Pergamon

SCIENCE DIRECT®

Tetrahedron 59 (2003) 10093–10096

TETRAHEDRON

Non-template synthesis of 'N_4' di- and tetra-amide macrocylic ligands with variable ring sizes☆

S. J. Swamy,* B. Veerapratap, D. Nagaraju, K. Suresh and P. Someshwar

Department of Chemistry, Kakatiya University, Vidyaranyapuri, Warangal 506 009, India

Received 22 June 2003; revised 3 September 2003; accepted 26 September 2003

Abstract—Nine new macrocyclic ligands containing two- or four-amide groups have been prepared by the cyclization reaction of three different diamines with acid chlorides (oxalyl dichloride or malonyl dichloride), diesters (diethyl oxalate or diethyl malonate) or 1,2-dichloroethane. The macrocycles prepared are four tetraaza-14-crown-4, four tetraaza-15-crown-4 and one tetraaza-16-crown-4. All the macrocyclic ligands were characterized by elemental analysis and, IR, UV, NMR and mass spectral investigations.

The synthesis and applications of tetraaza macrocyclic ligands have been areas of wide interest and diversity in recent years.[1] The template approach[2] to the synthesis of metal complexes of macrocyclic ligands and their subsequent release has serious limitations in the case of a number of metal ions, notably iron.[3] Another major drawback of this technique is the lack of information about the properties of the free ligands in order to interpret and correlate the properties of metal complexes. As part of our research, we have developed a number of polydentate ligands containing amide group.[4–8] In addition to the established importance of macrocyclic ligands, the past few years have witnessed growing interest in establishing and developing supramolecular interactions between different polydentate ligands capable of binding (1) metal ions through strong and weak coordinate covalent bonds,[9] and (2) other neutral molecules or anions through hydrogen bonds or by encapsulation.[10] The different techniques adopted to prepare macrocyclic ligands are condensation of carbonyls and amines in presence of Zn(II) salts,[11,12] or by using conditions of 'high dilution'[13] or by displacement of the metal ion from a suitable metal complex.[14]

We report here the non-template synthesis of nine new tetraaza macrocyclic compounds and their characterization. The advantages of this cyclization procedure are: (1) the process is a simple two-step reaction involving inexpensive starting materials; (2) the amide nitrogen atoms are non-reactive under the reaction conditions which alleviate the need for nitrogen-protecting groups and their subsequent removal and (3) the process is shorter and the overall yields are considerably higher.

1. Results and discussion

1.1. Non-template synthesis of macrocyclic ligands

The intermediates required for the synthesis of the new macrocycles, the diamine–diamides, were prepared by ring opening followed by condensation reaction[15] between 2 mol of 1*H*-benzo[*d*][1,3]oxazine-2,4-dione (isatoic anhydride) **1** and 1 mol of diamines; 1,2-diamino ethane **2**, 1,3-diamino-propane **3**, or 1,2-diaminobenzene **4**. The reactions yield compounds 2-amino-*N*-[2-(2-amino-benzoylamino)-ethyl]-benzamide **5**, 2-amino-*N*-[2-(2-amino-benzoylamino)-propyl]-benzamide **6**, 2-amino-*N*-[2-(2-amino-benzoylamino)-phenyl]-benzamide **7**, respectively. Subsequently, [1+1] condensation reaction of the intermediates, **5**, **6** or **7** with diacid chlorides **8**, diesters **9** or alkyl dichlorides **10** in the presence of anhydrous sodium carbonate resulted in the isolation of pure macrocycles **11**–**19** in high yields.

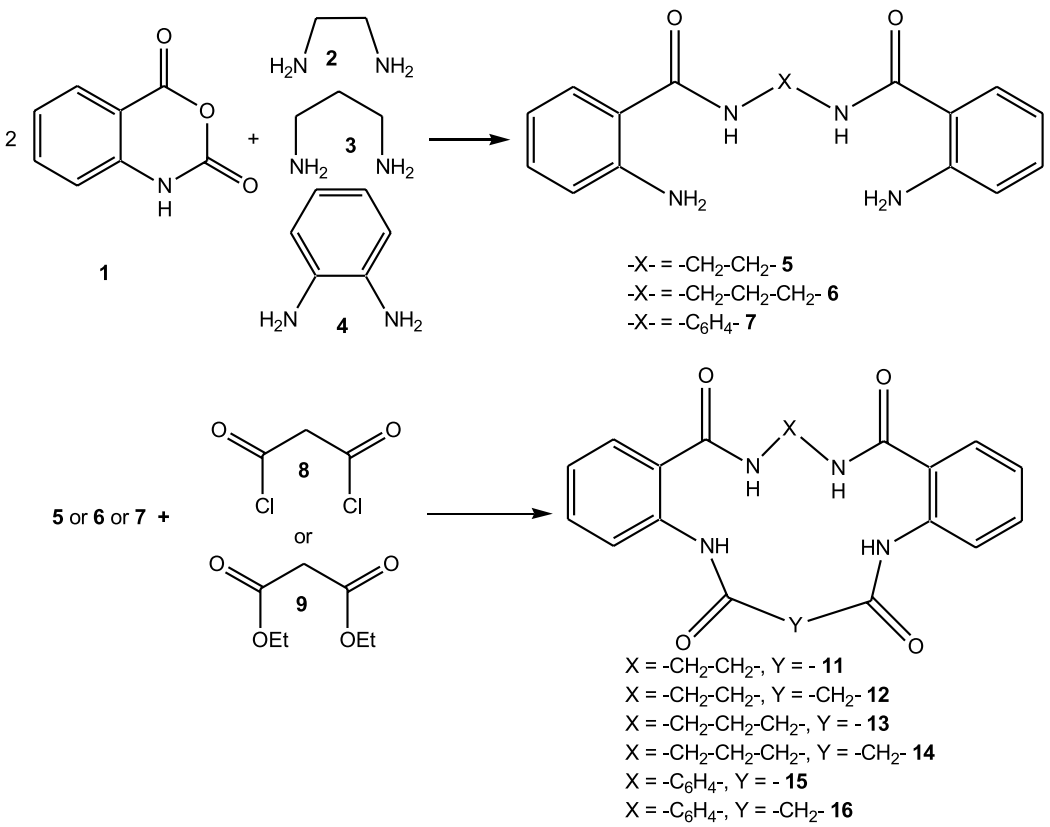
The reaction between compounds **5**, **6** or **7** and diacid chlorides or diesters (Scheme 1) yields the same products, tetraamide tetraaza macrocycles, **11**–**16**. The physical characteristics and the analytical data of the compounds are presented in Section 2. The infrared spectra of the compounds **11**–**16** do not show the characteristic absorptions of the $-NH_2$ group that are found in the intermediates **5**–**7**. This is further confirmed by the absence of a signal around 4.0–5.0 ppm, corresponding to the Ar-NH_2 protons. Further, the intensity of the signal at very low field

☆ Supplementary data associated with this article can be found at doi: 10.1016/j.tet.2003.09.091

Keywords: macrocyclic ligands; tetraaza macrocycles; amide ligands; non-template synthesis.

* Corresponding author. Tel.: +91-870-2438369; fax: +91-870-2453533; e-mail: sj_swamy@yahoo.com

0040–4020/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2003.09.091



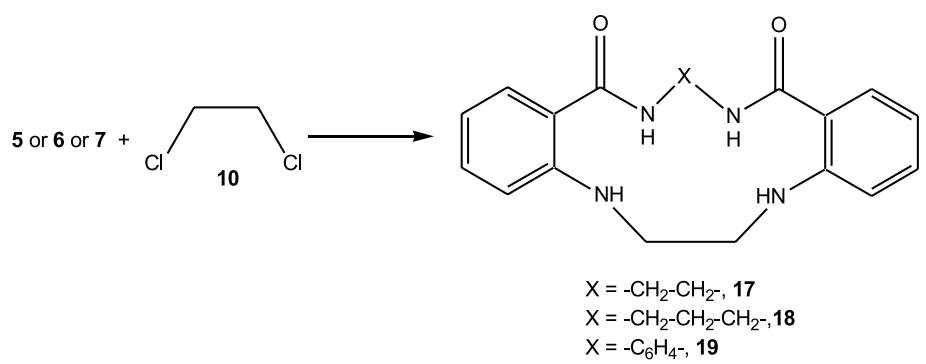
Scheme 1.

(>8.5 ppm) has increased, indicating the presence of four amide hydrogen atoms as compared to only two in the starting compounds. The mass spectra of compounds **11**–**16** exhibit the molecular ion and other corresponding fragment ion peaks. The ^{1}H NMR spectra of compounds, **12**, **14** and **16**, obtained in the reaction of the intermediates with malonyl dichloride or diethyl malonate show a signal around 2.5 ppm assignable to OC–CH_2–CO protons.

The IR spectra of three compounds **17**, **18** and **19** derived in the reaction between diamines with 1,2-dichloroethane (Scheme 2) exhibit absorptions corresponding to an aromatic secondary amine, >NH, group in the high frequency region. This is further confirmed by the presence of the signal at 4.74 ppm assignable to Ar-N*H* protons. The signal intensity in all the cases corresponds to two protons only as against that of four in the case of starting compounds **5**, **6** or **7**. This indicates the cyclization by the loss of HCl. The signals of the methylene protons are observed around 3.5 ppm. All three compounds exhibit molecular ion peaks in the mass spectra and the fragmentation patterns confirm the formation of the products as shown in Scheme 2.

The tetraaza macrocycles obtained in the reactions presented in Scheme 1 are of 14-, 15- or 16-membered rings with four amide nitrogen atoms (**11**–**16**) or two amide and two secondary amine nitrogen atoms (**17**–**19**) in the ring.

The isolation of tetraaza (tetraamide or diamide–diamine) macrocycles with such a range of ring sizes is interesting, for the choice of reaction conditions and solvents that allow the separation of free macrocyclic ligands to separate from solution even in the absence of any catalyst. These results suggest that an important consideration in devising methods for preparing metal-free tetraaza macrocycles, particularly those with relatively planar 'N_4'-donor sets, is the potential



Scheme 2.

occurrence of unfavourable intraannular interactions of lone pairs of electrons.

Significantly, there have been very limited reports[2,16] of successful ring closure reactions to give metal free 14-, 15- or 16-membered 'N_4' macrocycles, unless there are at least two secondary amine hydrogen atoms are present. These can apparently operate as an alternative to a metal ion as a 'thermodynamic template'[17] in stabilizing the molecule by reducing the lone-pair repulsions.

2. Experimental

Isatoic anhydride was obtained from Aldrich, USA and used as received. All other compounds are analytical grade products from Merck. The starting compounds **5**–**7** were prepared following the procedures described elsewhere.[15] The solvents were distilled and stored over molecular sieves. Purity of the compounds was checked by TLC using Merck $60F_{254}$ silica gel plates. IR spectra in KBr discs were recorded using a Perkin–Elmer-BX series FT-IR spectrophotometer. ^{1}H NMR spectra were recorded on Bruker ARX200 spectrometer. Mass spectra were recorded using Finnigan MAT-8230 and Varian MAT 3111 A/AMD mass spectrometer. The electronic spectra in methanol were recorded on Shimadzu 2401 PC spectrophotometer. Melting points (uncorrected) were determined in open capillary tubes using Cintex apparatus. The microanalyses were carried out using the Perkin–Elmer Series II CHNS analyzer-2400 instrument. It is to be noted that the elemental analysis of this type of compound has been criticised by other authors as an inappropriate criterion for purity in synthetic macrocyclic chemistry due to inclusion of solvent molecules.[18,19] We have found the signals of solvent molecules in the ^{1}H NMR spectra of a few macrocycles. Such compounds were stored for several days under vacuum after heating them in a vacuum drying pistol using steam and then obtained analytical data that agree well with the theoretical values.

2.1. Preparation of Oxo_4Bzo_2[14]diene-N_4 11, Oxo_4Bzo_2[15]diene-N_4 12, Oxo_4Bzo_2[15]diene-N'_4 13, Oxo_4Bzo_2[16]diene-N_4 14, Oxo_4Bzo_3[14]diene-N_4 15, Oxo_4Bzo_3[15]diene-N_4 16

Method 1. 0.01 mol each of compounds **5** (2.98 g), **6** (3.12 g) or **7** (3.46 g) was suspended in 50 mL of benzene separately in two necked flasks to which a refluxing condenser with a guard tube and a pressure equalizing dropping funnel were attached. The dropping funnel was charged with the solution of 0.01 mol (1.27 g) oxalyl dichloride or 0.01 mol (1.41 g) of malonyl dichloride in 30 mL dry benzene. The solution was added at room temperature drop wise over a period of 8 h while stirring continuously. After the addition, the dropping funnel was replaced with a stopper and heated at reflux for 15 h. Then it was cooled and the product was filtered and washed thoroughly with dry benzene. The products were recrystallized from methanol until pure by TLC. The product yields and analytical data and the spectral data are given below.

Method 2. 0.01 mol each of compounds **5**, **6** or **7** was dissolved in 30 mL dioxane or methanol and transferred to a pressure equalizing dropping funnel. 1.46 g (0.01 mol) of diethyl oxalate or 1.60 g (0.01 mol) of diethyl malonate was dissolved in 30 mL methanol taken in a pressure equalizing dropping funnel. Both were fitted to a three necked flask containing 100 mL methanol and fitted with a reflux condenser and a guard tube. Methanol was allowed to boil and the two reagents were added simultaneously over a period of 8 h. The reaction mixture was boiled for 24 h and then the solvent was removed completely under vacuum. The solid left was recrystallized from methanol until pure products (by TLC) were obtained.

2.1.1. Macrocycle 11. White crystalline, yield 2.76 g, (78%); mp 251–52°C; UV λ_{max} (nm) (10^3 ε_{max}) 212 (5.209), 249 (2.969), 324 (0.538); IR 3476, 3368, 3285, 1630, 1550 cm^{-1}; ^{1}H NMR spectrum (δ) 8.56, (4H, br, CO–N*H*), 7.06–7.78 (8H, m, Aromatic-*H*s), 3.45 (4H, d, HN–CH_2, J=4 Hz); mass spectrum, m/z 352 (0.7%, M^+), 297 (20%), 149 (17%), 120 (100%), 92 (28%), 65 (17%); CHN calcd for $C_{18}H_{16}N_4O_4$: C, 61.34; H, 4.58; N, 15.90; found: C, 61.39; H, 4.42; N, 15.75.

2.1.2. Macrocycle 12. White crystals, yield 6.9 g, (77%); mp 260–62°C; UV λ_{max} (nm) (10^3 ε_{max}) 212 (3.543), 248 (3.254), 312 (1.431); IR 3476, 3368, 3285, 1630, 1551 cm^{-1}; ^{1}H NMR (δ) 8.62 (4H, br, CO–N*H*), 7.07–7.96 (8H, m, Aromatic-*H*s), 3.45 (4H, d, HN–CH_2, J=4.6 Hz), 2.52 (2H, s, OC–CH_2–CO); mass spectrum, m/z 366 (0.5%, M^+), 149 (25%), 120 (100%), 92 (28%), 65 (14%); CHN calcd for $C_{19}H_{18}N_4O_4$: C, 62.27; H, 4.96; N, 15.29; found: C, 62.38; H, 4.99; N, 15.14.

2.1.3. Macrocycle 13. White crystalline, yield 3.08 g, (84%); mp 258–60°C; UV λ_{max} (nm) (10^3 ε_{max}) 214 (5.587), 249 (5.257), 326 (2.075); IR 3287, 3140, 1649, 1556 cm^{-1}; ^{1}H NMR (δ) 8.62, (4H, br, CO–N*H*), 7.12–7.98 (8H, m, Aromatic-*H*s), 3.34 (4H, d, HN–CH_2, J=5.2 Hz), 1.8 (2H, m, H_2C–CH_2–CH_2); mass spectrum, m/z 366 (0.8%, M^+), 311 (60%), 149 (30%), 148 (8%) 120 (100%), 92 (29%), 65 (12%); CHN calcd for $C_{19}H_{18}N_4O_4$: C, 62.27; H, 4.96; N, 15.29; found: C, 62.42; H, 4.62; N, 15.32.

2.1.4. Macrocycle 14. White, yield 3.24 g, (85%); mp 265–66°C; UV λ_{max} (nm) (10^3 ε_{max}) 214 (4.923), 249 (5.182), 326 (1.948); IR 3406, 3300, 1643, 1554 cm^{-1}; ^{1}H NMR (δ) 8.63, (4H, br, CO–N*H*), 7.05–8.10 (8H, m, Aromatic-*H*s), 3.34 (4H, d, HN–CH_2, J=4.5 Hz), 2.55 (2H, s, OC–CH_2–CO), 1.83 (2H, quintet, H_2C–CH_2–CH_2, J=8.5 Hz); mass spectrum, m/z 380 (0.2%, M^+), 311 (0.05%), 149 (100%), 121 (2%), 120 (2%), 105 (6%), 92 (2%), 77 (5%); CHN calcd for $C_{20}H_{20}N_4O_4$: C, 63.15; H, 5.30; N, 14.73; found: C, 63.28; H, 5.17; N, 14.85.

2.1.5. Macrocycle 15. Grey coloured, yield 3.2 g, (80%); mp 169–72°C; UV λ_{max} (nm) (10^3 ε_{max}) 216 (13.539), 242 (13.670), 324 (9.124); IR 3456, 3298, 1766, 1618 cm^{-1}; ^{1}H NMR (δ) 7.94, (4H, br, CO–N*H*), 6.78–7.59 (12H, m, Aromatic-*H*s); mass spectrum, m/z 400 (1.2%, M^+), 346 (6%), 239 (68%), 238 (4%), 227 (26%), 210 (15%), 209 (68%) 120 (100%), 92 (36%), 77 (4%), 65 (25%); CHN

calcd for $C_{22}H_{16}N_4O_4$: C, 65.98; H, 4.02; N, 13.98; found: C, 65.72; H, 4.13; N, 13.89.

2.1.6. Macrocycle 16. Grey coloured, yield 3.4 g, (83%); mp 171–73°C; UV λ_{max} (nm) (10^3 ε_{max}) 213 (14.303), 254 (17.056), 333 (7.775); IR 3454, 3302, 1726, 1618 cm^{-1}; ^1H NMR (δ) 7.86, (4H, br, CO–N*H*), 6.67–7.85 (12H, m, Aromatic-*H*s), 2.83 (2H, s, OC–CH_2–CO); mass spectrum, *m*/*z* 414 (1.6%, M^+), 227 (25%), 210 (10%), 209 (34%), 120 (100%), 92 (44%), 77 (8%), 65 (35%); CHN calcd for $C_{23}H_{18}N_4O_4$: C, 66.64; H, 4.38; N, 13.52; found: C, 66.92; H, 4.52; N, 13.49.

2.2. Preparation of Oxo$_2$Bzo$_2$[14]diene-N_4 17, Oxo$_2$Bzo$_2$[15]diene-N_4 18, Oxo$_2$Bzo$_3$[14]triene-N$_4$ 19

0.01 mol each of the compounds **5**, **6** or **7** was dissolved in 50 mL of solvent (**5** in DMF and **6** and **7** in methanol) and 10 g of Na_2CO_3 was added to the solution. To this a solution of 1,2-dichloro ethane (0.99 g, 0.01 mol in 50 mL methanol) was added. The reaction mixture was stirred for about 20 h. Then it was poured into ice-cold water and stirred for 2 h. The products were filtered and dried under vacuum. Recrystallization from methanol was performed until TLC pure compounds were obtained. The physical characteristics, spectral properties and analytical data are as follows.

2.2.1. Macrocycle 17. Light yellow, yield 2.2 g, (68%); mp 229–31°C; UV λ_{max} (nm) (10^3 ε_{max}) 249 (4.097), 324 (1.994), 430 (0.785); IR 3454, 3372, 1646, 1584, 1550 cm^{-1}; ^1H NMR (δ) 8.43, (2H, br, CO–N*H*), 6.7–7.5 (8H, m, Aromatic-*H*s), 4.85 (2H, s, Ar-N*H*–C–), 3.64 (4H, d, OC–NH–CH_2–, J=4.7 Hz), 3.48 (4H, d, Ar-HN–CH_2–, J=3.5 Hz); mass spectra, *m*/*z* 324 (0.6%, M^+), 298 (25%), 178 (10%), 120 (100%), 92 (44%), 77 (8%), 65 (35%), 56 (14%); CHN calcd for $C_{18}H_{20}N_4O_2$: C, 66.65; H, 6.21; N, 17.27; found: C, 66.43; H, 5.97; N, 17.04.

2.2.2. Macrocycle 18. Light yellow, yield 2.6 g, (77%); mp 144–45°C; UV λ_{max} (nm) (10^3 ε_{max}) 212 (3.103), 248 (3.763), 324 (2.513); IR 3481, 3383, 1631, 1584, 1548 cm^{-1}; ^1H NMR (δ) 8.43, (2H, br, CO–N*H*), 6.63–7.56 (8H, m, Aromatic-*H*s), 4.74 (2H, br, Ar-N*H*–C–), 3.52 (4H, s, –HN–CH_2–) 3.48 (4H, m, OC–HN–CH_2–CH_2), 1.82 (2H, quintet, –H_2C–CH_2–CH_2–, J=8 Hz); mass spectra, *m*/*z* 338 (0.01%, M^+), 313 (8.5%), 312 (41.5%), 192 (.44%), 120 (100%), 92 (25.3%), 65 (13.2%); CHN calcd for $C_{19}H_{22}N_4O_2$: C, 67.44; H, 6.55; N, 16.56; found: C, 67.05; H, 6.26; N, 16.47.

2.2.3. Macrocycle 19. White crystals, yield 2.9 g, (78%); mp 163–65°C; UV λ_{max} (nm) (10^3 ε_{max}) 250 (7.907), 290 (5.379), 298_{sh}, 336 (5.468); IR 3485, 3372, 1626, 1584, 1526 cm^{-1}; ^1H NMR (δ) 8.37, (2H, br, CO–N*H*), 6.65–7.56 (12H, m, Aromatic-*H*s), 4.68 (2H, br, Ar-N*H*–C–), 3.54 (4H, s, HN–CH_2–); mass spectra, *m*/*z* 372 (0.3%, M^+), 361 (7%), 346 (30%), 226 (22%), 120 (100%), 109 (8.2%), 92 (45%), 65 (17%); CHN calcd for $C_{22}H_{20}N_4O_2$: C, 70.95; H, 5.41; N, 15.04; found: C, 70.58; H, 5.18; N, 14.86.

Acknowledgements

The financial assistance from DST, Government of India, New Delhi (ERIP/ER/0003280/M/01) is gratefully acknowledged.

References

1. Wainwright, K. P. *Coord. Chem. Rev.* **1997**, *166*, 35–90.
2. Melson, G. A. In *Co-ordination Chemistry of Macrocyclic Compounds*; Melson, G. A., Ed.; Plenum: New York, 1979; Chapter 2.
3. Green, M.; Taskar, P. A. *Inorg. Chim. Acta* **1971**, *5*, 65–69.
4. Ravinder, V.; Jagannatha Swamy, S.; SriHari, S.; Lingaiah, P. *Transition Met. Chem.* **1984**, *9*, 103–106.
5. Kumar, B. K.; Ravinder, V.; Swamy, G. B.; Swamy, S. J. *Indian J. Chem.* **1994**, *33A*, 136–142.
6. Swamy, S. J.; Kumar, B. K. *Indian J. Chem.* **1996**, *35A*, 489–493.
7. Swamy, S. J.; Dharma Reddy, A. *J. Indian Chem. Soc.* **2000**, *77*, 336–338.
8. Swamy, S. J.; Bhaskar, K. *Indian J. Chem.* **1999**, *38A*, 961–966.
9. Cotton, F. A.; Lin, C.; Murillo, C. A. *Inorg. Chem.* **2001**, *40*, 6413.
10. Okubo, T.; Kitawaga, S.; Kondo, M.; Matsuzaka, H.; Ishii, T. *Angew Chem. Int. Ed. Engl.* **1999**, *38*, 931.
11. Black, D. St. C.; Bos Vanderzalm, C. H.; Wong, L. C. H. *Aust. J. Chem.* **1979**, *32*, 2303–2311.
12. Green, M.; Smith, J.; Taskar, P. A. *Inorg. Chim. Acta* **1971**, *5*, 17.
13. Black, D. St. C.; Hartshorn, E. B. *Aust. J. Chem.* **1977**, *30*, 2493–2514.
14. Taskar, P. A.; Fleischer, E. B. *J. Am. Chem. Soc.* **1970**, *92*, 7072–7077.
15. Swamy, S. J.; Suresh, K.; Someshwar, P.; Nagaraju, D. Synth. Commun. (Communicated, No. 10-0400, 15-5-2003)..
16. Owston, P. G.; Peters, R.; Ramsammy, E.; Taskar, P. A.; Trotter, J. *J. Chem. Soc. Chem. Commun.* **1980**, 1218–1220.
17. Donaldson, P. B.; Taskar, P. A.; Alcock, N. W. *J. Chem. Soc., Dalton Trans.* **1976**, 2262–2268.
18. Lazzarotto, M.; Sansone, F.; Baldini, M.; Casnati, A.; Cozzini, P.; Ungaro, R. *Eur. J. Org. Chem.* **2001**, 595–602.
19. Gutsche, C. D.; See, K. A. *J. Org. Chem.* **1992**, *57*, 4527–4539.