Solid Phase Synthesis of Pyridazine Derivatives Using Polymer-Bound Sodium Benzenesulfinate

Yu Chen, Yulin Lam,* and Soo-Ying Lee
Department of Chemistry, National University of Singapore, 3 Science Drive 3, Singapore 117543, Singapore

(Received November 1, 2000; CL-000996)

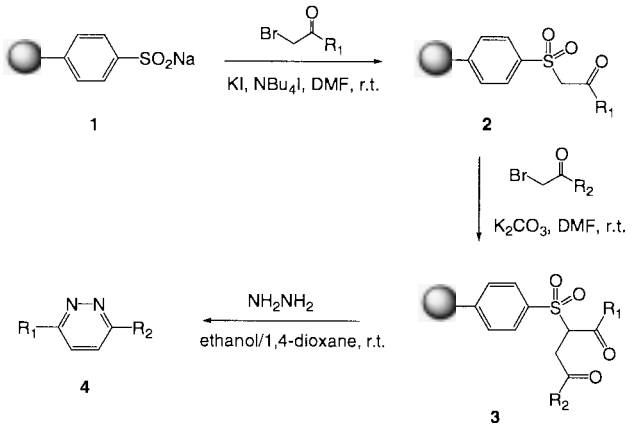
A new solid phase synthesis of 3,6-disubstituted pyridazine derivatives, resulting from the reaction of polymer-bound sodium benzenesulfinate with α-bromoketone substrates followed by condensation with hydrazine, is described. Mild basic conditions for the condensation reaction simultaneously release the desired product from the solid support. The crystal structure of 3,6-bis(*p*-chlorophenyl)pyridazine is reported.

Rapid developments in solid phase organic synthesis have been made recently, driven largely by the impetus of combinatorial and parallel syntheses in drug[1] and materials[2] developments. Central to the effective application of solid phase organic synthesis is the choice of linker through which the organic molecule is attached to the solid support. The linker must be inert to the synthetic sequence and subsequently permit the final product to be chemoselectively released from the resin.

Sodium benzenesulfinate is used widely in the preparation of sulfone which plays an important role in organic synthesis.[3] However the use of polymer-bound sodium benzenesulfinate resin **1** in solid phase synthesis has received little attention.[4–6] We were interested in the solid-phase synthesis of pyridazine derivatives as they have been shown to exhibit various antitumour, antibacterial and herbicidal activites.[7] Spurred by the diverse biological activities of these compounds, a variety of solution-phase strategies have been developed earlier.[8–10] Herein, we describe the solid-phase synthesis of 3,6-disubstituted pyridazine derivatives on sodium benzenesulfinate resin. To our knowledge, only one earlier report on the solid phase route to pyridazines has been published. This was achieved through the Diels–Alder reactions of 3,6-disubstituted-1,2,4,5-tetrazines on a solid phase format.[11]

In our reaction (Scheme 1), sodium benzenesulfinate resin **1** in DMF was treated with a variety of α-bromoketone (5 equiv) in the presence of tetrabutylammonium iodide (1 equiv) and potassium iodide (5 equiv) for 1 day to afford β-ketosulfone resin **2** in a reaction which could be monitored by KBr FT-IR.[12] Formation of up to 94% of sulfone by transformation of the resin-bound sodium benzenesulfinate was observed during this step.

The resulting resin-bound intermediate **2** was treated with α-bromoketone (5 equiv) in the presence of a base (1.2 equiv) for 2 days to give the 1,4-diketo resin **3**. During the synthesis of pyridazine **4a**, two different systems were used for this alkylation step. The first system utilized NaOMe/THF as base whilst the other system was treated with K_2CO_3/DMF. We found that K_2CO_3/DMF gave cleaner results with an overall yield of 42% as compared to 15% in the reaction with NaOMe/THF. Hence K_2CO_3/DMF was used for the synthesis of the other members of the 3,6-disubstituted pyridazine library. Treatment of **3** with hydrazine (5 equiv) for 12 h resulted not only in the condensation reaction but also simultaneously cleaved the product from the solid support to give the dehydrogenated 3,6-disubstituted pyridazine derivatives. Unlike in solution-phase synthesis,[13] no *N*-aminopyrrole derivatives were observed in the product mixture even under refluxing ethanol conditions.



Scheme 1. Solid phase synthesis of 3,6-disubstituted pyridazines

In the library synthesis, 7 representative α-bromoketones containing various functionalities were tested. Using the process illustrated in Scheme 1, 20 pyridazines were synthesized and analyzed by ^{1}H NMR and high resolution MS (Table 1).

Single crystals of 3,6-bis(*p*-chlorophenyl)pyridazine **4g** were obtained from diethyl ether/dichloromethane mixture. Intensity data were collected at room temperature using a Siemens R3m/V diffractometer with Mo Kα radiation (λ = 0.71060 Å). Lorentz and polarization corrections, structure solution by direct methods, full-matrix least-squares refinements and preparation of figures were all performed by the SHELXTL-Plus PC program package.[14,15] All non-hydrogen atoms were refined anisotropically whereas hydrogen atoms were placed at calculated positions with isotropic displacement coefficient being assigned a value that is 1.6 times that of the atom to which it is attached. Tables of atomic coordinates, bond lengths and angles and thermal parameters have been deposited in the Cambridge Crystallographic Data Centre.

Figure 1 depicts the structure and defines the atomic numbering of the molecule. The pyridazine and phenyl rings are planar but the molecule as a whole is skewed with the phenyl groups C1C2C3C4C5C6 and C11C12C13C14C15C16 being oriented at 18.9° and 10.0° respectively to the pyridazine ring.

In summary, this paper demonstrated the first direct synthesis of pyridazines on a solid-phase format. This application to the synthesis of large pyridazine libraries is presently under investigation.

Table 1. Yield and MS data of 3,6-disubstituted pyridazines

Entry	R_1	R_2	M^{+a}	Yield[b]/%
4a	C_6H_5	C_6H_5	232.10001	41.6
4b	C_6H_5	*p*-ClC_6H_5	266.06024	49.5
4c	C_6H_5	*p*-$NO_2C_6H_5$	277.08455	23.2
4d	C_6H_5	*p*-$CH_3OC_6H_5$	262.11139	40.8
4e	C_6H_5	furyl	222.07993	14.0
4f	C_6H_5	*t*-butyl	212.13177	35.0
4g	*p*-ClC_6H_5	*p*-ClC_6H_5	300.01940	46.0
4h	*p*-ClC_6H_5	*p*-$NO_2C_6H_5$	311.04817	30.3
4i	*p*-ClC_6H_5	*p*-$CH_3OC_6H_5$	296.07149	40.2
4j	*p*-ClC_6H_5	furyl	256.04030	14.1
4k	*p*-ClC_6H_5	*t*-butyl	246.09229	32.9
4l	*p*-$NO_2C_6H_5$	*p*-$CH_3OC_6H_5$	307.09484	19.9
4m	*p*-$NO_2C_6H_5$	thienyl	283.04032	12.3
4n	*p*-$NO_2C_6H_5$	*t*-butyl	257.11785	22.4
4o	*p*-$CH_3OC_6H_5$	*p*-$CH_3OC_6H_5$	292.12062	24.6
4p	*p*-$CH_3OC_6H_5$	furyl	252.09048	13.6
4q	*p*-$CH_3OC_6H_5$	*t*-butyl	242.14254	25.3
4r	furyl	thienyl	228.03616	9.0
4s	furyl	*t*-butyl	202.10929	11.2
4t	*t*-butyl	*t*-butyl	192.16258	10.1

[a]M^+ determined by high-resolution MS. [b]Overall yield based on recrystallization from $MeOH/H_2O$.

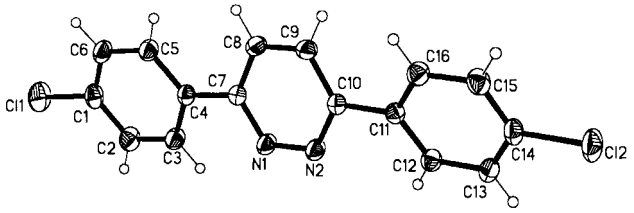


Figure 1. Thermal ellipsoid diagram of 3,6-bis(*p*-chlorophenyl) pyridazine.

References and Notes

1 D. V. Patel, in "Annual Reports in Combinatorial Chemistry and Molecular Diversity," ed. by W. H. Moos, M. R. Pavia, A. D. Ellington, and B. K. Kay, ESCOM, Leiden (1997), Vol. 1, pp. 3–5.

2 E. W. McFarland and W. H. Weinberg, *Trends Biotechnol.*, **17**, 107 (1999).

3 For general reviews, see: a) K. Tanaka and A. Kaji, in "The Chemistry of Sulfones and Sulfoxides," ed. by S. Patai, Z. Rappoport, and C. Stirling, J. Wiley & Sons, Chichester (1988), Chap 15, pp. 759–821. b) N. S. Simpkins, in "Sulfone in Organic Synthesis," Pergamon Press, Oxford (1993). c) K. Schank and N. Schott, in "The Synthesis of Sulfones, Sulfoxides and Cyclic Sulphides," ed. by S. Patai and Z. Rappoport, J. Wiley & Sons, Chichester (1994), Chap. 2, pp. 69–108.

4 C. Halm, J. Evarts, and M. J. Kurth, *Tetrahedron Lett.*, **38**, 7709 (1997).

5 W. Huang, X. Hou, C. Li, and B. He, *Lizi Jiaohuan Yu Xifu*, **14**, 171 (1998).

6 Q. Ren, W. Huang, and B. He, *Youji Huaxue*, **9**, 463 (1998).

7 W. J. Coates, in "Comprehensive Heterocyclic Chemistry II," ed. by A. R. Katritzky, C. W. Rees, and E. F. V. Scriven, Pergamon Press, Oxford (1996), Vol. 6, pp 86–91.

8 M. J. Haddadin, S. J. Firsan, and B. S. Nader, *J. Org. Chem.*, **44**, 629 (1979).

9 D. L. Boger and M. Patel, *J. Org. Chem.*, **52**, 1405 (1988).

10 R. E. Lutz and S. M. King, *J. Org. Chem.*, **17**, 1519 (1952).

11 J. S. Panek and B. Zhu, *Tetrahedron Lett.*, **37**, 8151 (1996).

12 FT-IR data: sulfinate resin **1** (957,1024,1602,1664 cm^{-1}), β-ketosulfone resin (R_1=Ph, 1679, 1324, 1273, 1087,1032 cm^{-1}).

13 K. Gorlitzer and M. Bomeke, *Arch. Pharm.*, **325**, 13 (1992)

14 G. M. Sheldrick, SHELXTL PLUS, Siemens Analytical Instruments, Madison, WI, 1986.

15 Crystal data of **4g**: $C_{16}H_{10}Cl_2N_2$, MW = 301.16, Monoclinic, colourless plates, a = 15.5196(8) Å, b = 13.9790(7) Å, c = 6.2508(3) Å, β = 100.1050(10)°, V = 1334.96(12) $Å^3$, space group $P2_1/c$, Z = 4, D_x = 1.498 g/cm^3. Crystal dimension: 0.40 × 0.02 × 0.16 mm, μ = 0.475 mm^{-1}, 8439 reflections measured, 3315 unique (R_{int} = 0.0228) which were used in all calculations. The final R and R_w were 3.37% and 9.19% (for $I>2\sigma(I)$).