 1.97 (1H, dt J 12.4, 3.3), 3.85 (1H, $W_{1/2}$=21 Hz, H-3), 4.84 (1H, $W_{1/2}$=19 Hz, NH); Anal. calcd. for $C_{32}H_{57}NO_2$: C 78.79, H 11.78, N 2.87%. Found:C 78.74, H 11.56, N 2.97%. Preparation of <u>authentic sample</u>: A solution of **1j** (29.5 mg, 0.071 mmol) in ethyl acetate (2 ml) was reacted with H_2, Pd/C and Boc_2O following literature procedure[3a]. The crude product was purified as before to give **2j** (34.4 mg, 99 %), m.p. 147.5-148.5°C (hexane); $[\alpha]^{25}_D$ = +26.1 (c 0.41, $CHCl_3$); +24.6 (c 1.05, $CHCl_3$).

2k: purified by flash chromatography (9.5:0.5 hexane / diethyl ether); yield 32%; white needles, m.p. 137-138°C (diethyl ether / hexane); lit.[39] m.p. 137°C; lit.[40] m.p. 136°C; ν_{max} (film) 3309, 1690 cm^{-1}; ^1H δ(400 MHz, $CDCl_3$) 1.52 (3H, s, *t*-Bu), 6.46 (1H, br, NH), 7.03 (1H, t J 7.3, Ph), 7.29 (2H, dd J 8.0, 7.3, Ph), 7.35 (1H, d J 8.0, Ph); Anal. calcd. for $C_{11}H_{15}NO_2$: C 68.37, H 7.82, N 7.25%. Found: C 68.22, H 7.88, N 7.27%.

5 and **6**: The crude mixture was purified by flash chromatography (8.5 / 1.5 to 0 / 1 hexane / diethyl ether) to give, in order of elution; **5** yield 15%; clear colourless viscous oil, ν_{max} (film) 3343, 2111, 1702 cm^{-1}; ^1H δ(400 MHz, $CDCl_3$) 1.26 (3H, d J 6.4, H-5), 1.45 (9H, s, *t*-Bu), 1.47-1.62 (4H, m, H-2 and H-3), 3.14 (2H, d, J 5.9, H-1), 3.47 (1H, quintet, J 6.4, H-4), 4.55 (1H, br $W_{1/2}$=24.5 Hz, NH); ^{13}C δ(100.61 MHz, $CDCl_3$) 19.3 (C5), 26.7 (C2 or C-3), 28.3 ($C(\underline{C}H_3)_3$), 33.3 (C2 or C3), 40.1 (C1), 57.5 (C4), 79.1 ($\underline{C}Me_3$), 155.9 (CO); m/z (FAB) 229 (MH^+), 201, 186, 173, 154; HRMS calcd. for $C_{10}H_{21}N_4O_2$: 229.1664; found: 229.1666; and **6** yield 25%, after two crystallizations (dichloromethane / hexane); white cubes; m.p. 172-174°C (ethanol / diethyl ether); ν_{max} (nujol) 3338, 1690, 1628, cm^{-1}; ^1H δ(400 MHz, $CDCl_3$) 1.12 (6H, d J 6.4, H-5), 1.44 (18H, s, *t*-Bu), 1.42-1.53 (8H, m, H-2 and H-3), 3.12 (4H, m, H-1), 3.76 (2H, quintet, J 6.4, H-4), 4.34 (2H, br $W_{1/2}$=18.2 Hz, NH), 4.73 (2H, br $W_{1/2}$=18.2 Hz, NH); ^{13}C δ(100.61 MHz, $CDCl_3$) 21.7 (C5), 26.8 (C2 or C3), 28.4 ($C(\underline{C}H_3)_3$), 34.5 (C2 or C3), 40.4 (C1), 45.7 (C4), 79.1 ($\underline{C}Me_3$), 156.2 ($\underline{C}ONHBoc$), 157.5 (CO); m/z (FAB) 431 (MH^+), 331, 312, 257, 231, 203; Anal. calcd. for $C_{21}H_{42}N_4O_5$: C 58.58, H 9.83, N 13.01%. Found:C 58.32, H 9.62, N 12.75%. Preparation of <u>authentic sample</u>: **5** (0.303 g, 1.97 mmol) in ethanol (2 ml) was reacted with H_2 (balloon), and Pd/C 10% (21 mg) with vigorous stirring at room temperature for 15 h. The mixture was filtered, evaporated to dryness and the residue was reacted with bis(4-nitrophenyl)carbonate following literature procedure[13]. The crude product was purified by flash chromatography (diethyl ether) to give **6** (0.032 g, 47 %), m.p. 168-171°C (dichloromethane / hexane).

8: purified by flash chromatography (8:2 to 0:1 hexane / diethyl ether); yield 32%, clear colourless viscous oil, ν_{max} (film) 3338, 1702, 1657 cm^{-1}; ^1H δ(400 MHz, $CDCl_3$) 1.10 (6H, d J 6.6, H-6), 1.35-1.73 (12H, m), 1.44 (18H, s, *t*-Bu), 3.10 (4H, d J 6.1, H-1), 3.76 (2H, quintet, J 6.6, H-5), 4.65 (2H, br $W_{1/2}$=21 Hz, NH), 4.78 (2H, br $W_{1/2}$=21 Hz, NH); ^{13}C δ(100.61 MHz, $CDCl_3$) 21.5 (C6), 23.7 ($\underline{C}H_2$), 28.2 ($C(\underline{C}H_3)_3$), 29.6 ($\underline{C}H_2$), 37.1 ($\underline{C}H_2$), 40.2 (C1), 45.0 (C5), 78.6 ($\underline{C}Me_3$), 156.0 (CONHBoc), 157.9 (CO); m/z (FAB) 459 (MH^+), 359, 285, 259, 215, 187; HRMS calcd. for $C_{23}H_{47}N_4O_5$: 459.3546; found: 459.3541.

10: purified by flash chromatography (9:1 to 1:1 hexane / diethyl ether); yield 34%, white solid, mixture of isomers; ν_{max} (film) 3338, 1702, 1656 cm^{-1}; ^1H δ(400 MHz, $CDCl_3$) 0.86-0.97 (12H, m), 1.24-1.54 (14H, m), 1.43 (9H, s, *t*-Bu), 3.02-3.90 (6H, m), 4.53-6.0 (4H, m, NH); ^{13}C δ(100.61 MHz, $CDCl_3$) 12.04

(Me), 13.46, 13.90 (Me), 19.55, 19.85 ($\underline{C}H_2$), 21.84 ($\underline{C}H_2$), 35.57, 35.82 ($\underline{C}H_2$), 40.80, 40.11 (C1), 44.56, 45.64 (C2), 49.39 50.58 (C3), 78.9 ($C(\underline{C}H_3)_3$), 156.4, 156.6 (CONHBoc), 158.8, 159.3 (CO); m/z (FAB) 515 (MH^+), 415, 342, 315, 298, 286, 243; HRMS calcd. for $C_{27}H_{54}N_4O_5$: 515.4173; found: 515.417.

Acknowledgements: We would like to thank JNICT for financial support (project PBIC/C/EN 1048/92), S. Candeias and E. Cabrita for providing the azides **1d** and **1k**, Dr. M. Mata and Dr. S. Caddick for helpful comments and Prof. W. B. Motherwell for his encouragement.

References and Notes

1 a) Larock, R. C. *Compreensive Organic Transformations: A Guide to Functional Group Preparations*; VCH Publishers, Inc. 1989. b) Scriven, E. F. V.; Turnbull, K. *Chem. Rev.* **1988**, 88, 297.

2 Greene, T. W.; Wuts, G.P. *Protective Groups in Organic Synthesis*, 2nd ed., John Wiley & Sons, INC, 1991.

3 a) Saito, S.; Nakajima, H.; Inaba, M.; Moriwake, T. *Tetrahedron Lett.* **1989**, 30, 837. b) Kotsuki, H.; Ohishi, T.; Araki, T. *Tetrahedron Lett.* **1997**, 38, 2129.

4 For reviews, see: a) Gololobov, Y. G.; Kasukhin, L. F. *Tetrahedron* **1992**, 48, 1353. b) Johnson, A. W.; Kaska, W. C.; Starzewski, K. A. O.; Dixon, D. A. *Ylides and Imines of Phosphorus*; John Wiley & Sons, Inc; **1993**; pp. 435. c) Taber, D. F.; You, K. K. *J. Am. Chem. Soc.* **1995**, 117, 5757.

5 a) Heathcock, C. H.; Smith, S. C.*J. Org. Chem.* **1994**, 59, 6828. b) Ganem, B.; Nagarajan, S. *J. Org. Chem.* **1987**, 52, 5044.

6 Some reported examples of hydrolysis using basic conditions: a) Kappe, Th.; Pfaffenschlager, A.; Stadlbauer, W. *Synthesis* **1989**, 666. b) Baum, K.; Berkowitz, P.; Grakauskas, V.; Archibald, T. G. *J. Org. Chem.* **1983**, 48, 2953. c) Mungall, W. S.; Greene, G. L.; Heavner G. A.; Letsinger R. L. *J. Org. Chem.* **1975**, 40, 1659. d) Murashi, S.-I.; Tanigawa, Y.; Imada, Y.; Taniguchi, Y. *Tetrahedron Lett.* **1986**, 27, 227. e) Katritzky, A. R.; Jiang, J.; Urogdi, L. *Tetrahedron Lett.* **1989**, 25, 3303.

7 Some reported examples of hydrolysis using acidic conditions: a) Koziara, A.; Osowska-Pacewicka, K.; Zawadzki, S.; Zwierzak, A. *Synthesis* **1985**, 202. b) Koziara, A.; Zwierzak, A. *Tetrahedron Lett.* **1987**, 28, 6513. c) Hankovszky, H. O.; Hideg, K.; Lex, L. *Synthesis* **1981**, 147. d) Fabiano, E.; Golding, B. T.; Sadeghi, M. M. *Synthesis* **1987**, 190. e) Knouzi, N.; Vaultier, M.; Carrié, R. *Bull. Soc. Chim. Fr* **1985**, 815.

8 Afonso, C. A. M. *Tetrahedron Lett.* **1995**, 36, 8857.

9 When ethyl amine (10 eq.) was added to the reaction mixture of azide **1h**/tri-n-butylphosphine at -50 °C followed by $H_2O/NaHCO_3$ work-up, the product **2h** was isolated in the same overall yield.

10 Using a 1:1 mixture of the iminophosphorane of **1h** (0.14 mmol) and benzylamine in $CDCl_3$ (0.5 ml) at room temperature, no amine-iminophosphorane exchange was observed by ^1H NMR.

11 See ref. 4b pag. 416.

12 When $ZnCl_2$ (1.2 eq), $Ti(OiPr)_4$ (1 eq) or $ClTi(OiPr)_3$ (1 eq) where used, only traces of **2h** and **2b** were detected by TLC.

13 An authentic sample of **6** was prepared from monoazide **5** using known methodology for the synthesis of symmetrical ureas: Izdebski, J.; Pawlak, D. *Synthesis* **1989**, 423.

14 The formation of more polar compounds was observed but they were unsuccessfully isolated because of extensive contamination with tri-*n*-butylphosphine oxide.

15 a) Molina, P.; Alajarín, M.; Sánchez-Andrada, P. *J. Org. Chem.* **1994**, 59, 7306. b) The effect of DMAP on the conversion of amines to isocyanates using Boc_2O/DMAP has been recently studied: Knölker, H.-J.; Braxmeier, T.; Schlechtingen, G. *Angew. Chem. Int. Ed. Engl.* **1995**, 34, 2497; Knölker, H.-J.; Braxmeier, T.; Schlechtingen, G. *Synlett* **1996**, 502.

16 Vedejs, E.; Diver, S. T. *J. Am. Chem. Soc.* **1993**, 115, 3358.

17 Afonso, C. M. A; Barros, M. T.; Godinho, L. S.; Maycock, C. D. *Tetrahedron* **1994**, 50, 9671 and references cited therein.

18 Ed. Verkade, J. G.; Quin, L. D. *Methods in Stereochemical Analysis: Phosphrous-31 NMR Spectroscopy in Stereochemical Analysis; Organic Compounds and Metal Complexes;* VCH Publishers, 1987.

19 Bosch, I.; González, A.; Urpí, F.; Vilarrasa, J. *J. Org. Chem.* **1996**, 61, 5638.

20 Alkyl isocyanates are known to react slowly at room temperature with tertiary

alcohols to give the corresponding carbamates: Benalil, A.; Roby, P.; Carboni, B.; Vaultier, M. *Synthesis* **1991**, 787..

21 Koziara, A.; Osowska-Pacewicka, K.; Zawadzki, S.; Zwierzac, A. *Synthesis* **1985**, 202.

22 Reeves, W. P.; Bahr, M. L. *Synthesis* **1976**, 823.

23 Lieber, E.; Chao, T. S.; Rao, C. N. R. *J. Org. Chem.* **1957**, 22, 238.

24 Rolla, F. *J. Org. Chem.* **1982**, 47, 4327.

25 Alvarez, S. G.; Alvarez, M. T. *Synthesis* **1997**, 413.

26 Moulin, F. *Helv. Chim. Acta* **1952**, 35, 167.

27 Juranic, I.; Husinec, S.; Savic, V.; Porter, A. E. A *Collect. Czech. Chem. Commun.* **1991**, 56, 411.

28 Viaud, M. C.; Rollin, P. *Synthesis* **1990**, 130.

29 Ito, M.; Koyakumaru, K.-I.; Ohta, T.; Takaya, H. *Synthesis* **1995**, 376.

30 Barton, D. H. R.; Chavasiri, W. *Tetrahedron* **1994**, 50, 47.

31 Moore, A. T.; Rydon, H. N. *Org. Synth.* **1965**, 42, 47.

32 Loibner, H.; Zbiral, E. *Helv. Chim. Acta* **1976**, 59, 2100.

33 Schmidt, U.; Lieberknecht, A.; Griesser, H.; Utz, R.; Beuttler, T.; Bartkowiak, F. *Synthesis* **1986**, 361.

34 Hiroi, K.; Abe, J. *Chem. Pharm. Bull.* **1991**, 39, 616.

35 Gunnarsson, K.; Ragnarsson, U. *Acta Chem. Scand.* **1990**, 44, 944.

36 Padwa, A.; Dean, D. C.; Fairfax, D. J.; Xu, S. L. *J. Org. Chem.*

37 Tanaka, K.-I.; Yoshifuji, S.; Nitta, Y. *Chem. Pharm. Bull.* **1988**, 36, 3125.

38 Münster, P.; Steglich, W. *Synthesis* **1987**, 223.

39 Muchowski, J. M.; Venuti, M. C. *J. Org. Chem.* **1980**, 45, 4798.

40 Knoevenagel, E. *Justus Liebigs Ann. Chem.* **1897**, 297, 113.

(Received in The Netherlands 11 August 1997)