JOC Note

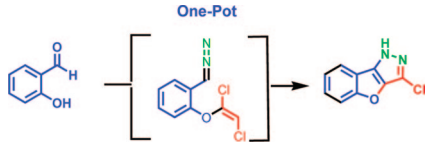
An Efficient Intramolecular 1,3-Dipolar Cycloaddition Involving 2-(1,2-Dichlorovinyloxy)aryldiazomethanes: A One-Pot Synthesis of Benzofuropyrazoles from Salicylaldehydes

Zachary S. Sales and Neelakandha S. Mani*

Johnson & Johnson Pharmaceutical Research and Development, L.L.C., 3210 Merryfield Row, San Diego, California 92121

nmani@its.jnj.com

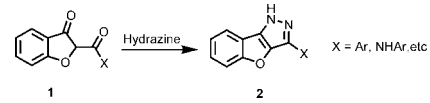
Received October 03, 2008



A novel intramolecular 1,3-dipolar cycloaddition strategy for a rapid entry into benzofuropyrazoles is described. In a three-step sequence, (*E*)-2-(1,2-dichlorovinyloxy)aryldiazomethanes were generated in situ from the corresponding salicylaldehydes. Intramolecular cycloaddition followed by dehydrohalogenation garnered 3-chlorobenzofuropyrazoles in excellent yields. By careful choice of solvent, base, and reaction conditions, the entire sequence can be carried out in a one-pot procedure.

Fused pyrazoles such as benzofuropyrazoles are structural motifs increasingly found in a wide array of medicinal chemistry programs. For example, 1*H*-benzofuro[3,2]pyrazolyl-3-amine derivatives have been reported to have analgesic and anticonvulsant properties due to their ability to inhibit selectively the cyclooxygenase 2 (COX 2) enzyme.[1] A class of 3-arylbenzofuropyrazoles has been developed as inhibitors of certain tyrosine kinases for the treatment of diseases and disorders associated with abnormal cell proliferation.[2] Fused pyrazoles, including benzothieno- and benzofuropyrazoles, have been identified as selective histamine H_3 antagonists, which are potentially useful in the treatment of a host of CNS disorders such as ADHD, Parkinson's disease, memory, Alzheimer's, narcolepsy, sleep apnea, insomnia, etc.[3] A number of benzothieno- and benzofuropyrazolyl compounds have also been identified as modulators of the $5HT_{2c}$ receptor. Potentially treatable disorders associated with this receptor are obesity, eating disorders, and obesity-related diabetes.[4] New synthetic methods that allow efficient access to this class of fused heterocycles is therefore of great value especially in the early stages of drug discovery and structure−activity studies. We wish to report herein an efficient intramolecular dipolar cycloaddition strategy for a rapid, one-pot assembly of benzofuropyrazoles starting from the corresponding salicylaldehydes.

SCHEME 1. Classical Route to Benzofuropyrazoles



Despite their gaining prominence, preparation of this class of fused pyrazoles has relied mostly on the Knorr pyrazole synthesis involving the condensation of a 1,3-dicarbonyl substrate with hydrazine[5] (Scheme 1).

This condensation involving an acylbenzofuranone is not always very efficient due to other competing reaction pathways such as deacylation and ring opening.[5] In our experience, these side reactions appear to be particularly dominant in the case of those acylbenzofuranones that contain electron-donating substituents on the aromatic ring. These difficulties prompted us to explore novel disconnections that might be more efficient. 1,3-Dipolar cycloaddition of nitrile imines or diazo compounds with olefinic or acetylenic dipolarophiles has been reported to offer an alternative method to construct pyrazoles.[6] Kirmse and Dietrich[7] have reported that 2-(allyloxy)phenyldiazomethane undergoes intramolecular 1,3-dipolar cycloaddition to form a fused benzopyranopyrazoline derivative. Subsequently, Padwa and Ku[8] showed that thermolysis of a 2-(2- alkenyl)phenyldiazomethane gave tetrahydroindenopyrazole cycloadduct in high yields. More recently, Aggarwal[9] and Chandrasekharan[10] have reported cycloaddition of aryldiazomethanes with dipolarophiles in which they describe a safe, in situ generation of aryldiazomethanes by the base-mediated decomposition of tosylhydrazones under mild conditions. We thus envisaged an intramolecular 1,3-dipolar cycloaddition involving an in situ generated 2-(vinyloxy)aryldiazomethane **3** as outlined in Scheme 2. The initial pyrazoline adduct **4** was then proposed to be aromatized

(1) (a) Philipp, A.; Jirkowsky, I.; Martel, R. US Patent 4420,476 (December 1983), Appl. No 380,973. (b) Talley, J.; Stephen, R. WO 96/09304, PCT/US 95/11403. (c) Caruso, F. S. WO 00/29023, PCT/US 98/24317.

(2) (a) Murata, K.; Kumagai, H.; Kawashima, T.; Tamitsu, K.; Irie, M.; Nakajima, H.; Suzu, S.; Shibuya, M.; Kamihira, S.; Nosaka, T.; Asano, S.; Kitamura, T. *J. Biol. Chem.* **2003**, *278*, 32892–32898. (b) Donald, S.; Whartenby, K.; Pardoll, D. WO 2006/020145, PCT/US 2005/025318and references cited therein.

(3) Bennani, Y. L.; Campbell, M. G.; Dastrup, D.; Porterhuck, E. WO 2007/094962, A2 PCT/US2007/002547.

(4) Ladoucur, G. H.; Choi, S.; Wang, Y. WO 2003/057161, A2 PCT/US02/41859.

(5) (a) Mosher, W. A.; Serridge, P. M.; Lipp, D. W. *J. Org. Chem.* **1972**, *37*, 2402–2405. (b) Gatta, F.; Settimj, G. *J. Heterocycl. Chem.* **1984**, *21*, 937–943.

(6) (a) Padwa, A. *1,3-Dipolar Cycloaddition Chemistry*; John Wiley & Sons: New York, 1984; Vol. 1. (b) Regitz, M.; Maas, G. *Diazo Compounds: Properties and Synthesis*; Academic Press: London, 1996. (c) Maas, G. In *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*; Padwa, A., Taylor, E. C., Pearson, W. H., Eds.; John Wiley & Sons: New York, 2002.

(7) Kirmse, W.; Dietrich, H. *Chem. Ber.* **1967**, *100*, 2710–2718.

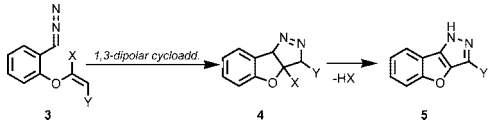
(8) Padwa, A.; Ku, H. *J. Org. Chem.* **1980**, *45*, 3756–3766. We are grateful to the reviewers for bringing the earlier works of Kirmse and Padwa to our attention.

(9) Aggarwal, V. K.; de Vicente, J.; Bonnert, R. V. *J. Org. Chem.* **2003**, *68*, 5381–5383.

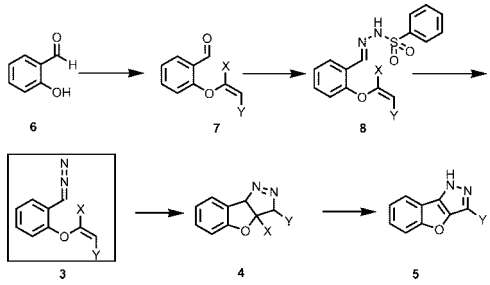
(10) Chandrasekhar, S.; Rajaiah, G.; Srihari, P. *Tetrahedron Lett.* **2001**, *42*, 6599–6601.

10.1021/jo802193z CCC: $40.75 © 2009 American Chemical Society
Published on Web 12/03/2008

SCHEME 2. 1,3-Dipolar Cycloaddition Strategy toward Benzofuropyrazoles



SCHEME 3. Proposed Route to Benzofuropyrazoles from Salicylaldehyde



to the pyrazole either by oxidation (X = H) or by base-induced elimination (X = halogen).

We proposed that a suitably substituted aryldiazomethane **3** could be generated in situ starting from the corresponding salicylaldehyde as shown in Scheme 3.

After considering a variety of groups that could serve as an internal dipolarophile, we chose the dichlorovinyloxy group as the most suitable for our purpose. The main considerations which guided our selection were as follows: (1) A leaving group at the 3a-position of the initially formed pyrazoline adduct **4** is highly desirable as it could eliminate HX to form the pyrazole **5**. (2) A second leaving group retained at the 3-position of the pyrazole is needed for further substitution reactions leading to more complexity. (3) Accessibility from readily available precursors as well as stability toward reagents needed for generating the proposed aryldiazomethane is also critical. Formation of aryl dichlorovinyl ethers by reaction of phenols with readily available trichloroethylene has been reported. Extensive studies by Kende,[11] Pielichowski,[12] and Green[13] have shown that under strongly basic conditions trichloroethylene undergoes dehydrohalogenation to form highly reactive dichloroacetylene, and this readily reacts with nucleophiles such as alcohols and phenols to form the corresponding dichlorovinyl ethers. However, initial attempts following a reported procedure[12] gave only modest yields of the desired vinyloxy derivative. Thus, heating a mixture of salicylaldehyde and trichloroethylene in a biphasic medium (aqueous NaOH and heptane) in the presence of a phase-transfer catalyst gave a 40% yield of the desired (*E*)-(1,2-dichlorovinyloxy)benzaldehyde **9** as a single isomer. The regio- and stereochemical assignments were based on the elimination−addition mechanism established by Kende and co-workers.[11] After considerable experimentation involving a number of solvent and base combinations, we determined that optimum yields could be obtained by reacting salicylaldehyde with a slight excess of trichloroethylene in DMF using K_2CO_3 as the base at 70−80 °C (Scheme 4).

A number of dichlorovinyl ethers were thus prepared by this method as outlined in Table 1. In general, substrates with

SCHEME 4. Synthesis of (*E*)-2-(1,2-Dichlorovinyloxy)benzaldehyde

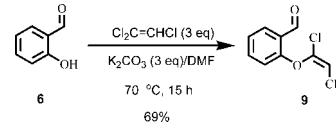
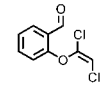
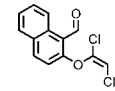
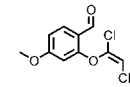
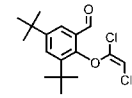
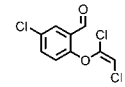
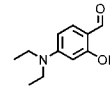
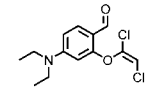
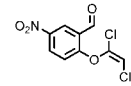
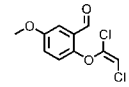
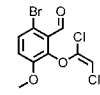
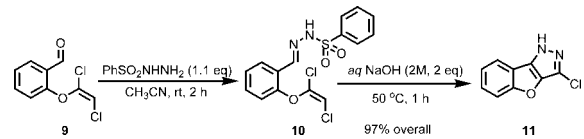


TABLE 1. Synthesis of (*E*)-2-(1,2-Dichlorovinyloxy)arylcarboxaldehydes

Entry	Substrate	Product	Yield (%)
1			69
2			63
3			76
4			76
5			78
6			37
7			82
8			trace
9			63
10			54

SCHEME 5. Synthesis of Benzofuropyrazoles



electron-donating substituents gave very good yields of the dichlorovinlyl ethers, whereas strong electron-withdrawing groups (see entry 8) appeared to be less favored.

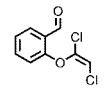
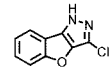
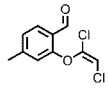
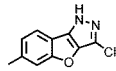
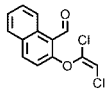
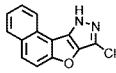
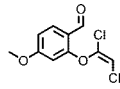
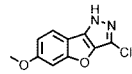
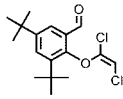
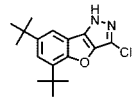
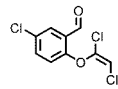
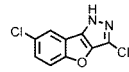
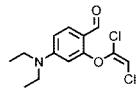
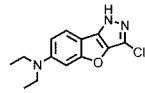
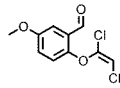
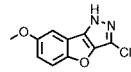
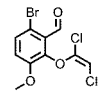
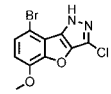
With an efficient method for the synthesis of dichlorovinyl ethers in hand, we examined the intramolecular cycloaddition. Treatment of 2-(1,2-dichlorovinyloxy)benzaldehyde **9** with benzenesulfonyl hydrazide in acetonitrile at room temperature resulted in fast conversion to the corresponding hydrazone **10** (Scheme 5). Upon adding a slight excess of aqueous NaOH solution and heating to 50 °C, the diazo compound was generated in situ, which then spontaneously cyclized to form the chloropyrazole **11** in almost quantitative yield. A number of substrates were examined, and all of them gave uniformly excellent yields of the desired benzofuropyrazoles (Table 2).

(11) Kende, A. S.; Fludzinski, P.; Hill, J. H.; Swenson, W.; Clardy, J. *J. Am. Chem. Soc.* **1984**, *106*, 3551–3562.

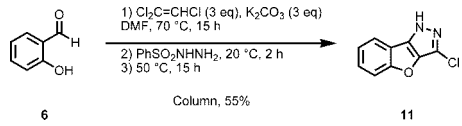
(12) Pielichowski, J.; Bogdal, D. *Pol. J. Chem.* **1988**, *62*, 483–487.

(13) (a) Moyano, A.; Charbonnier, F.; Greene, A. E. *J. Org. Chem.* **1987**, *52*, 2919–2922. (b) Imbroglio, J. E.; Rainier, J. D. *Tetrahedron Lett.* **2001**, *42*, 6987–6900.

TABLE 2. Synthesis of Benzofuropyrazoles

Entry	Substrate	Product	Yield (%)
1			97
2			98
3			98
4			98
5			95
6			95
7			97
8			95
9			95

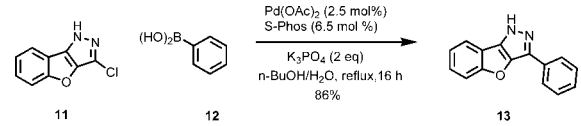
SCHEME 6. One-Pot Synthesis of Benzofuropyrazoles



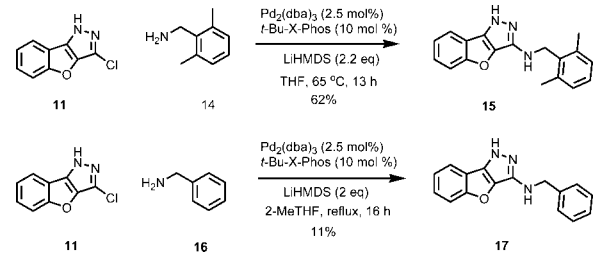
The efficient one-pot conversion of 2-(1,2-dichlorovinlyloxy-)benzaldehydes to benzofuropyrazoles under basic conditions suggested the possibility of carrying out this reaction using the same solvent−base combination (DMF−K_2CO_3) used for the first step, namely the preparation of the dichlorovinyl ether. Starting from salicylaldehyde, this would allow the entire sequence to be carried out in a one-pot operation.[14] Indeed, this turned out to be quite feasible in a test experiment as outlined in Scheme 6. Thus, salicylaldehyde was reacted with trichloroethylene in presence of K_2CO_3 at 70 °C in DMF. After the dichlorovinyl ether formation was judged complete by monitoring the reaction by TLC, the mixture was cooled to room temperature and benzenesulfonyl hydrazide was added directly to the reaction flask. Formation of the hydrazone **10** was complete in about 2 h, and when this reaction mixture was warmed to 50 °C, we were delighted to observe steady consumption of the hydrazone and formation of the desired chloropyrazole. After completion, workup followed by chromatography furnished **11** in 55% overall yield.

With a large collection of substituted *o*-hydroxy benzaldehydes readily available, the above protocol allows a rapid entry to a variety of benzofuropyrazoles. These can then be further elaborated by substitution using palladium catalyzed coupling strategies.[15] To demonstrate this utility, we investigated cross-coupling reaction of chloropyrazole **11** with phenylboronic acid. Using the catalyst system $Pd(OAc)_2$/S-Phos/K_3PO_4, the cross-coupling went smoothly to furnish the 3-aryl derivative **13**, a known tyrosine kinase inhibitor GTP-14564,[2] in 86% yield (Scheme 7).

SCHEME 7. Elaboration of the Pyrazole by Palladium-Catalyzed Cross-Coupling with Phenylboronic Acid



SCHEME 8. Elaboration of the Pyrazole by Palladium-Catalyzed Amination with Benzylamines



Unlike the Suzuki−Miyaura coupling reactions, palladium-catalyzed aminations appeared to be more capricious. The nature of palladium catalyst, ligand, solvent, and base used all appeared to have some influence on the outcome. Thus, for the amination with benzylamines, best results were obtained using the catalyst system $Pd_2(dba)_3$/*t*-Bu-X-Phos/LiHMDS.[16] In the two cases, which we examined, poor to moderate yields were obtained (Scheme 8). A considerable amount of dehalogenation was observed indicating an unfavorable reductive elimination step. Further optimization of this chemistry is currently ongoing.

In conclusion, an efficient construction of the benzofuropyrazole skeleton using an intramolecular 1,3-dipolar cycloaddition strategy has been accomplished. The methodology appears to be suited for preparing a wide variety of pharmaceutically active benzofuropyrazoles by further elaborations using palladium-catalyzed coupling strategies. Application of this methodology toward our ongoing medicinal chemistry program will be reported in due course.

Experimental Section

General Procedure for the Synthesis of (*E*)-2-(1,2-Dichlorovinyloxy)arylcarboxaldehydes (Table 1). Trichloroethylene (13.5 mL, 0.150 mol) was added over 30 min to a mechanically stirred suspension of a substituted salicylaldehyde (0.050 mol), powdered potassium carbonate (20.8 g, 0.150 mol),

(14) Hulme, C.; Gore, V. *Curr. Med. Chem.* **2003**, *10*, 302–312. (b) Broadwater, S. J.; Roth, S. L.; Price, K. E.; Kobaslija, M.; McQade, D. T. *Org. Biomol. Chem.* **2005**, *3*, 2889–2906.

(15) (a) Miyaura, N. *Top. Curr. Chem.* **2002**, *219*, 11–59. (b) Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685–4696. (c) Marion, N.; Navarro, O.; Mei, J.; Stevens, E. D.; Scott, N. M.; Nolan, S. P. *J. Am. Chem. Soc.* **2006**, *128*, 4101–4111. (d) Billingsley, K.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 3358–3366.

(16) (a) Huang, X.; Buchwald, S. L. *Org. Lett.* **2001**, *3*, 3417–3419. (b) Harris, M. C.; Huang, X.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 2885–2888. (c) Hooper, M. W.; Hartwig, J. F. *Organometallics* **2003**, *22*, 3394–3403. (d) Charles, M. D.; Schultz, P.; Buchwald, S. L. *Org. Lett.* **2005**, *7*, 3965–3968. (e) Anderson, K. W.; Tundel, R. E.; Ikawa, T.; Altman, R. A.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 6523–6527.

and DMF (35 mL) at 60 °C and under N_2. The resulting mixture was heated to 70 °C and stirred for 15 h. Upon cooling to room temperature, it was partitioned between 150 mL of EtOAc and 100 mL of H_2O. The organic layer was dried over $MgSO_4$ and filtered and the solvent removed under vacuum (30 °C, 100−10 mmHg). Purification of the resulting residue by column chromatography (silica gel; 0−30% EtOAc in hexanes) yielded the title compound. In most cases, the products were isolated as low-melting solids.

General Procedure for the Synthesis of 3-Chloro-1*H*-benzofuro[3,2-*c*]pyrazoles (Table 2). Benzenesulfonyl hydrazide (0.39 g, 2.3 mmol) was added all at once to a solution of the 2-(1,2-dichlorovinyloxy)arylcarboxaldehyde (2.1 mmol) in acetonitrile (21 mL) at room temperature. After the solution was stirred for 2 h, aqueous NaOH (2 M, 2.1 mL, 4.2 mmol) was added dropwise over 10 min. The solution was heated to 50 °C and stirred for 1 h. After the solution was cooled to room temperature, the solvents were removed under vacuum (30 °C, 100−10 mmHg). The residue was partitioned between 20 mL of EtOAc and 15 mL of H_2O. The organic layer was dried over $MgSO_4$ and filtered and solvent removed under vacuum yielding the title compound. In most cases, the products isolated were crystalline solids of excellent purity, and no chromatographic purification was necessary.

One-Pot Synthesis of 3-Chloro-1*H*-benzofuro[3,2-*c*]pyrazole (11). Trichloroethylene (10.8 mL, 0.120 mol) was added over 30 min to a mechanically stirred suspension of salicylaldehyde **6** (4.26 mL, 0.040 mol), powdered potassium carbonate (16.6 g, 0.120 mol), and DMF (28 mL) at 60 °C under N_2. The resulting mixture was heated to 70 °C and stirred for 15 h. Upon cooling to room temperature, benzenesulfonyl hydrazide (6.03 g, 0.035 mol) was added all at once. After 2 h, the reaction mixture was heated to 50 °C and stirred for 15 h. This heterogeneous mixture was then cooled to room temperature and partitioned between 200 mL EtOAc and 100 mL H_2O. The organic layer was dried over $MgSO_4$ and filtered and the solvent removed under vacuum (30 °C, 100−10 mmHg). Purification via column chromatography (silica gel; 20−40% EtOAc in hexanes) yielded the title compound as a tan solid (4.24 g, 55% yield): mp 222−223 °C; ^{1}H NMR (THF-d_8, 600 MHz) δ (ppm) 7.31 (m, 1H), 7.41 (m, 1H), 7.59 (d, J = 8.4 Hz, 1H), 7.72 (d, J = 7.2 Hz, 1H), 12.44 (s, 1H); ^{13}C NMR (THF-d_8, 150 MHz) δ (ppm) 114.1, 117.9, 119.6, 120.2, 124.1, 127.4, 135.7, 144.0, and 162.9. Anal. Calcd for $C_9H_5ClN_2O$: C, 56.12; H, 2.62; Cl, 18.41; N, 14.54. Found: C, 56.14; H, 2.52; Cl, 18.14; N, 14.38.

Acknowledgment. We thank Dr. Jiejun Wu, Ms. Bita Naderi, and Ms. Heather McAllister for analytical support.

Supporting Information Available: Experimental procedures for the synthesis of **13**, **15**, and **17**, copies of ^{1}H and ^{13}C NMR spectra, and analytical data of all new compounds (Tables 1 and 2). This material is available free of charge via the Internet at http://pubs.acs.org.

JO802193Z