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Vilsmeier methodology for the synthesis of 3-(2-*N*-phthaloylacyl)indole derivatives, and its application to the synthesis of the GCDEF rings of diazonamide

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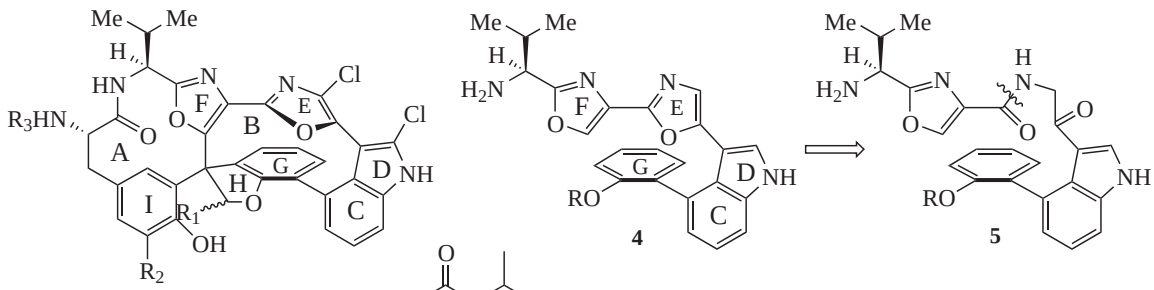
Abstract—The synthesis of the GCDEF fragment of diazonamide was achieved using a modified Vilsmeier procedure that allows ready access to 3-(2-*N*-phthaloylacyl)indole derivatives.

In 1991 Fenical and Clardy reported the structure of diazonamide A, **1** and diazonamide B, **2**, Scheme 1.[1] The diazonamides have generated some considerable synthetic interest,[2] and the synthesis of oxazoles and bis-oxazoles has undergone renewed interest.[3–5] In this letter we report the synthesis of the GCDEF fragment (right-hand side) **4** of diazonamide, and a Vilsmeier-based method to introduce the oxoethylamine side chain at the 3-position of an indole ring.[6] The synthesis of **4** is most readily accomplished from the Robinson–Gabriel oxazole dehydration of **5**.[7] Consequently, we required a method that would convert an indole into its 3-aminoacyl derivative.[8] Surprisingly, there is little information describing this transformation.[9]

Treatment of **6** with ethyl magnesium chloride followed by **8**[10] gave a mixture of **9**, **10** and **11** (14%) (Scheme 2). Transmetallation of the magnesium bromide salt of **6** with zinc chloride[11] and addition of **8** gave **11** (40–46%), but upon scale-up (500 mg) substantial amounts of **10** were formed.

The *N*,*N*-dimethylamide derivative **13**,[12] in dioxane, was treated with $POCl_3$ and heated at 100°C for 1 h. The solution was cooled to room temperature, **6** was added, and the mixture heated at 95°C for 3 h. The hot solution was poured into water, the pH adjusted to 8 (2.5 M NaOH), and the mixture was boiled for 10 min, cooled in ice and filtered to give **11** (80%). Extension of the procedure to **7** gave **12** (95%).



1, Diazonamide A, R_1 = OH, R_2 = H, R_3 =

2, Diazonamide B, R_1 = OH, R_2 = Br, R_3 = H.

3, R_1 = O2 (acetal), R_2 = Br, R_3 = COC_6H_4Br-*p*.

Scheme 1.

Keywords: diazonamide; Vilsmeier; acylamino indoles.

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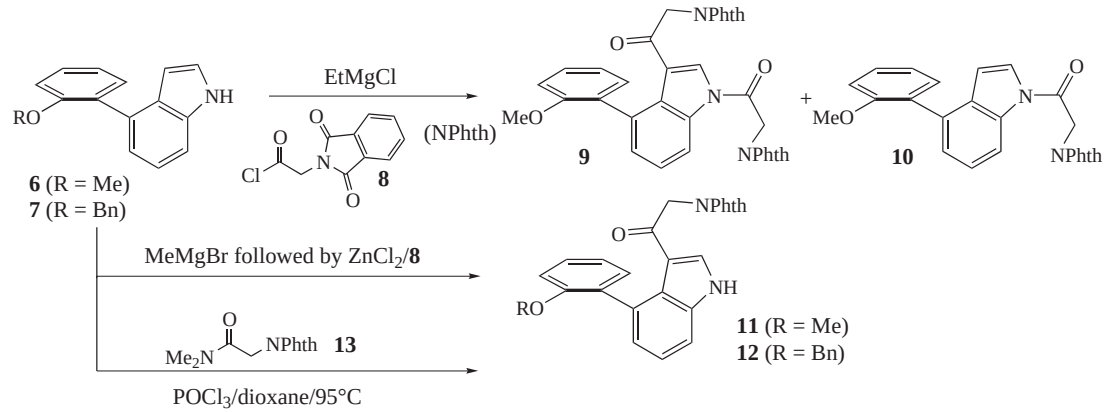
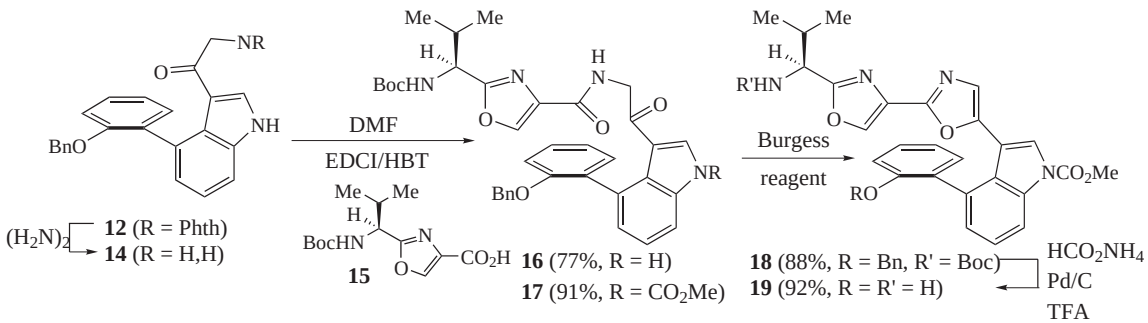


Scheme 2.



Scheme 3.

Table 1.

Substrate	Product (s)	Yield
20	**21**	63%
22	**23**	40%
24	**25** **26**	49% and 37% respectively
27	**28**	ca. 50% (impure)

Hydrazinolysis of **12** (R = Phth), Scheme 3, gave **14**, which was coupled to **15**[13] to give **16** (77% from **12**). Protection of the indole **16** as the carbamate derivative **17** followed by dehydration with the Burgess reagent gave **18** (71%). Hydrogenolysis of the benzyl ether followed by treatment with trifluoroacetic acid resulted in the aminophenol **19** (77% from **18**).[14] The overall sequence provides a convenient route to the GCDEF fragment (right-hand side) of diazonamide in multigram quantities, and avoids the dehydrogenation methodology used to introduce the 3-carbonyl group that requires 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ).[15]

Further examples of the Vilsmeier procedure for the synthesis of 3-(2-*N*-phthaloylacyl)indole derivatives are listed in Table 1. Interestingly, 2-phenyl indole **24** gave **25** and the remarkably stable enamine derivative **26**. The enamine **26** was converted into **25** (87%) by treatment with 2 M HCl in THF heated at reflux (2 h).

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References

1. Lindquist, N.; Fenical, W.; Van Duyne, G. D.; Clardy, J. *J. Am. Chem. Soc.* **1991**, *113*, 2303.
2. Moody, C.; Doyle, K.; Elliott, M.; Mowlem, T. *Pure Appl. Chem.* **1994**, *66*, 2107. Moody, C.; Doyle, K.; Elliott, M.; Mowlen, T. *J. Chem. Soc., Perkin 1* **1997**, 2413. Konopelski, J.; Hottenroth, J.; Oltra, H.; Veliz, E.; Yang, Z.-C. *Synlett* **1996**, 609. Hang, H. C.; Drotleff, E.; Elliott, G. I.; Ritsema, T. A.; Konopelski, J. P. *Synthesis* **1999**, 398. Boto, A.; Ling, M.; Meek, G.; Pattenden, G. *Tetrahedron Lett.* **1998**, *39*, 8167. Jeong, S.; Chen, X.; Harran, P. G. *J. Org. Chem.* **1998**, *63*, 8640. Chen, X.; Esser, L.; Harran, P. G. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 937.
3. Molina, P.; Fresneda, P. A.; lmendros, P. *Synthesis* **1993**, 54. Ang, K.; Prager, R.; Smith, J.; Weber, B.; Williams, C. *Tetrahedron Lett.* **1996**, *37*, 675. Barrett, A. G. M.; Kohrt, J. *Synlett* **1995**, 415. Bagley, M.; Buck, R.; Hind, S. L.; Moody, C.; Slawin, A. *Synlett* **1996**, 825.
4. Doyle, K.; Moody, C. *Tetrahedron Lett.* **1992**, *33*, 7769. Doyle, K.; Moody, C. *Tetrahedron* **1994**, *50*, 3761. Wipf, P.; Miller, C. *J. Org. Chem.* **1993**, *58*, 3604. Yoo, S.-K. *Tetrahedron Lett.* **1992**, *33*, 2159. Vedejs, E.; Wang, J. *Org. Lett.* **2000**, *2*, 1031. Vedejs, E.; Barda, D. A. *Org. Lett.* **2000**, *2*, 1033. Lach, F.; Moody, C. J. *Tetrahedron Lett.* **2000**, *41*, 6893. Bagley, M. C.; Hind, S. L.; Moody, C. J. *Tetrahedron Lett.* **2000**, *41*, 6897. Bagley, M. C.; Moody, C. J.; Pepper, A. G. *Tetrahedron Lett.* **2000**, *41*, 6901.
5. Wipf, P.; Venkatraman, S. *Synlett* **1997**, 1.
6. Chan, F.; Magnus, P.; McIver, E. G. *Tetrahedron Lett.* **2000**, *41*, 835. Magnus, P.; McIver, E. G. *Tetrahedron Lett.* **2000**, *41*, 831. Magnus, P.; Kreisberg, J. D. *Tetrahedron Lett.* **1999**, *40*, 451.
7. Lister, J.; Robinson, R. *J. Chem. Soc.* **1912**, 1297. Robinson, R. *J. Chem. Soc.* **1909**, 2167. Gabriel, S. *Chem. Ber.* **1907**, *40*, 2648. Gabriel, S. *Chem. Ber.* **1910**, *43*, 1283. For the use of the Burgess reagent for this transformation, see: Brain, C. T.; Paul, J. M. *Synlett* **1999**, *10*, 1642.
8. Mingoia, Q. *Gazz. Chim. Ital.* **1931**, *61*, 646.
9. Barret, R.; Roue, N. *Tetrahedron Lett.* **1999**, *40*, 3889. Oikawa, Y.; Yoshida, T.; Mohri, K.; Yonemitsu, O. *Heterocycles* **1979**, *12*, 1457. Bergman, J. *J. Heterocycl. Chem.* **1970**, *7*, 1071. DeGraw, J. I.; Kennedy, J. G.; Skinner, W. A. *J. Heterocycl. Chem.* **1966**, *3*, 9. Jackson, A. H.; Smith, A. E. *J. Chem. Soc.* **1965**, 3498. Bergman, J.; Bäckvall, J.-E.; Lindström, J.-O. *Tetrahedron* **1973**, *29*, 971.
10. Griffiths, D. V.; Hughes, J. M.; Brown, J. W.; Caesar, J. C.; Swetnam, S. P.; Cumming, S. A.; Kelly, J. D. *Tetrahedron* **1997**, *53*, 17815.
11. Bergman, J.; Venemalm, L. *Tetrahedron* **1990**, *46*, 6061.
12. Takechi, H.; Machida, M.; Kanaoka, Y. *Liebigs Ann. Chem.* **1986**, 859.
13. Downing, S. V.; Aguilar, E.; Meyers, A. I. *J. Org. Chem.* **1999**, *64*, 826.
14. Spectral data for **19**. IR ($CHCl_3$) 3366, 1742, 1504, 1444 cm^{-1}. ^1H NMR (300 MHz, MeOD) δ 0.89–0.96 (6H, m), 2.18 (1H, m), 4.06 (3H, s), 4.80 (4H, b), 6.28 (1H, d, $J=12.7$ Hz), 6.70 (2H, m), 7.00 (2H, m), 7.27 (1H, d, $J=8.3$ Hz), 7.47 (1H, t, $J=7.8$ Hz), 7.87 (2H, d, $J=7.0$ Hz), 8.29 (1H, d, $J=8.4$ Hz). HRMS (CI) calcd for $C_{26}H_{25}N_4O_5$ (MH^+); 473.1747. Found: 473.1751.
15. Oikawa, Y.; Yoshioka, T.; Mohri, K.; Yonemitsu, O. *Heterocycles* **1979**, *12*, 1457. Oikawa, Y.; Yonimitsu, O. *J. Org. Chem.* **1977**, *42*, 1213.