A Facile One-Pot Three-Component Synthesis of Macrocyclic Imidazolidines by [3+2] Cycloaddition Reaction of Azomethine Ylides

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Abstract: One-pot three-component synthesis of novel macrocyclic imidazolidines has been accomplished in good yields via a facile [3+2] cycloaddition reaction of azomethine ylide, derived from paraformaldehyde and sarcosine, with various macrocyclic imines as dipolarophiles. The effect of solvent on the [3+2]-dipolar cycloaddition reaction is also studied.

Key words: macrocycle, bisimidazolidine, cycloaddition, azomethine ylide

Macrocycles have received great attention from the scientific community as a result of their widespread occurrence in nature and their astounding applicability in biological and supramolecular chemistry.[1] A key feature of macrocycles is their ability to combine flexibility and conformational preorganization, which makes them a preferred target for the design of new ligands and receptors. Considerable efforts have been directed to the development of new synthetic strategies that allow a more efficient access to this extremely significant class of compounds.

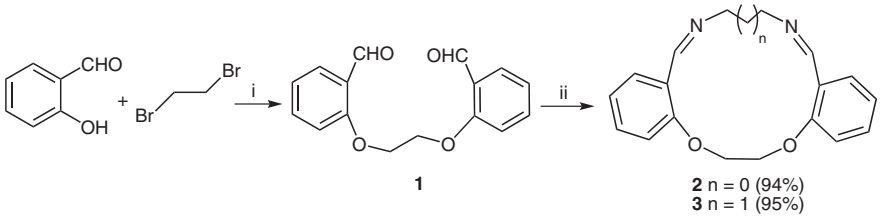
Imidazolidines are important as intermediate in the biosynthesis of nucleotides, cytotoxic metallopharmaceuticals,[2] building blocks in biologically active compounds,[3] and as naturally occurring substances characterized by highly pronounced biological properties.[4,5] Although many methods are available for the synthesis of imidazolidines, many of them requires vigorous reaction conditions and use of expensive catalyst which also results in poor yield of the products.[6] Recent synthesis of imidazolidine includes 1,3-dipolar cycloaddition reaction of N-metallated azomethine ylides with isocyanates,[7] acid-catalyzed reaction of isocyanide with Schiff base,[8] reductive cleavage of imidazolidine using borane leads to the corresponding *N*,*N*,*N*^{1}-trisubstituted ethylenediamines,[9] conversion of aldehyde to imidazolidines by reaction with ethylene diamine,[10] Mannich reactions of 1,2-ethane diamine or *N*-methyl-1,2-benzene diamine with benzotriazole and formaldehyde.[11]

The intermolecular [3+2] cycloaddition reaction of azomethine ylides with olefinic and acetylenic dipolarophiles has resulted in a number of novel heterocyclic scaffolds, which are particularly useful for the creation of diverse chemical libraries of drug-like molecules for biological screening.[12,13] As part of our ongoing program for the synthesis of novel heterocycles through intermolecular 1,3-dipolar cycloaddition,[14] herein we report an expeditious and facile protocol for the synthesis of novel macrocycle-grafted bisimidazolidines by a one-pot three-component 1,3-dipolar cycloaddition of azomethine ylides with macrocyclic imines.

The macrocyclic imines **2** and **3** were prepared by the condensation of dialdehyde **1**[15] with 1,2-diaminoethane or 1,3-diaminopropane in nearly quantitative yields in boiling methanol or ethanol (Scheme 1).[16,17] The reaction conditions have been tuned up to avoid the formation of dimers or oligomers as by-products.[17]

The reaction of paraformaldehyde with α-amino acid derivatives generates azomethine ylide which undergoes 1,3-dipolar cycloaddition reaction with imines to give imidazolidines in a one-pot three-component reaction. The mechanism for the generation of azomethine ylide is shown in Scheme 2.

Diimines **2**, **3**, **8a–c** and **9a–c** reacted with the azomethine ylide derived from paraformaldehyde (**4**) and sarcosine (**5**) in refluxing toluene under Dean–Stark conditions to give bisimidazolidines **6**, **7**, **10a–c** and **11a–c** in moderate yield[18] (Scheme 3 and 4). The formation of cycloadducts was confirmed through spectral and elemental analyses.[19]



Scheme 1 *Reagents and conditions*: (i) anhyd K_2CO_3, anhyd MeCN, KI, reflux, 12 h; (ii) $H_2N(CH_2)_2NH_2$ or $H_2N(CH_2)_3NH_2$, EtOH or MeOH, reflux, 12 h.

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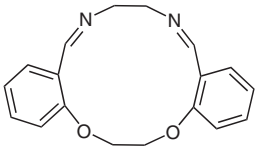
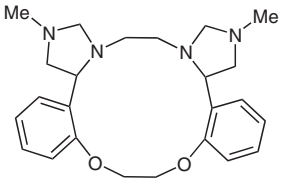
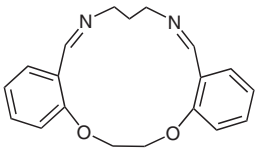
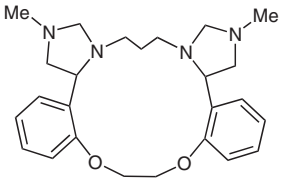
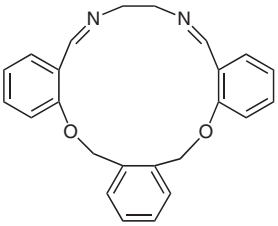
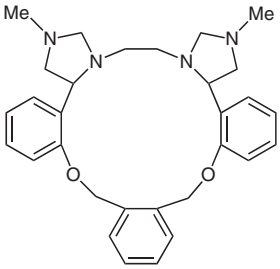
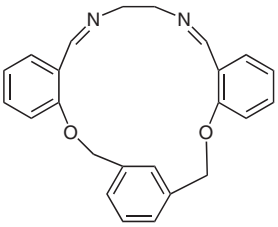
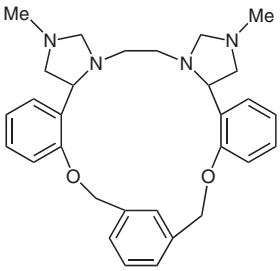
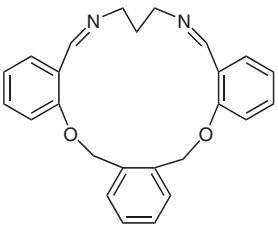
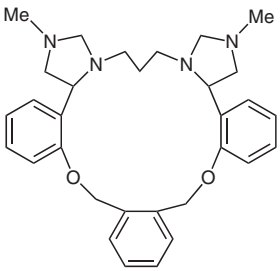
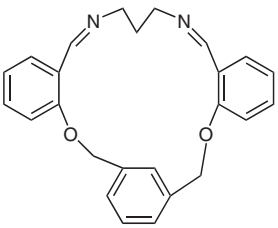
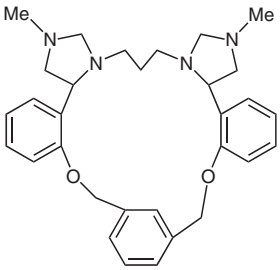
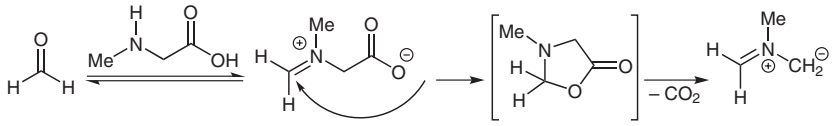
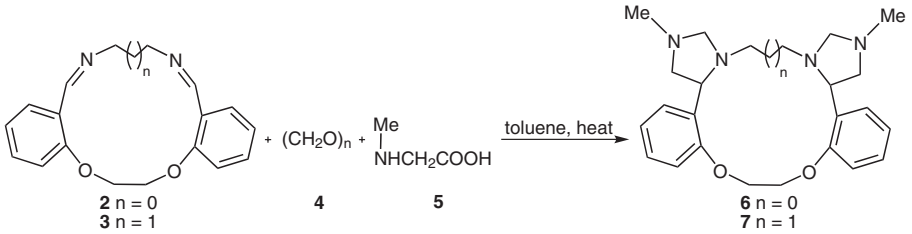
Table 1 Synthesis of Macrocyclic Imidazolidines Using Macrocyclic Imines[20–23]

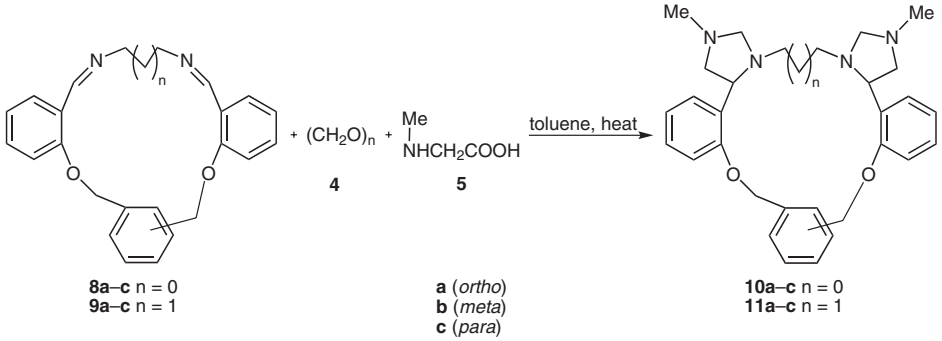
Entry	Imine	Cycloadduct	Yield (%)
1	 **2**	 **6**	68
2	 **3**	 **7**	63
3	 **8a**	 **10a**	65
4	 **8b**	 **10b**	69
5	 **9a**	 **11a**	60
6	 **9b**	 **11b**	63



Scheme 2 Mechanism for the generation of azomethine ylide



Scheme 3



Scheme 4

Thus the ^{1}H NMR spectrum of **6** exhibited a singlet at δ = 2.33 due to the NCH_3 protons of the imidazolidine moiety. The NCH_2 protons of the imidazolidine ring occurred as doublet of doublets at δ = 2.56 (J = 7.2, 7.5 Hz). The NCH_2N protons of the imidazolidine ring appeared as two doublets at δ = 3.24 and δ = 3.30 (J = 6.3 Hz). The benzylic proton exhibited multiplets in the region δ = 5.12–5.18. The -OCH_2- protons attached to the ethylene unit appeared as multiplets in the region δ = 4.17–4.29. The methylene groups joining the two imidazolidine rings occurred as a quartet at δ = 4.33 (J = 4.8 Hz). The aromatic protons resonated as multiplets in the region δ = 6.77–7.43. The off-resonance proton-decoupled ^{13}C spectrum of **6** exhibited peaks at δ = 40.71 due to the imidazolidine NCH_3 bonds. The imidazolidine methylene groups resonated at δ = 65.60 and δ = 71.30. The structure of the product **6** was confirmed by a peak at m/z = 422.3 [M^+] in the mass spectrum and it showed satisfactory elemental analysis. The results are summarized in Table 1.

Scheme 4 depicts the formation of cycloadducts **10a–c** and **11a–c** wherein the imine dipolarophiles **8** and **9a–c** reacted with the azomethine ylide generated from **4** and **5**. The formation of the cycloadducts was confirmed by spectroscopic techniques.

To improve the yields of the product, we carried out the reaction in various solvents. We found that using benzene or acetonitrile as solvent did not give the products in good yield. However, when the reaction was carried out in toluene, the reaction was found to give better yield of the products with the reduction of reaction time (Table 2).

The synthesis of the *p*-isomer of the bisimidazolidine **10c** and **11c** could not be achieved due to the poor solubility of bisimines **8c** and **9c** in organic solvents.

In conclusion we have synthesized a series of hitherto unknown macrocycle-based bisimidazolidines through one-pot three-component [3+2] cycloaddition of azomethine ylides with unusual macrocyclic imines as dipolarophiles.

Acknowledgment

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References and Notes

(1) (a) Von Nussbaum, F.; Brands, M.; Hinzen, B.; Weigand, S.; Häbich, D. *Angew. Chem. Int. Ed.* **2006**, *45*, 5072. (b) Gibson, S. E.; Lecci, C. *Angew. Chem. Int. Ed.* **2006**, *45*, 1364. (c) Kahne, D.; Leimkuhler, C.; Lu, W.; Walsh, C. *Chem. Rev.* **2005**, *105*, 425. (d) Hruby, V. J.; Al-Obeidi, F.; Kazmierski, W. *Biochem. J.* **1990**, *268*, 249. (e) Kessler, H. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 512.

Table 2 Solvent Effects on Cycloaddition of Macrocyclic Dipolarophiles with Paraformaldehyde and Sarcosine

Product	Benzene, reflux		Acetonitrile, reflux		Toluene, reflux	
	Time (h)	Yield (%)	Time (h)	Yield (%)	Time (h)	Yield (%)[a]
6	48	19	56	12	24	68
7	46	17	58	11	23	63
10a	40	15	54	12	22	65
10b	43	12	57	10	23	69
11a	42	11	60	7	25	62
11b	45	8	55	9	26	60

[a] Based on recovered starting material.

(2) (a) Chang-Fong, J.; Benamour, K.; Szymonski, B.; Thomasson, F.; Morand, J. M.; Cussac, M. *Chem. Pharm. Bull.* **2000**, *48*, 729. (b) Sage, C. R.; Michelistich, M. D.; Stout, J.; Biermann, D.; Nissen, R.; Finer-Moore, N.; Stroud, R. M. *Biochemistry* **1998**, *37*, 13893.

(3) (a) Sharma, V.; Crankshaw, C. L.; Piwnica-Worms, D. *J. Med. Chem.* **1996**, *39*, 3483. (b) Sage, C. R.; Michelitsch, M. D.; Stout, T. J.; Blermann, D.; Nissen, R.; Finer-Moore, J.; Stroud, R. M. *Biochemistry* **1998**, *37*, 13893. (c) Olmos, G.; Rinera, J.; Varcia-Sevilla, H. A. *Eur. J. Pharm.* **1996**, *310*, 273. (d) Chang-Fong, J.; Benamour, K.; Szymonski, B.; Thomasson, F.; Morangd, J. M.; Cussac, M. *Chem. Pharm. Bull.* **2000**, *48*, 729. (e) Sakuta, H.; Okamotto, K. *Eur. J. Pharm.* **1994**, *259*, 223.

(4) (a) Sharma, V.; Khan, M. S. Y. *Eur. J. Med. Chem.* **2001**, *36*, 651. (b) Kalyaham, N.; Sparthasarathy, P. C.; Ananthan, L.; Manjunatha, S. G.; Likhate, M. A. *Indian J. Chem. Sect. B: Org. Chem. Incl. Med. Chem.* **1992**, *31*, 243.

(5) (a) Van Hook, J. O.; Craig, W. E. U.S. Patent, 2675387, **1955**; *Chem. Abstr*. **1955**, 49, 4729. (b) Craig, W. E.; Van Hook, J. O. U.S. Patent, 2675381, **1956**; *Chem. Abstr*. **1956**, 50, 411.

(6) (a) Li, X.; Bera, M.; Musie, G. T.; Powell, D. R. *Inorg. Chim. Acta* **2007**. (b) Li, J.; Wang, S.; Hu, J.; Chein, H. *Tetrahedron Lett.* **1999**, *40*, 1961.

(7) Erkizia, E.; Aldaba, E.; Vara, Y.; Arrieta, A.; Gornitzka, H.; Cossio, F. P. *ARKIVOC* **2005**, *(ix)*, 189.

(8) Saegusa, T.; Taka-ishi, N.; Tamura, I.; Fujii, H. *J. Org. Chem.* **1969**, *34*, 1145.

(9) Northrop, R. C.; Russ, P. L. *J. Org. Chem.* **1975**, *40*, 558.

(10) Wanzlick, H. W.; Lochel, W. *Chem. Ber.* **1963**, *86*, 1463.

(11) Katritzky, A. R.; Suzuki, K.; He, H. Y. *J. Org. Chem.* **2002**, *67*, 3109.

(12) (a) *1,3-Dipolar Cycloaddition Chemistry*, Vol. 1; Padwa, A., Ed.; Wiley: New York, **1984**. (b) *1,3-Dipolar Cycloaddition Chemistry*, Vol. 2; Padwa, A., Ed.; Wiley: New York, **1984**. (c) Pandey, G.; Banerjee, P.; Gadre, S. R. *Chem. Rev.* **2006**, *106*, 4484.

(13) Grigg, R.; Sridharan, V. In *Advances in Cycloaddition*, Vol. 3; Curran, D. P., Ed.; Jai Press: London, **1993**, 161.

(14) (a) Suresh Babu, A. R.; Raghunathan, R. *Tetrahedron Lett.* **2007**, *48*, 6809. (b) Subramaniyan, G.; Raghunathan, R.; Martin Castro, A. M. *Synthesis* **2002**, 2440. (c) Jayashankaran, J.; Rathna Durga, R. S. M.; Raghunathan, R. *Tetrahedron Lett.* **2004**, *45*, 7303. (d) Suresh Babu, A. R.; Raghunathan, R. *Tetrahedron Lett.* **2008**, *49*, 4487.

(15) **Representative Procedure for Dialdehyde 1**: A mixture of freshly distilled salicylaldehyde (2 mmol), dibromoethane (1 mmol), anhyd K_2CO_3 (2 mmol) and KI (0.1 mmol) in anhyd MeCN (20 mL) was refluxed overnight. After completion of the reaction MeCN was distilled off under vacuum. The reaction mixture was then washed with H_2O and extracted with $CHCl_3$. The organic layer was concentrated by distillation under reduced pressure to give the required dialdehyde in an excellent yield (97%).

(16) **Representative Experimental Procedure for the Synthesis of Imine Derivative 2**: A mixture of dialdehyde **1** (1 mmol), 1,2 diamino ethane (1 mmol), and EtOH (100 mL) was refluxed for 12 h. After completion of the reaction the solvent was carefully removed under reduced pressure to give the required bisimine **2**.

(17) Arumugam, N.; Raghunathan, R. *Tetrahedron Lett.* **2006**, *47*, 8855.

(18) (a) Simon, A.; Simon, C.; Kanda, T.; Nagashima, S.; Mitoma, T.; Yamada, T.; Mimura, K.; Tashiro, M. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2071. (b) Armstrong, L. G.; Lindoy, L. F. *Inorg. Chem.* **1975**, *14*, 1322.

(19) **Representative Procedure for the Synthesis of Bisimidazolidine Derivatives 6**, **7**, **10**, **11**: A mixture of sarcosine (4.0 equiv), paraformaldehyde (12 equiv) and the corresponding macrocyclic diimine (1 equiv) was heated under reflux in toluene in a Dean–Stark apparatus (10 mL for 1 mmol of dipolarophile). After completion of the reaction as evidenced by TLC the reaction mixture was filtered through a pad of Celite and the solvent was removed under reduced pressure. The crude product was subjected to column chromatography using petroleum ether–EtOAc (3:2) as eluent to get the pure product.

(20) **Macrocyclic Schiff Base 8b**: R_f = 0.6 (Hex–EtOAc, 3:1); pale yellow solid; yield: 95%; mp 126–129 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.12 (s, 4 H), 5.22 (s, 4 H), 6.78–7.80 (m, 12 H), 8.78 (s, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 60.6, 68.1, 112.1, 120.8, 123.6, 125.2, 125.5, 128.3, 128.6, 131.4, 137.7, 159.3. MS: *m/z* = 366 [M$^+$]. Anal. Calcd for $C_{24}H_{22}N_2O_2$: C, 77.79; H, 5.99; N, 7.56; Found: C, 77.84; H, 6.04; N, 7.48.

(21) **Macrocyclic Imidazolidine 6**: R_f = 0.5 (Hex–EtOAc, 3:2); yellow liquid; yield: 68%. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.33 (s, 6 H), 2.56 (dd, *J* = 7.2, 7.5 Hz, 4 H), 3.24 (d, *J* = 6.3 Hz, 2 H), 3.32 (d, *J* = 6.3 Hz, 2 H), 4.17–4.29 (m, 4 H), 4.33 (q, *J* = 4.8 Hz, 4 H), 5.12–5.18 (m, 2 H), 6.77–7.43 (m, 8 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 40.71, 60.52, 65.60, 71.30, 87.69, 109.85, 120.13, 124.59, 126.98, 130.23, 154.03. MS: *m/z* = 422.32 [M$^+$]. Anal. Calcd for $C_{24}H_{32}N_4O_2$: C, 70.54; H, 7.89; N, 13.72; Found: C, 70.68; H, 7.98; N, 13.84.

(22) **Macrocyclic Imidazolidine 10a**: R_f = 0.5 (Hex–EtOAc, 3:2); yellow liquid; yield: 65%. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.35 (s, 6 H), 2.60 (dd, *J* = 7.2, 7.5 Hz, 4 H), 2.83

(d, J = 6.9 Hz, 2 H), 3.27 (d, J = 6.9 Hz, 2 H), 4.35–4.39 (q, J = 4.8 Hz, 4 H), 5.09 (s, 4 H), 5.19 (t, 2 H), 6.81–7.46 (m, 12 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 40.74, 48.43, 52.40, 67.30, 71.43, 110.31, 120.23, 125.94, 127.27, 127.80, 127.93, 128.29, 142.32, 153.57, 161.53. MS: m/z = 484.30 [M$^+$]. Anal. Calcd for $C_{30}H_{36}N_4O_2$: C, 74.33; H, 7.49; N, 11.56. Found: C, 74.48; H, 7.60; N, 11.68.

(23) **Macrocyclic Imidazolidine 11b**: yellow liquid; yield: 60%. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.79–0.83 (m, 2 H), 2.23–2.33 (m, 4 H), 2.39 (s, 6 H), 2.63 (dd, J = 7.2, 7.2 Hz, 4 H), 2.81 (d, J = 6.3 Hz, 2 H), 2.88 (d, J = 6.0 Hz, 2 H), 4.41 (q, J = 4.8 Hz, 4 H), 5.23 (t, J = 6.9 Hz, 2 H), 6.81–7.47 (m, 12 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 29.35, 41.85, 49.43, 61.63, 69.83, 72.49, 88.81, 111.36, 121.08, 125.53, 125.87, 126.74, 127.99, 128.99, 130.72, 131.38, 137.53, 155.12. MS: m/z = 497.15 [M$^+$]. Anal. Calcd for $C_{31}H_{38}N_4O_2$: C, 74.65; H, 7.68; N, 11.24. Found: C, 74.78; H, 7.54; N, 11.32.