First total synthesis of a guanidine alkaloid Nitensidine D using immobilized ionic liquid, microwaves and formamidinesulfinic acid

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Abstract. An efficient first total synthesis of a naturally occurring guanidine alkaloid, Nitensidine D isolated from ethanol extract of *Pterogyne nitens* has been described. Geraniol has been used as the starting material. N-alkylation of phthalimide has been achieved using immobilized ionic liquid and formamidinesulfinic acid acts as the guanylation reagent.

Keywords. Guanidine alkaloid; microwaves; immobilized ionic liquid; formamidinesulfinic acid.

1. Introduction

The discovery of biologically active molecules is crucial for both the development of new therapeutics¹ and to provide tools for the elucidation of cellular processes.² Natural extracts, collections and combinatorial libraries of synthetic compounds are screened for searching these compounds. Natural products play an important role, particularly in the anti-cancer and anti-infective areas as greater than 60% of the drugs that are now available were estimated to be derived from them.³

Many natural products containing guanidine have been isolated and have attracted a lot of attention owing to their wide range of biological activities,⁴ basically arising from the two parallel interactions of the guanidinium ion with phosphate and carboxylate-containing biomolecules.⁵ In addition, due to the strong binding ability of guanidine with anionic compounds, guanidine containing molecules have applications as chemical tools. Synthetic guanidine compounds have also been utilized as host receptor molecules for phosphate and carboxylate containing guest molecules.⁶

A number of unusual guanidine alkaloids displaying a broad spectrum of biological activities have been isolated from marine organisms⁷ whereas, in the plant kingdom, these are restricted to the families of Euphorbiaceae and Leguminosae.⁸ *Pterogyne nitens* Tul. (Fabaceae, Caesalpinoideae) popularly known as ‘bálsamo,’ ‘yvira-ró,’ ‘cocal’ and ‘amendoinzeiro’ is a native tree common in South America. Previous

phytochemical studies with the leaves and fruits of *P. nitens* have demonstrated the presence of two terpenoid guanidine alkaloids (pterogynine,⁹ pterogynidine^{8a}), three guanidine alkaloids (Nitensidine A, B, C) which exhibited cytotoxic activity towards the DNA-repair-deficient yeast mutant RS 321 and moderate cytotoxic activity against CHO Aux B1 cells¹⁰ and phenolic compounds with myeloperoxidase inhibitory and radical scavenging activities.¹¹ Further investigations of the ethanolic extracts of *P. nitens* due to its cytotoxic activity in the MTT assay resulted in the isolation of two new guanidine alkaloids Nitensidine D and E.¹²

Ionic liquids (ILs) have become increasingly used solvents and catalysts in ‘green’ chemistry due to their unique properties.¹³ The most important technical problems in the industrial IL applications using soluble IL catalysts, are their recovery and subsequent reuse or disposal. Immobilization of the catalyst on a solid support provides the advantage of easy isolation at the end of the reaction by simple filtration, avoiding tedious processes of distillation, chromatographic separation, etc.¹⁴ Past few years have witnessed a growing interest in the use of microwaves in organic synthesis as they make the reactions extremely fast, cleaner than conventional reactions and lead to higher atom economy (less chemical waste).¹⁵

In continuation of our interest¹⁶ in the development of economic and rapid protocol, utilizing microwave energy¹⁷ and ionic liquids, we report herein a simple synthesis of Nitensidine D.

Retrosynthetic analysis of Nitensidine D (scheme 1) revealed that geranyl amine could well act as the starting precursor.

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Scheme 1. Retrosynthetic Analysis.

2. Experimental

^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded (δ /ppm) on a Jeol A1 300F spectrophotometer for solutions in CDCl_3 with tetramethylsilane (TMS) as internal standard. FT-IR was recorded using Perkin Elmer model 1430 spectrometer. Microwave oven used was focused mono-mode Plazmatronika RM 2001 PC (800W). Melting points were recorded on a Buchi R-535 apparatus.

2.1 Geranyl bromide (**2**)

A solution of geraniol (**1**, 26 mmol, 4.0 g) and CBr_4 (30 mmol, 10.0 g) in DCM (11 mL) was prepared in a 100 mL flask and cooled to 0°C . PPh_3 (28 mmol, 7.3 g) was added in portions for over 30 min with vigorous stirring. Upon addition of triphenyl phosphine, the colourless solution turns pale brown and stirred for an additional 4 h at room temperature. The mixture was concentrated to brown oil, quickly added to stirring hexane (22 mL), white ppt. so formed were filtered and remaining solution was concentrated and was purified over a silica gel column (98:2 hexane:EtOAc) to give geranyl bromide (**2**) in 80% yield (4.5 g) as pale yellow oil.

^1H NMR (CDCl_3 , 300 MHz): δ 1.68 (s, 3H, $-\text{CH}_3$), 1.74 (s, 3H, $-\text{CH}_3$), 1.75 (s, 3H, $-\text{CH}_3$), 2.04–2.14 (m, 4H, $-\text{CH}_2-\text{CH}_2-$), 4.02 (d, 2H, $J = 8.4$ Hz, $-\text{CH}_2-\text{Br}$),

5.06 (t, 1H, $J = 4.2$ Hz, $-\text{CH}=\text{C}(\text{Me})_2$), 5.30 (t, 1H, $J = 8.4$ Hz, $=\text{CH}-\text{CH}_2-\text{Br}$). ^{13}C NMR (CDCl_3 , 75 MHz): δ 15.90, 17.71, 25.67, 26.17, 29.66, 39.50, 120.54, 123.53, 131.96, 143.56. IR (neat)/ ν_{max} (cm^{-1}): 838, 985, 1082, 1108, 1376, 1594, 1654, 2855, 2925, 2966.

2.2 *N*-geranyl phthalimide (**3**)

A mixture of phthalimide (4.8 mmol, 0.70 g), geranyl bromide (**2**, 6.0 mmol, 1.30 g), immobilized IL (0.20 g, 0.20 mmol, 3 mol%) and potassium carbonate (18.8 mmol, 2.6 g) was heated in a commercial microwave oven in an open Erlenmeyer flask at 60 – 65°C for 9 min. having 50:10s heating:cooling cycle each at 80% power level. After cooling down, the reaction mixture was extracted with methylene chloride (2×25 mL). The combined extract was dried over anhydrous Na_2SO_4 , filtered and evaporated to get a dark brown residue. It was purified over a silica gel column using hexane:EtOAc (96:4) as the eluent to give *N*-geranyl phthalimide (**3**) in 83% yield (1.127 g) as white crystalline powder. M.p. = 57 – 58°C .¹⁸

^1H NMR (CDCl_3 , 300 MHz): δ 1.48 (s, 3H, $-\text{CH}_3$), 1.54 (s, 3H, $-\text{CH}_3$), 1.74 (s, 3H, $-\text{CH}_3$), 1.91–1.99 (m, 4H, $-\text{CH}_2-\text{CH}_2-$), 4.19 (d, 2H, $J = 6.9$ Hz, $-\text{CH}_2-\text{N}-$), 4.94 (t, 1H, $J = 6.9$ Hz, $-\text{CH}=\text{C}(\text{Me})_2$), 5.18 (t, 1H, $J = 6.9$ Hz, $=\text{CH}-\text{CH}_2-\text{N}-$), 7.59–7.62 (m, 2H, ArH), 7.73–7.75 (m, 2H, ArH). ^{13}C NMR (CDCl_3 , 75 MHz): δ 16.34, 17.63, 25.69, 26.28, 35.73, 39.46, 118.00, 123.07, 123.82, 131.56, 132.36, 133.67, 140.53, 167.93. IR (neat)/ ν_{max} (cm^{-1}): 946, 1085, 1171, 1395, 1653, 1711, 1770, 2929.

2.3 Geranyl amine (**4**)

Hydrazine hydrate (0.66 mL, 21 mmol) was added to a stirred solution of *N*-geranyl phthalimide (**3**, 2.6 mmol, 0.736 g) in absolute EtOH (10 mL) and the solution was heated to reflux for 8 h. Further, it was cooled to r.t. and the solvent was removed under reduced pressure. Then 20% NaOH solution (10 mL) was added to the residue and extracted with CH_2Cl_2 (3×15 mL). The combined organic extract was dried over anhydrous Na_2SO_4 , filtered and evaporated to get pure geranyl amine (**4**) in 93% yield (0.37 g) as light yellow oil.

^1H NMR (CDCl_3 , 300 MHz): δ 1.53 (s, 3H, $-\text{CH}_3$), 1.56 (s, 3H, $-\text{CH}_3$), 1.61 (s, 3H, $-\text{CH}_3$), 1.92–2.00 (m, 4H, $-\text{CH}_2-\text{CH}_2-$), 2.14 (bs, 2H, $-\text{NH}_2$), 3.22 (d, 2H, $J = 6.9$ Hz, $-\text{CH}_2-\text{NH}_2$), 5.01 (t, 1H, $J = 5.4$ Hz, $-\text{CH}=\text{C}(\text{Me})_2$), 5.18 (t, 1H, $J = 6.9$ Hz, $=\text{CH}-\text{CH}_2-\text{NH}_2$). ^{13}C NMR (CDCl_3 , 75 MHz): δ 16.05, 17.60,

25.60, 26.45, 39.31, 124.06, 124.82, 131.47, 137.08. IR (neat)/ $\nu_{\max}$ (cm^{-1}): 830, 984, 1045, 1107, 1376, 1446, 1587, 1667, 2856, 2916, 2966, 3289, 3363.

2.4 Formamidinesulfinic acid (**6**)

Peracetic acid was prepared by slowly adding acetic anhydride (50 mL) to 30% hydrogen peroxide (45 g) cooled in an ice bath. The addition of two drops of concentrated sulphuric acid caused a violent reaction. After the reaction has subsided, acetic anhydride (110 mL) was slowly added to the cooled mixture. The mixture was allowed to warm gradually to r.t. and left to stand for at least one day. Methanol (160 mL) was added and the solution was cooled to 10°C in an ice bath. A solution of thiourea (**5**, 10 g) in methanol (500 mL) was also cooled. The latter was added to the oxidizing mixture in portions at such a rate as to maintain the temperature below 10°C (hotter reaction mixtures led to more formamidinesulfonic acid as the product). The solid started forming along with the addition of thiourea and after the complete addition it was filtered and washed with several portions of cold methanol. The product (**6**) was obtained in 86% yield (12.2 g) as white powder. M.p. = 125°C.

IR (neat)/ $\nu_{\max}$ (cm^{-1}): 597, 1054, 1186, 1462.

2.5 *N*-Hexyl guanidine (**8**)

To an aqueous solution of NaOH (1.0 mL, 4.6 mmol, 0.184 g) and hexyl amine (**7**, 2.0 mmol, 0.202 g), formamidinesulfinic acid (**6**, 2.30 mmol, 0.248 g) was added in small portions over 30 min. After approx. 1/3 of formamidinesulfinic acid was added, the reaction mixture became a viscous suspension. The suspension was stirred at r.t. overnight, then heated to 60°C and stirred for additional 30 min. The solid product was obtained by cold filtration. White solid was crystallized from H₂O and the resulting white crystals were washed with small portions of cold MeOH giving *N*-hexyl guanidine (**8**) in 85% yield (0.24 g). M.p. = 140°C.

¹H NMR (CDCl₃/DMSO-*d*₆, 300 MHz): δ 0.82 (t, 3H, *J* = 6.6, -CH₃), 1.22 (m, 6H, -(CH₂)₃-CH₃), 1.45 (m, 2H, -CH₂-CH₂-N=C(NH₂)₂), 3.02 (t, 1H, *J* = 7.2, -CHH-N=C(NH₂)₂), 3.24 (t, 1H, *J* = 7.2, -CHH-N=C(NH₂)₂), 7.2 (bs, 1H, -CH₂-NH-C(=NH)-NH₂), 7.9 (bs, 3H, -NH₂-C=NH). ¹³C NMR (CDCl₃/DMSO-*d*₆, 75 MHz): δ 14.37, 22.65, 26.48, 29.04, 31.55, 40.21, 157.21. IR (neat)/ $\nu_{\max}$ (cm^{-1}): 997, 1063, 1269, 1376, 1463, 1633, 1718, 2852, 2922, 3167, 3333.

2.6 Nitenzidine D (**9**)

To an aqueous solution of NaOH (1.0 mL, 4.6 mmol, 0.184 g) and geranyl amine (**4**, 2.0 mmol, 0.306 g), formamidinesulfinic acid (**6**, 2.30 mmol, 0.248 g) was added in small portions over 30 min. After approx. 1/3 of formamidinesulfinic acid was added, the reaction mixture became a viscous suspension. The suspension was stirred at r.t. overnight, then heated to 60°C and stirred for additional 30 min. It resulted into the formation of light brown oil which was extracted from the aqueous solution by CHCl₃, washed with brine and dried over anhydrous Na₂SO₄. Solvent was evaporated under reduced pressure and the viscous liquid thus obtained was purified over a column of neutral Al₂O₃ using CHCl₃: MeOH (96:4) as the eluent to give Nitenzidine D (**9**) as colourless oil in 81% (0.32 g) yield in the form of a mixture of tautomers in 25.8:74.2 ratio (figure 1).

¹H NMR (CDCl₃, 300 MHz): δ 1.18 (bs, 2H, -NH₂), 1.52 (s, 3H, -CH₃), 1.59 (s, 6H, 2 × -CH₃), 1.93–1.99 (m, 4H, -CH₂-CH₂-), 3.65 (t, 2H, *J* = 6.0, -CH₂-N=C(NH₂)₂, 74.2%), 3.99 (d, 2H, *J* = 6.6, -CH₂-NH-C=NH(NH₂), 25.8%), 4.16 (bs, 1H, -NHH), 4.46 (bs, 1H, -NHH), 4.96 (t, 1H, *J* = 7.0, -CH=C(Me)₂), 5.11 (t, 1H, *J* = 6.0, =CH-CH₂-N=C(NH₂)₂). ¹³C NMR (CDCl₃, 75 MHz): δ 16.36, 17.85, 25.84, 26.58, 38.85, 39.65, 121.61, 124.12, 131.44, 138.73, 158.18. IR (neat)/ $\nu_{\max}$ (cm^{-1}): 815, 1073, 1567, 1631, 1722. MS *m/z*: [M+1]⁺ 196.2, [M+2]⁺ 197.2, 179.2 (calculated for C₁₁H₂₁N₃ 195.3079).

3. Results and Discussion

To start with the synthesis geranyl bromide was prepared from geraniol using CBr₄/PPh₃ in 80% yield (scheme 2).¹⁹

Further geranyl bromide was required to be converted to geranyl amine *via* Gabriel reaction. First step in the Gabriel reaction is the *N*-alkylation of phthalimide to prepare *N*-alkyl phthalimide, which is further hydrolysed to give an amine as the final product. Various routes are available for their synthesis, however, some of these methods are limited by harsh reaction conditions, long reaction times, low yields, use of toxic solvents or catalysts, etc.²⁰

To overcome these shortcomings, the *N*-alkylation of phthalimide has been carried out by using a novel method involving immobilized IL i.e., SiO₂-propyltri-butyl chloride ([SiO₂-PTB]Cl) as a heterogeneous phase transfer catalyst under microwave irradiation and solvent free conditions. The reaction conditions were first optimized taking *N*-benzylation of phthalimide with benzyl chloride as the model reaction to get the best

Scheme 2. (a) CBr_4 , PPh_3 , DCM , 4h, rt, stirr; (b) Phthalimide, K_2CO_3 , $\text{SiO}_2\text{-IL}$, MWI, 9min, 60-65°C; (c) $\text{NH}_2\text{NH}_2\cdot\text{H}_2\text{O}$, EtOH , 8h, reflux.

minimum reaction time. Not only time, but the power of microwave oven, temperature of operation, as well as quantity of the catalyst were also optimised to give the best conditions as reported.

Then, we proceeded towards geranyl bromide as the reactant which gave the best yield when it was irradiated for 9 min. The reaction resulted into the formation of *N*-geranyl phthalimide as a white solid in 89% yield. Hydrolysis of the so formed *N*-geranyl phthalimide was done using Ing-Manske procedure involving hydrazine hydrate in absolute EtOH under refluxing conditions i.e., hydrazinolysis²¹ to give geranyl amine as a light yellow oil in 93% yield.

The next task was the conversion of an amine to a guanidine, where amine nitrogen is incorporated into the newly formed guanidine functional group i.e., *guanylation*. The common methods for producing guanidino compounds are the reactions of ammonia or amine derivatives with cyanamides,²² carbodiimides,²³ chloroformamidines,²⁴ etc. Generally, these materials are toxic, corrosive and/or moisture sensitive. Other popular methods are reactions of amines with substituted *S*-methylisothiourea,²⁵ or 2,5-dimethyl-1-guanylpurazole.²⁶ The last two methods are generally

better than the rest ones, but the reactions usually require a strong basic media and/or heat for some substrates. There are several reports that use *S*-oxides of thiourea i.e., thiourea dioxide/formamidinesulfinic acid²⁷ [$\text{HN}=\text{C}(\text{NH}_2)\text{SO}_2\text{H}$] and thiourea trioxide/formamidinesulfonic acid²⁸ [$\text{HN}=\text{C}(\text{NH}_2)\text{SO}_3\text{H}$] for the preparation of *N*-formamidinylamines. Instead of the easy accessibility of formamidinesulfinic acid, only formamidinesulfonic acid and its derivatives were studied in detail. Reason for this neglect could be the earlier reports which claimed that formamidinesulfinic acid gave much poorer yields for guanylation reactions.²⁹ Recently, considering this fact that the valuable conversion was at least possible with this cheaper reagent, its *N*-formamidinylation capability with amino acids was explored.³⁰ The best yields were obtained (up to 92%) when the reactions were carried out in the presence of aqueous sodium hydroxide. The awesome results so found in this latest discovery for amino acids, prompted us to screen amines as well for the *N*-formamidinylation reaction using formamidinesulfinic acid. Formamidinesulfinic acid was prepared by oxidizing thiourea with peracetic acid in methanol (scheme 3).^{28a}

Scheme 3. (d) CH_3COOOH , MeOH , below 10°C; (e) aq. NaOH , stirr, 24h at rt, 30min at 60°C.

Figure 1. Imine tautomeric forms of guanidine alkaloid Nitensidine D.

In a preliminary experiment, we chose an aliphatic amine i.e., hexyl amine as the substrate and carried out its *N*-formamidinylation using aqueous sodium hydroxide at room temperature. It gave *N*-hexylguanidine as an off white solid in 85% yield. Then some aromatic amines like aniline, 4-chloroaniline and 4-amino benzoic acid were taken. In this case, either no or very little conversions (5%, 0% and 10% respectively) were obtained. Therefore, we believe that this approach would not be practical for aromatic amines, but it is indeed a reliable, inexpensive and efficient method for conversion of aliphatic amines into the corresponding *N*-formamidinyl derivatives. Thus, we proceeded towards the reaction of geranyl amine with formamidinesulfinic acid under the same set of conditions to obtain the title compound i.e., Nitensidine D in 81% yield (scheme 3). Spectral data of the synthesized title compound were compatible with that reported in literature.¹² Also, its structure was in agreement with a tautomeric form having imine feature which most of the natural guanidines occurring in plants and animals include (figure 1). It is also clear from the proton NMR data that both the tautomers are present in 25.8:74.2 ratio.

4. Conclusions

In conclusion, we have achieved an efficient first total synthesis of a naturally occurring guanidine alkaloid, Nitensidine D isolated from ethanol extract of *Pterogyne nitens*. Geraniol (1) has been used as the starting material. The key steps in the synthesis involved the microwave induced *N*-alkylation of phthalimide using immobilized ionic liquid [SiO₂-PTB]Cl⁻ and *N*-formamidinylation of geranyl amine using formamidinesulfinic acid [HN=C(NH₂)SO₂H] to afford the title compound (9).

Supporting Information

Supporting information is available at www.ias.ac.in/chemsci. ¹H NMR, ¹³C NMR, IR and Mass spectra of the title compound Nitensidine D are available in the electronic supplementary information.

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References

- Bauer A and Brönstrup M 2014 *Nat. Prod. Rep.* **31** 35
- Zachary D A and Larry E O 2004 *Chem. Commun.* **40** 253
- Newman D J 2008 *J. Med. Chem.* **51** 2589
- Berlinck R G S 2002 *Nat. Prod. Rep.* **19** 617
- Cotton F A, Day V W, Hazen E E and Larsen S 1973 *J. Am. Chem. Soc.* **95** 4834
- Schmidtchen F P and Berger M 1997 *Chem. Rev.* **97** 1609
- Laville R, Thomas O P, Berru F, Marquez D, Vacelet J and Amade P 2009 *J. Nat. Prod.* **72** 1589
- (a) Corral R A, Orazi O and Petruccelli M F 1969 **25** 1020; (b) Kamnaing P, Free S N Y F, Fornum Z T, Martin M T and Bodo B 1994 *Phytochemistry* **36** 1561
- Crivos M, Martinez M R, Pochettino M L, Remorini C, Sy A and Teves L 2007 *J. Ethnobiol. Ethnomed.* **3** 2 (1)
- Bolzani V D S, Gunatilaka A A L and Kingston D G I 1995 *J. Nat. Prod.* **58** 1683
- Regasini L O, Fernandes D C, Castro-Gamboa I, Silva D H S, Furlan M, Bolzani V S, Barreiro E J, Bolzani V S, Cardoso-Lopes E M, Young M C M, Torres L B, Velloso J C R and Oliveira O M M 2008 *Quim. Nova.* **31** 802
- Regasini L O, Castro-Gamboa I, Silva D H S, Furlan M, Barreiro E J, Ferreira PMP, Pessoa C, Lotufo LVC, de Moraes M O, Young M C M and Bolzani V 2009 *J. Nat. Prod.* **72** 473
- (a) Rodgers R and Seddon K 2003 In *Ionic Liquids as Green Solvents, Progress and Prospects* (Washington DC: American Chemical Society); (b) Wasserscheid P and Welton T 2007 In *Ionic Liquids in Synthesis* (Wiley-VCH: Weinheim)
- Thomson L A and Ellmann J A 1996 *Chem. Rev.* **96** 555
- Amarasekara A S and Owereh OS 2010 *Catal. Commun.* **11** 1072
- (a) Kad G L, Bhandari M, Kaur J, Rathee R and Singh J 2001 *Green Chem.* **6** 275; (b) Kad G L, Singh V, Kaur K P and Singh J 1997 *Tetrahedron Lett.* **38** 1079
- (a) Gupta N, Sonu, Kad G L and Singh J 2007 *Catal. Commun.* **8** 1323; (b) Singh J, Gupta N, Kad G L and Kaur J 2006 *Synth. Commun.* **36** 2893; (c) Shallu, Sharma M L and Singh J 2012 *Syn. Commun.* **42** 1306; (d) Singh A, Sharma M L and Singh J 2008 *J. Chem. Res.* 148; (e) Singh A, Sharma M L and Singh J 2009 *Nat. Prod. Res.* **23** 1029

18. Harned A M, He H S, Toy P H, Flynn D L and Hanson P R 2005 *J. Am. Chem. Soc.* **127** 52
19. Baughman T W, Sworen J C and Wagener K B 2004 *Tetrahedron* **60** 10943
20. (a) Onajole O K, Govender P, van Helden P D, Kruger H G, Maguire G E M, Wiid I and Govender 2010 *Eur. J. Med. Chem.* **45** 2075; (b) Więcek M, Kottke T, Ligneau X, Schunack W, Seifert R, Stark H, Handzlik J and Kieć-Kononowicz K 2011 *Bioorg. Med. Chem.* **19** 2850
21. (a) Tanyeli C and Ozeubukeu S 2003 *Tetrahedron Asymm.* **14** 1167; (b) March J 1992 In *Advanced Organic Chemistry: Reactions, Mechanisms and Structures* (4th ed.) (New York: John Wiley & Sons) p 426
22. Davis TL 1927 *Org. Synth.* **7** 46
23. Mikolajczyk MM and Kielbasinski P 1981 *Tetrahedron* **37** 233
24. Brederbeck H and Brederbeck K 1961 *Chem. Ber.* **94** 2278
25. Lal B and Gangopadhyay 1996 *Tetrahedron Lett.* **37** 2483
26. Short J H, Biermacher U, Dunnigan D A and Leth T D 1963 *J. Med. Chem.* **6** 275 and references therein
27. Durant G J, Young R C and Tashman Z 1980 *U.S. Patent* 4 210 658
28. (a) Miller CE and Bischoff JJ 1986 *Synthesis* 777; (b) Meryanoff C A, Stanzione R C, Plampin J N and Mills J E 1986 *J. Org. Chem.* **51** 1882
29. Walter W 1955 *Angew. Chem.* **67** 275
30. Jursic BS, Neumann D and McPherson A 2000 *Synthesis* **12** 1656