Pergamon

Tetrahedron Letters 43 (2002) 7393–7396

TETRAHEDRON LETTERS

Pummerer reaction methodology for the synthesis of 5-thiophenyl substituted oxazoles

Jennifer D. Kreisberg, Philip Magnus* and Shirin Shinde

Department of Chemistry and Biochemistry, University of Texas at Austin, Austin, TX 78712, USA

Received 31 July 2002; revised 9 August 2002; accepted 14 August 2002

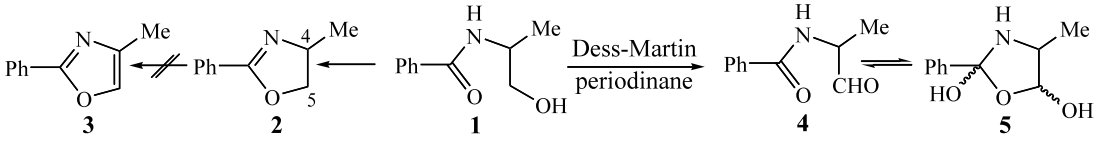
Abstract—Treatment of *N*-acylamino-2-thiophenyl derivatives with *N*-chlorosuccinimide (2.0 equiv.) followed by $SnCl_4$ (0.1–1.0 equiv.) provides a direct synthesis of 5-thiophenyloxazoles. © 2002 Published by Elsevier Science Ltd.

The first oxazole was prepared in 1840 from the reaction of benzil with alcoholic ammonia, although, of course, the structure was unknown at that time.[1,2] Subsequently, there has been considerable work in the area of oxazole synthesis with several reviews on the topic.[3] One of the most versatile syntheses of oxazoles is the classical Robinson–Gabriel synthesis which involves the dehydration of *N*-acylaminoketones.[4] In 1993, Wipf reported a modification of this reaction that uses triphenylphosphine, triethylamine, and iodine for the dehydration.[5] Although this synthesis works well for *N*-acylaminoketones, dehydration of the corresponding *N*-acylaminoaldehydes to form oxazoles occurs in low yields (ca. 17%).

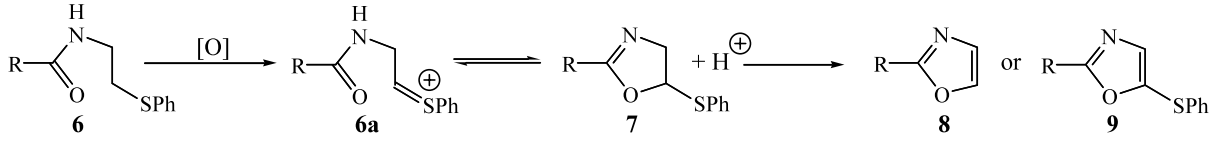
We have found that oxidation of **1** using the Dess–Martin periodinane reagent gave **4** which exists predominantly in the form of the hydrated adduct **5** (Scheme 1). All attempts to dehydrate[6] **5** to give **3** resulted in extensive decomposition to unidentified oligomeric material containing small amounts (<5%) of the oxazole **3**. Furthermore, while **1** could be dehydrated (Burgess reagent)[7] to give **2**, dehydrogenation of **2** to give **3** was not successful, presumably because **2** lacks an activating substitutent at either C4 or C5 (such as an ester) to facilitate this process.[8]

Since we required a convenient synthesis of 2,4-disubstituted oxazoles for the synthesis of model compounds related to the antitumor agent diazonamide A,[9] we have studied the conversion of *N*-acyl-2-amino sulfides **6** into either **8** and/or **9** via the sulfonium ion intermediate **6a** and 5-thiophenyl oxazoline **7**, as depicted in Eq. (1).

The required *N*-acylamino-2-sulfides and 2-aminosulfides were synthesized as indicated in Eqs. (2) and (3).[10]



Scheme 1.

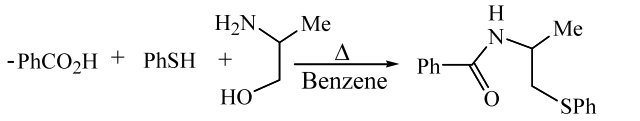


(1)

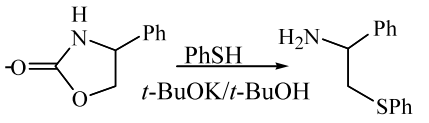
Keywords: oxazole; diazonamide A; 5-thiophenyloxazoles.

* Corresponding author.

0040-4039/02/$ - see front matter © 2002 Published by Elsevier Science Ltd.
PII: S0040-4039(02)01704-5



10 (65%) (2)



11 (72%) (3)

Treatment of **10** with *N*-chlorosuccinimide in chlorobenzene, followed by the addition of $SnCl_4$ at 100°C gave a 40% yield of **12** (mixture of *cis*- and *trans*-isomers) along with 20% of **13** (Scheme 2). The amount of **13** could be reduced by lowering the reaction temperature (entries 2–5) (Table 1). The yield of **12** could be increased to 73% (after purification) by cooling the reaction mixture to 0°C before addition of $SnCl_4$.

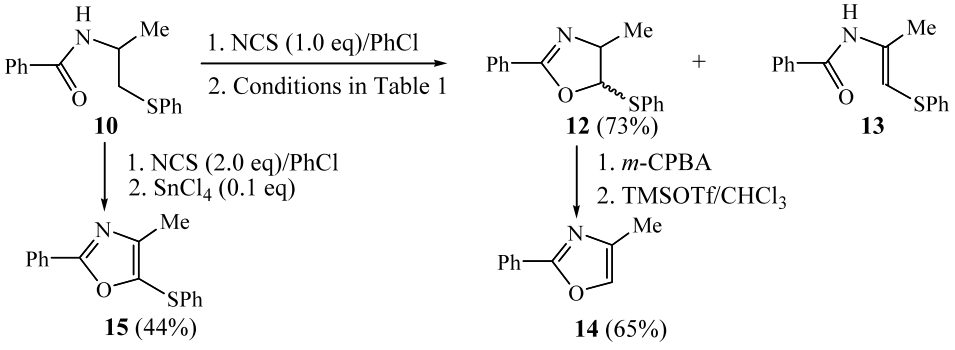
The elimination of the PhS- in **12** to give **14** was not readily accomplished. Similar eliminations that have been used for the syntheses of furans using mild conditions such as heating with mercuric chloride/mercuric oxide mixtures, or oxidation followed by warming did not work.[11]

Oxidation of **12** to the derived sulfoxide with *m*-CPBA, followed by heating the crude mixture in toluene with trifluoroacetic anhydride or *p*-toluenesulfonic acid did not give **14**, whereas treatment of the sulfoxide with TMSOTf/$CHCl_3$ (reflux) afforded 2-phenyl-4-methyloxazole in 65% yield.[12] Because of the difficulty in conducting the elimination of **12** to give **14** we examined the conversion of **10** to give **15**.

Treatment of **10** with two equivalents of *N*-chlorosuccinimide in chlorobenzene, followed by addition of $SnCl_4$ (0.1 equiv.) gave the 5-thiophenyloxazole **15** in 44% yield.[13] Application of this procedure to several *N*-acylamino-2-thiophenyl derivatives **16**, **18**, **20**, **22**, **24** and **26** gave the corresponding 5-thiophenyloxazoles **17**, **19**, **21**, **23**, **25** and **27**, respectively (Table 2).

Representative experimental procedure: To a stirred solution of the amide **24** (150 mg, 0.488 mmol) in chlorobenzene (2 mL) at 23°C was added *N*-chlorosuccinimide (130 mg, 0.975 mmol) in portions. After 35 min the yellow solution was filtered through a pad of glass wool into a dry flask under argon, rinsing with chlorobenzene. A solution of $SnCl_4$ in CH_2Cl_2 (3 M, 0.016 mL, 0.049 mmol) was added. After 1 h the mixture was quenched with a 30% aqueous solution of Rochelle's salt (10 mL), and the resulting mixture stirred vigorously for 1 h. The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (3×15 mL). The combined extracts were dried (Na_2SO_4), evaporated in vacuo, and the crude product was purified by chromatography over silica gel eluting with 40% EtOAc/hexanes and recrystallized from hexanes to give the oxazole **25** as white crystals (114 mg, 77%).

In summary, the above methodology provides a convenient synthesis of 5-thiophenyloxazoles from readily available *N*-acylamino-2-thiophenyl derivatives.[20]

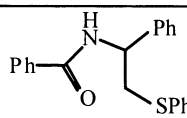
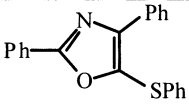
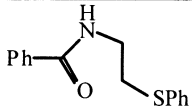
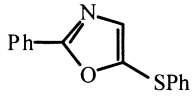
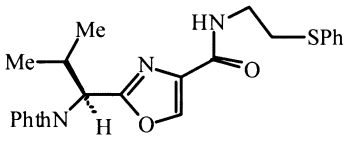
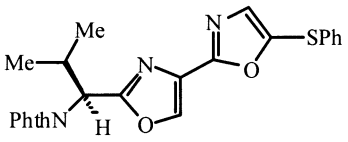
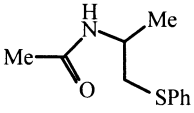
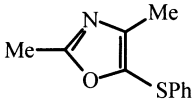
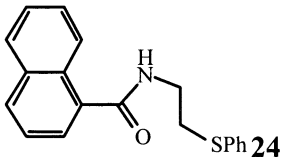
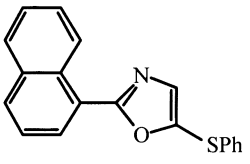
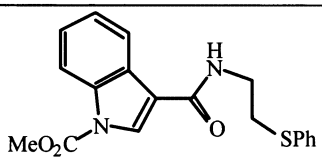
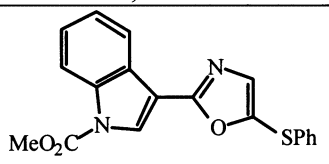


Scheme 2.

Table 1.

Entry	Conditions	Temp. (°C)	Yield of **12** (%)	Yield of **13** (%)
1	0.1 equiv. $SnCl_4$	100	40	20
2	0.1 equiv. $SnCl_4$	60	50	10
3	1.0 equiv. $SnCl_4$	25	50	5
4	0.1 equiv. $SnCl_4$	25	57	0–20
5	0.1 equiv. $SnCl_4$	0	73	0

Table 2.

Substrate	Conditions	Product(%)
 **16**	1. NCS (2.0 eq) in PhCl at 23°C. 2. $SnCl_4$ (0.1 eq).	 **17**, 65%[14]
 **18**	1. NCS (2.0 eq) in PhCl at 23°C. 2. $SnCl_4$ (1.0 eq).	 **19**, 51%[15]
 **20**	1. NCS (2.0 eq) in PhCl at 23°C. 2. $SnCl_4$ (1.0 eq).	 **21**, 55%[16]
 **22**	1. NCS (2.0 eq) in PhCl at 23°C. 2. $SnCl_4$ (1.0 eq).	 **23**, 50%[17]
 **24**	1. NCS (2.0 eq) in PhCl at 23°C. 2. $SnCl_4$ (1.0 eq).	 **25**, 77%[18]
 **26**	1. NCS (2.0 eq) in PhCl at 23°C.	 **27**, 53%[19]

Acknowledgements

The National Institutes of Health (CA 50512), Robert A. Welch Foundation, Merck Research Laboratories and Novartis are thanked for their support of this research.

References

1. Wiley, R. H. *Chem. Rev.* **1945**, *37*, 401.
2. (a) Japp, F. R.; Wilson, W. H. *J. Chem. Soc.* **1886**, 831; (b) Japp, F. R.; Murry, T. S. *J. Chem. Soc.* **1893**, 469.
3. (a) Cornforth, J. W. In *Oxazoles and Oxazolones*; Clarke, H. T., Ed.; Princeton University Press: Princeton, New Jersey, 1949; p. 688; (b) Turchi, I. J.; Dewar, M. J. S. *Chem. Rev.* **1975**, *75*, 389.
4. (a) Lister, J.; Robinson, R. *J. Chem. Soc.* **1912**, 1297; (b) Robinson, R. *J. Chem. Soc.* **1909**, 2167; (c) Gabriel, S. *Chem. Ber.* **1907**, *40*, 2647; (d) Gabriel, S. *Chem. Ber.* **1910**, *43*, 1283; for modifications by Cornforth, see: (e) Cornforth, J. W.; Cornforth, R. H. *J. Chem. Soc.* **1947**, 96; (f) Cornforth, J. W.; Cornforth, R. H. *J. Chem. Soc.* **1953**, 93; (g) Green, N.; LaForge, F. B. *J. Am. Chem. Soc.* **1948**, *70*, 2812.
5. Wipf, P.; Miller, C. P. *J. Org. Chem.* **1993**, *58*, 3604.
6. (a) Brain, C. T.; Paul, J. M. *Synlett* **1999**, *10*, 1642; (b) Wipf, P.; Lim, S. *J. Am. Chem. Soc.* **1995**, *117*, 558; (c) Morwick, T.; Hrapchak, M.; DeTuri, M.; Campbell, S. *Org. Lett.* **2001**, *4*, 2665.
7. (a) Atkins, G. M.; Burgess, E. M. *J. Am. Chem. Soc.* **1968**, *90*, 4744; (b) Spanka, C.; Clapham, B.; Janda, K. D. *J. Org. Chem.* **2002**, *67*, 3045.
8. (a) Evans, D. A.; Gage, J. R.; Leighton, J. L. *J. Am. Chem. Soc.* **1992**, *114*, 9434; (b) Barrish, J. C.; Singh, J.; Spergel, S. H.; Han, W.; Kissick, T. P.; Kronethal, D. R.; Mueller, R. H. *J. Org. Chem.* **1993**, *58*, 4494; (c) Meyers, A. I.; Tavares, F. X. *J. Org. Chem.* **1996**, *61*, 8207; (d) Williams, D. R.; Lowder, P. D.; Gu, Y.-G.; Brooks, D. A. *Tetrahedron Lett.* **1997**, *38*, 331.
9. (a) Lindquist, N.; Fenical, W.; Van Duyne, G. D.; Clardy, J. *J. Am. Chem. Soc.* **1991**, *113*, 2303; for structural revision, see: (b) Li, J.; Jeong, S.; Esser, L.; Harran, P. G. *Angew. Chem., Int. Ed.* **2001**, *40*, 4765; (c) Li, J.; Burgett, A. W. G.; Esser, L.; Amezcua, C.; Harran, P. G. *Angew. Chem., Int. Ed.* **2001**, *40*, 4770.
10. (a) Wehrmeister, H. L. *J. Org. Chem.* **1963**, *28*, 2587 and 2589; (b) Ishibashi, H.; Uegaki, M.; Sakai, M. *Synlett* **1997**, 915; (c) Ishibashi, H.; Uegaki, M.; Sakai, M.; Takeda, Y. *Tetrahedron* **2001**, *57*, 2115.

11. (a) Miyashita, M. K.; Toshiaki; Yoshikoshi, A. *J. Chem. Soc., Chem. Commun.* **1978**, *8*, 362; (b) Kulinkovich, O. G.; Tishchenko, I. G.; Roslik, N. A. *Zh. Org. Khim.* **1984**, *20*, 532; (c) Chan, W. H.; Lee, A. W. M.; Chan, E. T. T. *J. Chem. Soc., Perkin Trans. 1* **1992**, 945.
12. (a) Friedman, B. S.; Sparks, M.; Adams, R. *J. Am. Chem. Soc.* **1937**, *59*, 2262; (b) Hantzsch, A. *Chem. Ber.* **1888**, *21*, 943; (c) Lewy, M. *Chem. Ber.* **1888**, *21*, 2193; (d) Lewy, M. *Chem. Ber.* **1887**, *20*, 2576.
13. (a) Vinogradova, T. K.; Kisilenko, A. A.; Drach, B. S. *J. Org. Chem. USSR* **1982**, *18*, 1630; (b) Matsumura, K.; Miyashita, O.; Shimadzu, H.; Hashimoto, N. *Chem. Pharm. Bull. (Tokyo)* **1976**, *24*, 948; (c) Dewar, M. J. S.; Turchi, I. J. *J. Org. Chem.* **1975**, *40*, 1521; (d) Masaak, M.; Kumazawa, T.; Yoshikoshi, A. *J. Chem. Soc., Chem. Commun.* **1978**, 362; (e) Burger, K.; Hübl, D.; Geith, K. *Synthesis* **1988**, 194; (f) Jenny, C.; Heimgartner, H. *Helv. Chim. Acta* **1989**, 1639.
14. Mp 87–89°C. IR (film) 1552, 1486 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 8.08 (6H, m), 7.52 (9H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.8, 134.4, 130.9, 130.1, 129.0, 128.7, 128.4, 127.0, 126.9, 126.8, 126.5, 126.4. HRMS (CI) calculated for $C_{15}H_{12}NOS$ (MH^+) 330.0952, found 330.0951.
15. Mp 63.5–64.5°C. IR (film) 1546, 1476 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 8.05–8.08 (2H, m), 7.46–7.48 (4H, m), 7.23–7.31 (5H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.3, 142.0, 136.3, 134.6, 131.1, 129.5, 129.0, 128.5, 127.2, 126.7. HRMS (CI) calculated for $C_{15}H_{12}NOS$ (MH^+) 254.0639, found 254.0634.
16. Mp 77–79°C. IR (film) 1769, 1717, 1582, 1466 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 8.16 (1H, s), 7.83–7.80 (2H, m), 7.74–7.70 (2H, m), 7.41 (1H, s), 7.28–7.20 (5H, m), 5.21–5.18 (1H, d, $J=10$ Hz), 3.15 (1H, m), 1.15–1.13 (3H, d, $J=6$ Hz), 0.98–0.96 (3H, d, $J=6$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.4, 162.2, 158.3, 142.5, 141.1, 139.2, 135.9, 134.3, 131.5, 130.5, 129.3, 128.9, 128.5, 127.2, 123.6, 107.4, 54.0, 28.7, 20.6, 19.3. HRMS (CI) calculated for $C_{24}H_{20}N_3O_4S$ (MH^+) 446.4994, found 446.1175.
17. Yellow oil. IR (film) 1561, 1480 cm^{-1}. ^1H (300 MHz, $CDCl_3$) δ 7.03–7.16 (5H, m), 2.3 (3H, s), 2.1 (3H, s). ^{13}C (75 MHz, $CDCl_3$) δ 164.0, 144.7, 136.2, 135.4, 129.2, 127.4, 126.5, 14.4, 12.0. HRMS (CI) calculated for $C_{11}H_{12}NOS$ (MH^+) 206.0639, found 206.0631.
18. Mp 33–35°C. IR (film) 1542, 1476 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 9.29–9.26 (1H, d, $J=8$ Hz), 8.25–8.23 (1H, d, $J=7$ Hz), 7.99–7.97 (1H, d, $J=8$ Hz), 7.93–7.90 (1H, d, $J=7$ Hz), 7.41–7.68 (4H, m), 7.23–7.40 (5H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.3, 141.9, 135.9, 134.1, 132.2, 130.2, 129.5, 129.4, 129.0, 128.5, 127.9, 127.4, 126.5, 126.0, 125.1, 124.8, 123.6. HRMS (CI) calculated for $C_{19}H_{14}NOS$ (MH^+) 304.0796, found 304.0797.
19. Mp 59–61°C. IR (film) 1750, 1620, 1581, 1454 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 8.21–8.33 (3H, m), 7.51 (1H, s), 7.22–7.49 (7H, m), 4.11 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.0, 136.0, 135.6, 134.7, 129.5, 129.1, 128.4, 127.7, 127.2, 126.6, 126.0, 125.7, 124.4, 121.7, 115.3, 110.0, 54.9. HRMS (CI) calculated for $C_{19}H_{15}N_2O_3S$ (MH^+) 351.0803, found 351.0797.
20. Desulfurization of 2-phenyl-5-thiophenyloxazole with deactivated Raney nickel in acetone gave 2-phenyloxazole (67%).