Tetrahedron Letters 49 (2008) 6445–6447

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A convenient transformation of α-alkylserines into α-halogenomethyl-α-alkylglycines

Adam Kudaj, Aleksandra Olma *

Institute of Organic Chemistry, Technical University, 90-924 Łódź, Żeromskiego 116, Poland

ARTICLE INFO

Article history:
Received 4 July 2008
Revised 18 August 2008
Accepted 27 August 2008
Available online 31 August 2008

Keywords:
N-Boc-α-chloromethyl-α-alkylglycines
N-Boc-α-bromomethyl-α-alkylglycines
N-Boc-α-alkylserine β-lactones
α,α-Disubstituted glycines
Mitsunobu reaction

ABSTRACT

An efficient and facile synthesis of *N*-Boc-α-chloromethyl- and α-bromomethyl-α-alkylglycines is reported that involves cyclization of *N*-Boc-α-alkylserines to the corresponding β-lactones under Mitsunobu reaction conditions, followed by ring opening with anhydrous $MgCl_2$ or $MgBr_2$.

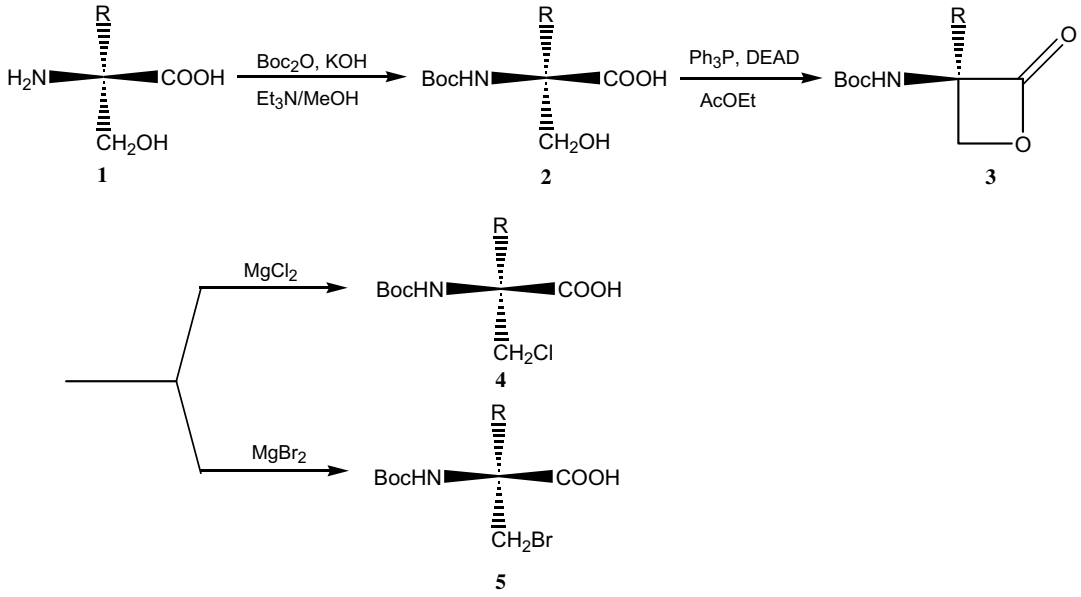
1. Introduction

α,α-Disubstituted glycines have been used widely in medicinal chemistry and biochemistry to restrict the flexibility of peptides and to enhance their potency and their resistance toward enzymatic hydrolyses.[1] Incorporation of this moiety into biologically active peptides might become a powerful method for the design of peptidomimetic therapeutics. Moreover the α,α-disubstituted glycines are often found in nature either in the free form or as constituents of biologically active natural products.[2] The biological significance and synthetic utility of α,α-disubstituted glycines continue to stimulate the development of new routes to these compounds. Our research has focused on the synthesis of constrained amino acid building blocks, α-alkylserines, and their incorporation into biologically active peptidomimetics.[3] Recently, we reported the synthesis of optically pure N-protected and free 3-amino-3-alkyl-2-oxetanones from α-alkylserines.[4] These β-lactones are excellent starting materials for further derivatization in medicinal chemistry. The ring opening of alkylserine lactones with sulfur nucleophiles resulted in S-protected *N*-Boc-α-alkylcysteines.[5] The use of sodium azide as a nucleophile provides *N*-Boc-α-alkyl-β-azidoalanines, which can be readily reduced to the corresponding *N*-Boc-α-alkyl-β-aminoalanines.[6] The optically active *N*-Boc-α-alkylserines, used as starting materials, are easily available following the procedure developed in our laboratory, involving the synthesis of the racemic α-hydroxymethyl analogue of various amino acids[7] and their resolution by fractional crystallization of appropriate diastereoisomeric salts. The absolute configuration of some α-hydroxymethylamino acids was determined by chemical correlation with the relevant α-methylamino acids or by X-ray analysis.[8] α-Alkylserines could also be obtained via the diastereoselective alkylation of pyramidalized bicyclic serine enolates (bicyclic *N,O*-acetals derived from serine).[9] The ease with which α-hydroxymethyl-α-amino acids can be prepared from the parent amino acids encouraged us to explore the possibility of utilizing these derivatives as starting materials for the synthesis of α-halogenomethyl-α-amino acids. Our attempts to transform the hydroxymethyl group into a chloromethyl group using the standard conditions for the transformation of serine into chloromethylalanine[10] failed. The low reactivity of the hydroxyl group may be explained by its location being similar to the neopentyl position.

Herein, we present the use of *N*-Boc-α-alkylserine β-lactones for the preparation of N-protected α-halogenomethyl-α-alkylamino acids. Only a few synthetic strategies directed toward the synthesis of the selected α-halogenomethylamino acids have been described.[11–14] Bey et al.[11] obtained various racemic α-halogenomethylamino acids in the regioselective alkylation of a Schiff base ester of amino acids with halomethanes. Han and Frey[12] synthesized *N*-benzylidene-D,L-α-bromomethylalanine ethyl ester by the alkylation reaction of *N*-benzylidene-D,L-alanine ethyl ester with CH_2Br_2 in the presence of potassium *tert*-butoxide and 18-crown-6. Furthermore, Kedrowski and Heathcock have described the synthesis of $ZNHC(CH_3)(CH_2X)COOMe$ (X = Cl, I) by alkylation

* Corresponding author. Tel.: +48 426313144; fax: +48 426365530.
E-mail address: aleksandra.olma@p.lodz.pl (A. Olma).

0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.08.098



R=CH_3 (**a**), $CH_2CH(CH_3)_2$ (**b**), $CH(CH_3)_2$ (**c**), $CH_2C_6H_5$ (**d**)

Scheme 1. Synthesis of α-chloromethyl-**4** and α-bromomethyl-α-alkylglycines **5**.

of 2-aryl-3-carbobenzyloxy oxazolidinones with ICH_2X.[13] Buchanan et al. obtained racemic γ-fluoroglutamic acid via two independent methods, both of which involved a Michael reaction.[14]

Scheme 1 outlines our method for the synthesis of N-protected α-chloromethyl- and α-bromomethyl-α-alkylamino acids.

The starting *N*-Boc-α-alkylserines **2** were synthesized from the potassium salt of α-alkylserines **1** and Boc_2O in boiling methanol in the presence of triethylamine as a base. Using these reaction conditions, we were able to obtain products **2** in high yields (79–84%) after 3–4 h. The standard procedure for the synthesis of *N*-Boc-α-alkylserines usually takes two to three days.[3] We optimized the conditions for the synthesis of **3**, using anhydrous ethyl acetate instead of THF. Most of the side products (mainly *N,N′*-diethoxycarbonylhydrazine) could be removed by filtration, which significantly simplified the purification procedure. The ring opening of *N*-Boc-α-alkylserine lactones **3** with magnesium chloride resulted in the formation *N*-Boc-α-chloromethyl-α-alkylglycines in 86–91% yields. The use of magnesium bromide provided *N*-Boc-α-bromomethyl-α-alkylglycines in 95–99% yields.

2. General procedure for the preparation *N*-Boc-α-hydroxymethylamino acids 2

A mixture of α-hydroxymethylamino acid **1** (20 mmol), KOH (1.12 g, 20 mmol), Et_3N (5.56 ml, 40 mmol), and methanol (40–60 ml) was stirred and heated under reflux, to afford a homogenous solution, and then Boc_2O (6.54 g, 30 mmol) dissolved in MeOH (5 ml) was added. The reaction mixture was stirred under reflux for 90 min, and an additional amount of Boc_2O (2.18 g, 10 mmol) was added. After 30 min stirring and heating, the reaction was continued at room temperature for another 90 min after which the methanol was evaporated. The residue was dissolved in water and extracted with diethyl ether (2 × 10 ml). The aqueous layer was cooled to 5–10 °C, acidified to pH 2–3 with 1 N $NaHSO_4$, saturated with NaCl, and extracted with EtOAc (3 × 50 ml). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The resulting colorless oil was crystallized from AcOEt/*n*-hexane (v/v 1:20) to yield *N*-Boc-α-alkylserines in 79–84% yields. Identification of compounds **2** was accomplished by comparison of the obtained data with those previously described by us.[3]

3. General procedure for the preparation *N*-Boc-α-alkylserine-β-lactones 3

To a solution of triphenylphosphine (866 mg, 3.3 mmol) in dry ethyl acetate (6 ml), DEAD (3.3 mmol) was added at −10 °C. The mixture was stirred for 15 min, and then *N*-Boc-α-alkylserine (3 mmol) was added. Stirring was continued for 1.5 h at −10 °C and then for 1.5 h at room temperature. The mixture was diluted with *n*-hexane (6 ml) and allowed to stand in a refrigerator for 2 h. The solid *N,N′*-diethoxycarbonylhydrazine and triphenylphosphine oxide were removed by filtration. The filtrate was concentrated in vacuo, and the oily residue was purified by flash chromatography on silica gel 60 (43–60 mesh) using ethyl acetate-*n*-hexane (1:3 and then 1:1) as eluent. The *N*-Boc-α-alkylserine-β-lactones were obtained in 74–85% yields. Compounds **3a–d** were characterized on the basis of ^1H NMR data.[15] The spectral data of compound **3d** are the same as those described by Broadrup et al.[16]

4. General procedure for the preparation of *N*-Boc-(*S*)-α-chloromethyl 4 and *N*-Boc-(*S*)-α-bromomethyl-α-alkylglycines 5, ((*S*)-2-alkyl-2-*N*-(*tert*-butoxycarbonyl)amino-3-halogenopropionic acids)

Anhydrous $MgCl_2$ or $MgBr_2$ (2 mmol) was suspended in dry THF and sonicated for 10 min, and then *N*-Boc-α-alkylserine-β-lactone **3** (1 mmol) was added as a solid. The mixture was stirred for 15–90 min (TLC). The solvent was removed in vacuo at 35 °C, and the residue was dissolved in water, washed with diethyl ether (2 × 10 ml), acidified to pH 2–3 with 1 N $NaHSO_4$, and extracted with AcOEt (3 × 10 ml). The combined organic phases were washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo at 35–40 °C. The crude material (colorless oil or white crystals, yields 83–99%) was chromatographically pure. All new compounds were characterized on the basis of ^1H and ^{13}C NMR data.[17,18]

In conclusion, we have demonstrated the utility of *N*-Boc-α-alkylserine-β-lactones for the efficient synthesis of optically pure C^{α}-tetrasubstituted α-amino acids, α-chloromethyl- and α-bromomethyl-α-alkylglycines in excellent yields.

Acknowledgment

This work was supported by the Ministry of Science and Higher Education (Grant No. 204 041 32/0879).

References and notes

1. Cativiela, C.; Dìaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **2007**, *18*, 569–623.
2. For example, see: Burgess, A. W.; Leach, S. *Biopolymers* **1973**, *12*, 2691–2712; Seebech, D.; Aebi, J. D.; Gander-Coquoz, M.; Naef, R. *Helv. Chim. Acta* **1987**, *70*, 1194–1216.
3. For example, see: Metzger, J.; Olma, A.; Leplawy, M. T.; Jung, G. *Z. Naturforsch.* **1987**, *42b*, 1195–1201; Olma, A.; Misicka, A.; Tourwe, D.; Lipkowski, A. W. *Lett. Pept. Sci.* **1998**, *5*, 383–385; Łempicka, E.; Slaninowa, J.; Olma, A.; Lammek, B. *J. Pept. Sci.* **1999**, *53*, 554–559; Olma, A.; Gniadzik, A.; Lipkowski, A. W.; Łachwa, M. *Acta Biochem. Pol.* **2001**, *48*, 1165–1168; Olma, A.; Tourwe, D. *Lett. Pept. Sci.* **2000**, *7*, 93–96; Olma, A.; Lipkowski, A. W.; Łachwa, M. *J. Pept. Res.* **2003**, *61*, 45–52; Zabłotna, E.; Kret, A.; Jaśkieiwcz, A.; Olma, A.; Leplawy, M. T.; Rolka, K. *Biochem. Biophys. Res. Commun.* **2006**, *340*, 823–828.
4. Olma, A.; Kudaj, A. *Tetrahedron Lett.* **2005**, *46*, 6239–6249.
5. Olma, A. *Pol. J. Chem.* **2004**, *78*, 831–835.
6. Kudaj, A.; Olma, A. *Tetrahedron Lett.* **2007**, *48*, 6794–6797.
7. Kamiński, Z. J.; Leplawy, M. T.; Zabrocki, J. *Synthesis* **1973**, 792–793.
8. Leplawy, M. T.; Olma, A. *Pol. J. Chem.* **1979**, *53*, 354–357; Olma, A. *Pol. J. Chem.* **1996**, *70*, 1442–1447; Wieczorek, W.; Bukowska-Strzyżewska, M.; Leplawy, M. T.; Olma, A. *J. Crystallogr. Spectrosc. Res.* **1989**, *19*, 257–265; Wieczorek, W.; Bukowska-Strzyżewska, M.; Leplawy, M. T.; Olma, A. *J. Crystallogr. Spectrosc. Res.* **1991**, *21*, 209–215; Wieczorek, W.; Bukowska-Strzyżewska, M.; Olma, A.; Kamiński, Z. J.; Leplawy, M. T. *J. Crystallogr. Spectrosc. Res.* **1991**, *21*, 107–112; Witkowska, R.; Kaczmarek, K.; Crisma, M.; Toniolo, C.; Zabrocki, J. *J. Pept. Sci.* **2001**, *7*, 619–625.
9. Jimenez-Oses, G.; Aydillo, C.; Busto, J. H.; Zurbano, M. M.; Peregrina, J.; Avenoza, A. *J .Org. Chem.* **2007**, *72*, 5399–5402.
10. Fischer, E.; Raske, K. *Ber* **1907**, *40*, 3717–3724.
11. Bey, P.; Vevert, J.-P.; Van Dorsselaer, V.; Kolb, M. *J. Org. Chem.* **1979**, *44*, 2732–2742.
12. Han, O.; Frey, P. A. *J. Am. Chem. Soc.* **1990**, *112*, 8982–8983.
13. Kedrowski, B. L.; Heathcock, C. H. *Heterocycles* **2002**, *58*, 601–634.
14. Buchanann, R. L.; Dean, F. H.; Pattison, F. L. M. *Can. J. Chem.* **1962**, *40*, 1571–1575.
15. *Spectral data*: Compound **3a** (*N*-Boc-(*S*)-3-amino-3-methyl-2-oxetanone) ^{1}H NMR (250 MHz, DMSO-d_6) δ 1.37 (s, 9H, *t*-Bu), 1.41 (s, 3H, CH_3) 4.11 (d, J = 4.5 Hz, 1H, CH_2), 4.45 (d, J = 4.5 Hz, 1H, CH_2), 7,69 (s, 1H, NH) **3b** (*N*-Boc-(*S*)-3-amino-3-*iso*-propyl-2-oxetanone) ^{1}H NMR (250 MHz, DMSO-d_6) δ 0.94 (d, J = 7.0 Hz, 3H, CH_3), 0.95 (d, J = 7.0 Hz, 3H, CH_3), 1.38 (s, 9H, *t*-Bu), 2.01 (sept, J = 7,0 Hz, CH), 4,21 (d, J = 5.0 Hz, 1H, CH_2), 4,39 (d, J = 5.0 Hz, 1H, CH_2), 7.50 (s, 1H, NH), **3c** (*N*-Boc-(*S*)-3-amino-3-*iso*-butyl-2-oxetanone) ^{1}H NMR (250 MHz, DMSO-d_6) δ 0.84 (d, J = 6.6 Hz, 3H, CH_3), 0.88 (d, J = 6.6 Hz, 3H, CH_3), 1.36 (s, 9H, *t*-Bu), 1.60–1.77 (m, 2H, CH_2), 1.82–1.98 (m, 1H, CH), 4.20 (d, J = 4.6 Hz, 1H, CH_2–O), 4,46 (d, J = 4.6 Hz, 1H, CH_2–O), 7.46 (s, 1H, NH).
16. Broadrup, R. L.; Wang, B.; Malachowski, W. P. *Tetrahedron* **2005**, *61*, 10277–10284.
17. *Characterization data for*: Compound **4a** (*N*-Boc-(*S*)-α-chloromethylalanine) yield 93%; white crystals: mp 109–110 °C (dec); IR (KBr) 727 cm^{-1}; $[\alpha]_D^{20}$ 49.4 (*c* 1, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.45 (s, 9H, *t*-Bu), 1.57 (s, 3H, CH_3), 4.01–4.06 (m, 2H, CH_2), ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.0, 28.2, 47.2, 60.0, 80.5, 154.0, 176.8; MS (FAB) m/z 238.1 (M+1); calcd for $C_6H_{16}O_4NCl$ 237.7; *Compound* **4b** (*N*-Boc-(*S*)-α-chloromethylleucine) yield 91%; white crystals: mp 138–139 °C (dec); IR (KBr) 727 cm^{-1}; $[\alpha]_D^{20}$ 12.6 (*c* 1, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.88 (d, J = 6.3 Hz, 3H, CH_3), 0.97 (d, J = 6.3 Hz, 3H, CH_3), 1,45 (s, 9H, *t*-Bu), 1.60–1.77 (m, 2H, CH_2), 2.24–2.33 (m, 1H, CH), 3.81 (d, J = 10.0 Hz, 1H, CH_2–Cl), 4.37 (d, J = 10.0 Hz, 1H, CH_2–Cl), 5.63 (s, 1H, NH), ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.0, 23.4; 24.7, 28.2, 41.5, 46.7, 64.1, 80.1, 153.9, 176.5; MS (FAB) m/z 280.3 (M+1); calcd for $C_{12}H_{22}O_4NCl$ 279.8; *Compound* **4c** (*N*-Boc-(*S*)-α-chloromethylvaline) yield 86%; white crystals: mp 146–147 °C (dec); IR (KBr) 727 cm^{-1} $[\alpha]_D^{20}$ −2.8 (*c* 1, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.07 (d, J = 7.0 Hz, 6H, $(CH_3)_2$), 1.50 (s, 9H, *t*-Bu), 2.47–2.63 (m, 1H, CH), 4.20 (d, J = 10.5 Hz, 1H, CH_2), 4.60 (d, J = 10.5 Hz, 1H, CH_2), 5.51 (s, 1H, NH), ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.2, 17.8, 28.2, 32.7, 45.2, 67.3, 80.0, 155.0, 174.6; MS (FAB) m/z 266.2 (M+1); calcd for $C_{11}H_{20}O_4NCl$ 265.7; *Compound* **4d** (*N*-Boc-(*S*)-α-chloromethylphenylalanine) yield 95%; colorless oil; IR (KBr) 727 cm^{-1}; $[\alpha]_D^{20}$ −42.1 (*c* 1, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.45 (s, 9H, *t*-Bu), 3.15 (d, J = 13.5 Hz, 1H, CH_2–Ph), 3.60 (d, J = 13.5 Hz, 1H, CH_2–Ph), 4.03 (d, J = 12.0 Hz, 1H, CH_2Cl), 4.54 (d, J = 12.0 Hz, 1H, CH_2–Cl), 5.53 (s, 1H, NH), 7.18–7.33 (m, 5H, C_6H_5), ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.3, 30.5, 38.9, 45.9, 65.6, 80.2, 127.3, 128.4, 129.8, 134.7, 154.2, 174.5; MS (FAB) m/z 314.1 (M+1); calcd for $C_{15}H_{20}O_4NCl$ 313.8;.
18. *Characterization data for* **5a** *(N-Boc-(S)-α-bromomethylalanine)*: yield 99%; colorless oil; IR (KBr) 533 cm^{-1}; $[\alpha]_D^{20}$ 10.69 (*c* 1, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.46 (s, 9H, *t*-Bu), 1.66 (s, 3H, CH_3), 3.94–3.98 (m, 2H, CH_2), 5.41 (s, 1H, NH), ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.8, 28.2, 36.8, 59.5, 80.2, 154.4, 176.2; MS (FAB) m/z 282.0; calcd for $C_9H_{16}O_4NBr$ 282.1; **5b** (*N*-Boc-(*S*)-α-bromomethyloleucine): yield 99%; white crystals: mp 112–113 °C (dec); IR (KBr) 533 cm^{-1}; $[\alpha]_D^{20}$ 9.37 (*c* 1, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.88 (d, J = 6.3 Hz, 3H, CH_3), 0.94 (d, J = 6.3 Hz, 3H, CH_3), 1.46 (s, 9H, *t*-Bu), 1.62–1.82 (m, 2H, CH_2), 2.25–2.41 (m, 1H, CH), 3.69 (d, J = 10.1 Hz, 1H CH_2–Br), 4.32 (d, J = 10.1 Hz, 1H, CH_2–Br), 5,75 (s, 1H, NH), ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.7, 21.8, 23.5, 26.5, 34.4, 40.4, 61.9, 78.3, 152.1, 174.5; MS (FAB) m/z; 324.1 calcd for $C_{12}H_{22}O_4NBr$ 324.2; **5c** (*N*-Boc-(*S*)-α-bromomethylvaline): yield 95%; colorless oil; IR (KBr) 533 cm^{-1}; $[\alpha]_D^{20}$ 6.66 (*c* 1, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.04 (d, J = 7.0 Hz, 6H, $(CH_3)_2CH$), 1.46 (s, 9H, *t*-Bu), 2.34–2.63 (m, 1H, CH), 4.06 (d, J = 10.1 Hz, 1H, CH_2), 4.40 (d, J = 10.1 Hz, 1H, CH_2), 5.51 (s, 1H, NH), ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.5, 18.1, 28.3, 33.5, 35.1, 66.9, 80.1, 154.2, 174.3; MS (FAB) m/z 310.2; calcd for $C_{11}H_{20}O_4NBr$ 310.2; *Compound* **5d** (*N*-Boc-(*S*)-α-bromomethylphenylalanine): yield 91%; colorless oil; IR (KBr) 533 cm^{-1}; $[\alpha]_D^{20}$ −43.21 (*c* 1, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.49 (s, 9H, *t*-Bu); 3.14 (d, J = 13.0 Hz, 1H,CH_2–Ph), 3.61 (d, J = 13.0 Hz, 1H, CH_2–Ph), 3.89 (d, J = 10.5 Hz, 1H, CH_2–Br), 4.39 (d, J = 10.5 Hz, 1H, CH_2–Br), 5.44 (s, 1H, NH), 7.10–7.30 (m, 5H, C_6H_5); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.3, 35.2, 39.6, 65.2, 80.3, 127.3. 128.4, 129.7, 135.0, 154.1, 174.6; MS (FAB) m/z 358.1; calcd for $C_{15}H_{20}O_4NBr$ 358.2.