ORGANIC LETTERS

2004
Vol. 6, No. 26
4957−4960

Synthesis of Diaryl Acetates and Oxindoles via a Sequential VNS_{Ar}–S_NAr Three-Component Coupling Reaction

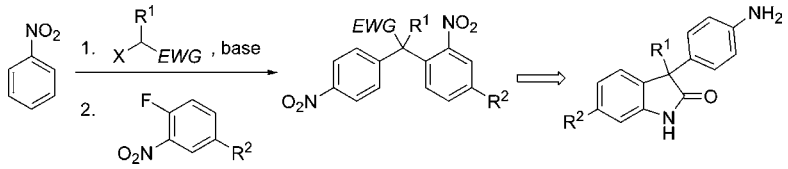
Nicholas J. Lawrence,*,† Christopher A. Davies,† and Matthew Gray‡

Department of Chemistry, Cardiff University, P.O. Box 912, Cardiff, CF10 3TB, UK, Drug Discovery Program, H. Lee Moffitt Cancer Center & Research Institute, Department of Interdisciplinary Oncology, University of South Florida, Tampa, Florida, 33612, and GlaxoSmithKline, Medicines Research Centre, Stevenage, SG1 2NY, UK

lawrennj@moffitt.usf.edu

Received October 12, 2004

ABSTRACT

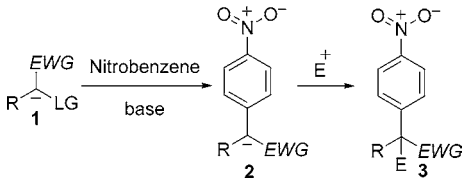


The VNS and S_NAr reactions combine to form an efficient three-component one-pot route to diarylmethanes. The products of selected diaryl acetates provide modular 3-aryloxindole derivatives.

The vicarious nucleophilic substitution (VNS_{Ar}) of hydrogen in aromatic systems provides a direct and efficient route to functionalized aromatics. The reaction, pioneered by Makosza and co-workers,[1] is most often encountered with nitroarenes, as illustrated in Scheme 1. In contrast to conventional nucleophilic aromatic substitution reactions, a good nucleofugal group is not required. We have shown that the anion **2** produced by addition of the nucleophile **1** to nitrobenzene, and elimination of HX from the σ-adduct, can react with a range of electrophiles.[2] This aspect of VNS chemistry provides a powerful process in which simple precursors can be elaborated in a three-component coupling reaction.

We have shown that **2** exhibits reactivity similar to that of the malonate ion. This is not too surprising given that other properties such as acidity are similar. For example the pK_a (DMSO) of ethyl *p*-nitrophenylacetate is 15.1,[3] while that of diethyl malonate is 16.4.[4] Malonate is an excellent nucleophile for many S_NAr reactions,[5] and some examples[6] of the use of nitrophenylacetates in the S_NAr reaction have been reported. We were therefore hopeful that the anion **2**, derived from the VNS reaction, would react in the S_NAr reaction.

Scheme 1. One-Pot VNS−Electrophilic Quench Process[a]



[a] LG = leaving group (e.g., Cl or PhS); EWG = electron-withdrawing group.

† Cardiff University and H. Lee Moffitt Cancer Center & Research Institute.

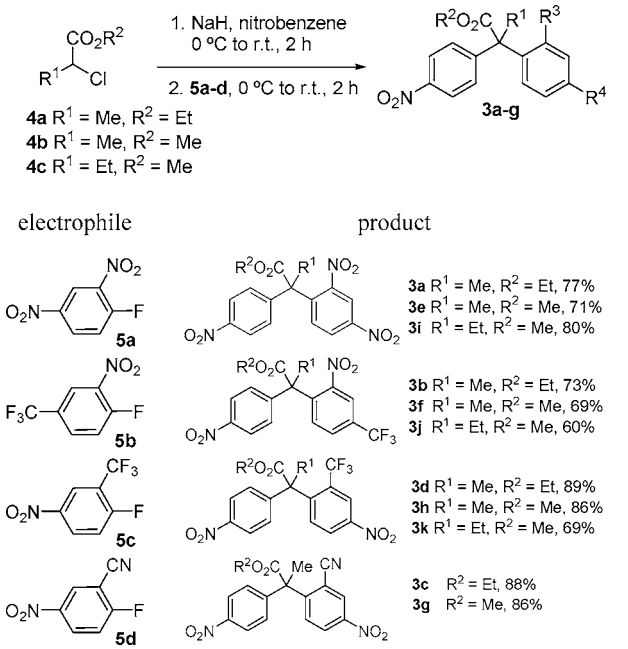
‡ GlaxoSmithKline.

(1) (a) Mąkosza, M.; Wojciechowski, K. *Chem. Rev.* **2004**, *104*, 2631−2666. (b) Mąkosza, M.; Winiarski, J. *Acc. Chem. Res.* **1987**, *20*, 282−289. (c) Mąkosza, M.; Wojciechowski K. *Heterocycles* **2001**, *54*, 445−474.

(2) Lawrence, N. J.; Lamarche, O.; Thurrab, N. *Chem. Commun.* **1999**, 689−690. Bushell, S. M.; Crump, J. P.; Lawrence, N. J.; Pineau, G. *Tetrahedron* **1998**, *54*, 2269−2274. Lawrence, N. J.; Liddle, J.; Jackson, D. A. *Tetrahedron Lett.* **1995**, *36*, 8477−8480. Lawrence, N. J.; Liddle, J.; Jackson, D. A. *Synlett* **1996**, 55−56. Drew, M. D.; Jackson, D. A.; Lawrence, N. J.; Liddle, J.; Pritchard, R. G. *Chem. Commun.* **1997**, 189−190. Lawrence, N. J.; Liddle, J.; Bushell, S. M.; Jackson, D. A. *J. Org. Chem.* **2002**, *67*, 457−464.

10.1021/ol047890y CCC: $27.50
Published on Web 11/24/2004

Scheme 2. Three-Component $VNS_{Ar}-S_NAr$ Coupling Reaction



Diarylmethanes are extremely useful synthetic intermediates,[7] and the diarylmethyl motif is found in many pharmacologically important agents.[8] A versatile route to this important scaffold incorporating several points of diversity is potentially useful. The diarylmethyl group is also embedded within many important drugs, e.g., 3-arylindole derivatives. Makosza[9] and Katritzky[10] have described the synthesis of diarylmethanes via VNS reaction of nucleophiles of type **1** in which the electron-withdrawing group comprises one of the aryl groups. The new method described below is ideally suited for the synthesis of functionalized diarylmethanes in which only one of the aryl groups is introduced in the VNS reaction.

We now report that the anion **2** can be arylated by the reaction with substituted *ortho*-halonitroarenes. The process not only is efficient but also uniquely combines two different sequential modes of aromatic nucleophilic substitution.

Reaction of ethyl 2-chloropropionate (**4a**) with nitrobenzene in the presence of NaH gave the usual dark blue-colored solution of the intermediate anion **2** (Scheme 1). Addition of 2,4-dinitrofluorobenzene (**5a**) in DMF resulted in rapid decolorization of the solution. The desired diarylmethane **3a** was isolated in 77% yield (Scheme 2).[11] The ^{1}H NMR spectrum clearly indicated the presence of both a 1,4-disubstituted and 1,2,4-trisubstituted aryl group.[12] This is consistent with the expected para-selective VNS reaction followed by S_NAr process.

To explore the scope of the reaction, a number of simple esters **4a**−**c** were combined with nitrobenzene and different S_NAr electrophiles **5a**−**d** under the reaction conditions described above. The results shown in Table 1 clearly indicate that the process is general and efficient. The efficiency of the S_NAr process is high, as the yields are close to that expected for the protonation of the anion **2**.[2] The use of activated arenes **5a**−**d** allows the S_NAr reaction to proceed conveniently at ambient temperature, avoiding the need for

Table 1. Yields of Product Diarylmethyl Sulfones **8a**−**h**

	R^1	R^3	R^4	yield (%)
a	Cl	NO_2	NO_2	74
b	Cl	NO_2	CF_3	75
c	Cl	CN	NO_2	74
d	Cl	CF_3	NO_2	75
e	CF_3	NO_2	NO_2	79
f	CF_3	NO_2	CF_3	81
g	CF_3	CN	NO_2	78
h	CF_3	CF_3	NO_2	78

(3) Kabachnik, M. I.; Lobanov, D. I.; Matveeva, A. G.; Kovsheva, O. E.; Terekhova, M. I.; Petrov, E. S.; Petrovskii, P. V.; Matrosov, E. I. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1991**, 1598−1604.

(4) Olstead, W. N.; Bordwell, F. G. *J. Org. Chem.* **1980**, *45*, 3299−3305;

(5) Gurjar, M.; Reddy, D. S.; Murugaiah, A.; Murugaiah, S. *Synthesis* **2000**, 1659−1661. Selvakumar, N.; Reddy, B. Y.; Kumar, G. S.; Iqbal, J. *Tetrahedron Lett.* **2001**, *42*, 8395−8398.

(6) Bluhm, A. L.; Sousa, J. A.; Weinstein, J. *J. Org. Chem.* **1964**, *29*, 636−640. Borsche, W.; Fiedler, A. *Chem. Ber.* **1913**, *46*, 2117−2131. Wrobel, Z.; Wojciechowski, K. *Pol. J. Chem.* **1992**, *66*, 1125−1129. Cheng, X.-M.; Lee, C.; Klutchko, S.; Winters, T.; Reynolds, E. E.; Welch, K. M.; Flynn, M. A.; Doherty, A. M. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2999−3002.

(7) For examples: (a) Itami, K.; Mineno, M.; Kamei, T.; Yoshida, J. *Org. Lett.* **2002**, *4*, 3635−3638. (b) Hermanns, N.; Dahmen, S.; Bolm, C.; Brase, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 3692−3694. (c) Vanier, C.; Lorge, F.; Wagner, A.; Mioskowski, C. *Angew. Chem., Int. Ed.* **2000**, *39*, 1679−1683.

(8) For examples: (a) Plobeck, N.; Delorme, D.; Wei, Z. Y.; Yang, H.; Zhou, F.; Schwarz, P.; Gawell, L.; Gagnon, H.; Pelcman, B.; Schmidt, R.; Yue, S. Y.; Walpole, C.; Brown, W.; Zhou, E.; Labarre, M.; Payza, K.; St-Onge, S.; Kamassah, A.; Morin, P. E.; Projean, D.; Ducharme, J.; Roberts, E. *J. Med. Chem.* **2000**, *43*, 3878−3894. (b) Hsin, L. W.; Dersch, C. M.; Baumann, M. H.; Stafford, D.; Glowa, J. R.; Rothman, R. B.; Jacobson, A. E.; Rice, K. C. *J. Med. Chem.* **2002**, *45*, 1321−1329. (c) Wai, J. S.; Egbertson, M. S.; Payne, L. S.; Fisher, T. E.; Embrey, M. W.; Tran, L. O.; Melamed, J. Y.; Langford, H. M.; Guare, J. P.; Zhuang, L. G.; Grey, V. E.; Vacca, J. P.; Holloway, M. K.; Naylor-Olsen, A. M.; Hazuda, D. J.; Felock, P. J.; Wolfe, A. L.; Stillmock, K. A.; Schleif, W. A.; Gabryelski, L. J.; Young, S. D. *J. Med. Chem.* **2000**, *43*, 4923−4926. (d) Hewawasam, P.; Gribkoff, V. K.; Pendri, Y.; Dworetzky, S. I.; Meanwell, N. A.; Martinez, E.; Boissard, C. G.; Post-Munson, D. J.; Trojnacki, J. T.; Yeleswaram, K.; Pajor, L. M.; Knipe, J.; Gao, Q.; Perrone, R.; Starrett, J. E. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1023−1026.

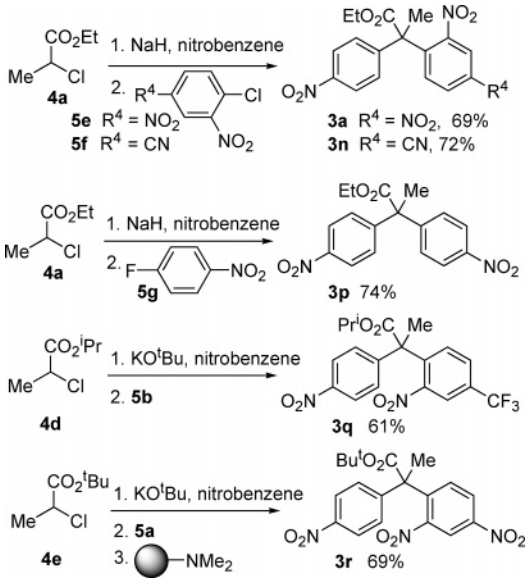
(9) Makosza, M.; Surowiec, M.; Voskresensky, S. *Synthesis* **2000**, 1237−1240.

(10) Katritzky, A. R.; Toader, D. *J. Org. Chem.* **1997**, *62*, 4137−4141.

(11) **General Procedure for the $VNS_{Ar}-S_NAr$ Reaction.** Sodium hydride (60% dispersion in oil) (0.813 g, 20.3 mmol) was added to anhydrous DMF (5 mL) and the mixture flushed with nitrogen and cooled to 0 °C. Chloroester **4** (8.13 mmol) and nitrobenzene (0.84 mL, 8.13 mmol) were dissolved in anhydrous DMF (5 mL) and added dropwise to the sodium hydride slurry. The reaction mixture was stirred at 0 °C for 30 min and then allowed to warm to room temperature. The reaction mixture was then cooled back to 0 °C using an ice-cooling bath. Aryl halide **5** (8.13 mmol) in anhydrous DMF (2 mL) was then added, and the resulting mixture was allowed to warm to room temperature and stirred for a further 2 h. The reaction mixture was poured onto ice/hydrochloric acid (50 mL, 1 M solution) and extracted with dichloromethane (3 × 30 mL). The combined organic extracts were washed well with distilled water (5 × 50 mL) and then saturated aqueous sodium bicarbonate solution (3 × 50 mL) and dried (magnesium sulfate), and the solvent was removed under reduced pressure to give the crude product, which was purified by column chromatography

(12) Other characterization data (e.g., ^{13}C NMR, MS, IR) support the product assignment.

Scheme 3. Further Examples of the $VNS_{Ar}-S_NAr$ Reaction



heating. This can be problematic for NaH in DMF when the reaction is performed on a large scale.[13] We have therefore shown that the process has potential for scale-up by using *tert*-BuOK as the base. In these cases, the VNS reaction between nitrobenzene (1 equiv) and **4a** (2 equiv) was performed with *tert*-BuOK (3 equiv) while carefully maintaining the temperature between −40 and −50 °C. The solution of the post-VNS anion was warmed to −20 °C before addition of **5a** or **5d** to give **3a** and **3d** in 57 and 69% yields, respectively.

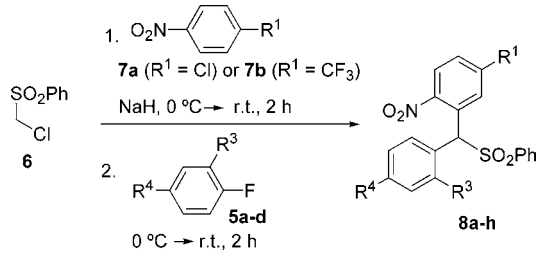
The process is not limited to the use of fluoronitroarenes (Scheme 3). 2,4-Dinitrochloronitrobenzene (**5e**) was used in place of 2,4-dinitrofluorobenzene (**5a**) to give **3a** from **4a** in 69% yield. Similarly, the $VNS-S_NAr$ reaction of 4-chloro-3-nitrobenzonitrile (**5f**) and **4a** gives the nitrile **3n** (Scheme 3). The use of the less activated 4-fluoronitrobenzene (**5g**) is still sufficiently reactive to engage ion the $VNS_{Ar}-S_NAr$ process to give **3p** in 74% yield.

Branched esters behave well in the reaction. The isopropyl ester **4d** gave ester **3q** when aryl fluoride **5b** was used as the electrophile. The *tert*-butyl ester **3r** was obtained in the same way from the VNS nucleophile **4e**. In the synthesis of **3r**, we were unable to separate the product from unreacted **5a** by chromatography. The unreacted aryl fluoride was scavenged using dimethylamino-functionalized polystyrene. Simply shaking the mixture of **5b** and **3r** with the resin in EtOAc cleanly removed the aryl fluoride, leaving the product ester pure.

The $VNS_{Ar}-S_NAr$ reaction was used for the synthesis of diarylmethyl sulfones, to provide examples of the process with ortho selectivity. Reaction of chloromethyl phenyl sulfone (**6**) with *p*-chloronitrobenzene (**7a**) and **5a** gave the

(13) For a summary of the safety hazards associated with the large-scale use of sodium hydride in DMF, see: am Ende, D. J.; Vogt, P. F. *Org. Proc. Res. Dev.* **2003**, *7*, 1029−1033.

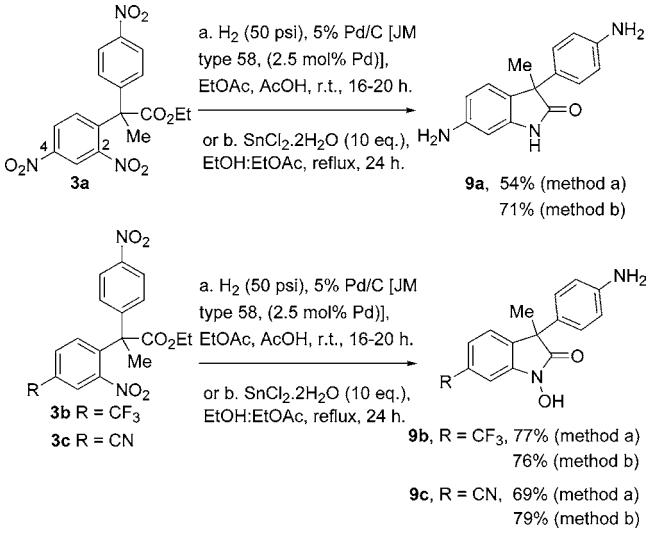
Scheme 4. $VNS_{Ar}-S_NAr$ Reaction of Sulfones



sulfone **8a** (Scheme 4). Other examples (Table 1) indicate that the arylation of the *ortho*-nitrobenzyl sulfonyl anion is not problematic.

The synthetic utility of the method is illustrated in Scheme 5, by the synthesis of oxindole derivatives. This class of

Scheme 5. Use of $VNS_{Ar}-S_NAr$ Products for Oxindole Synthesis



heterocycle is an important synthetic building block and also includes members with important biological activity.[8d,14] Those products **3** possessing an ortho nitro group ($R^3 = NO_2$), are converted into their corresponding 3,3-disubstituted oxindole, by hydrogenation (method a), or Sn(II)-mediated reduction (method b). The presence of other nitro groups that are also reduced under these conditions provides additional points for further functionalization and incorporation of extra diversity. The ester **3a** cleanly gave the oxindole

(14) (a) Hennessy, E. J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 12084−12085. (b) Gunesekara, N. S.; Spencer, C. M.; Keating, G. M. *Drugs* **2002**, *62*, 1217−1251. (c) Bromidge, S. M.; Dabbs, S.; Davies, D. T.; Duckworth, D. M.; Forbes, I. T.; Ham, P.; Jones, G. E.; King, F. D.; Saunders: D. V.; Starr, S.; Thewlis, K. M.; Wyman, P. A.; Blaney, F. E.; Naylor, C. B.; Bailey, F.; Blackburn, T. P.; Holland, V.; Kennett, G. A.; Riley, G. J.; Wood, M. D. *J. Med. Chem.* **1998**, *41*, 1598−1612. (d) Gallagher, G. J.; Lavanchy, P. G.; Wilson, J. W.; Hieble, J. P.; DeMarinis, R. M. *J. Med. Chem.* **1985**, *28*, 1533−1536. (e) Natarajan, A.; Fan, Y. H.; Chen, H.; Guo, Y. H.; Iyasere, J.; Harbinski, F.; Christ, W. J.; Aktas, H.; Halperin, J. A. *J. Med. Chem.* **2004**, *47*, 1882−1885.

9a by both methods. However, reduction of both **3b** and **3c** gave the 1-hydroxyoxindoles **9b** and **9c**.[15] It seems that the presence of the electron-withdrawing group impedes reduction of the intermediate hydroxylamine such that cyclization to form the indole occurs faster. The formation of **9a** from **3a** involves first reduction of the less hindered nitro group at position 4.

In conclusion, we have shown that the intriguing one-pot $VNS_{Ar}-S_NAr$ combination of two types of nucleophilic substitution reaction provides an excellent synthesis of diaryl acetate derivatives.

(15) Acheson, R. M.; Prince, R. J.; Proctor, G. *J. Chem. Soc., Perkin Trans. 1* **1979**, 595−598.

(16) Fletcher, D. A.; McMeeking, R. F.; Parkin, D. *J. Chem. Inf. Comput. Sci.* **1996**, *36*, 746−749.

Acknowledgment. The support of our work by the EPSRC (Research Grant GR/S25456/01: 500 MHz NMR spectrometer; EPSRC Chemical Database Service at Daresbury;[16] the EPSRC national mass spectrometry center at Swansea University for high-resolution mass spectrometry), GlaxoSmithKline, and Cardiff University (Senior Research Fellowship to N.J.L. and studentship to C.A.D.) is gratefully acknowledged.

Supporting Information Available: General experimental procedures and characterization data and ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL047890Y