A Library Synthesis of Pyrazoles by Azomethine Imine Cycloaddition to the Polymer-supported Vinylsulfone

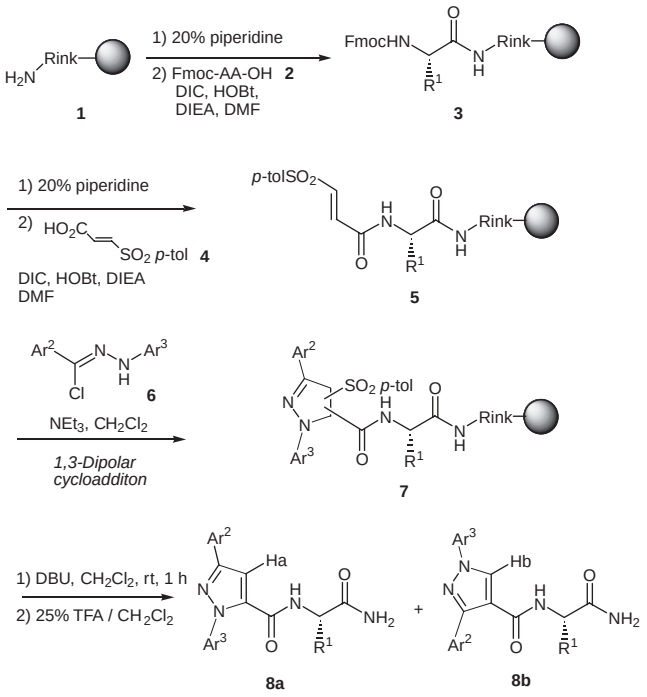
Nobuhiro Fuchi, Takayuki Doi, and Takashi Takahashi*
Department of Applied Chemistry, Tokyo Institute of Technology, 2-12-1, Ookayama, Meguro, Tokyo 152-8552

(Received January 6, 2005; CL-050025)

1,3-Dipolar cycloaddition of azomethine imines to the polymer-supported vinylsulfone was achieved. Pyrazole derivatives bearing various aryl groups were synthesized regioselectively.

In recent years, methods for the combinatorial synthesis of small-molecule libraries for the development of useful pharmaceuticals remain a formidable challenge. The application of solid-phase organic synthesis (SPOS) in the preparation of small compound libraries is of considerable significance in the discovery and development of new drug compounds.[1] The recent success of the pyrazole cyclooxygenase-2 (COX-2) inhibitor has further highlighted the importance of these heterocycles in medicinal chemistry.[2–4] Therefore, they are interesting targets in the development of new drug leads using solid-phase combinatorial chemistry.[5] 1,3-Dipolar cycloaddition is one of the useful synthetic methods for diversed heterocyclic compounds. In the past few years, a considerable number of solid-phase synthesis of heterocycles utilizing 1,3-dipolar cycloaddition has been reported.[6] Recently, we have demonstrated a practical synthetic route to a constrained β-strand mimetic template via the regioselective 1,3-dipolar cycloaddition of azomethine imines with β-(*p*-toluenesulfonyl)acrylate.[7] We applied this method to the combinatorial synthesis of a β-strand mimetic templates library using polymer-supported β-(*p*-toluenesulfonyl) acrylate.[8] Herein, we report a regioselective 1,3-dipolar cycloaddition of azomethine imines to polymer-supported β-(*p*-toluenesulfonyl)acrylate and subsequent β-elimination of the toluenesulfonyl group in the synthesis of pyrazole derivatives.[9]

Scheme 1 shows the general outline of our approach. Fmoc-glycine **2** ($R^1 = H$) was attached to the Rink-amino resin **1** in the usual manner.[10] After removal of the Fmoc group (20% piperidine/CH_2Cl_2), coupling of (*E*)-3-(*p*-toluenesulfonyl)-acrylic acid (**4**) to polymer-supported amide (DIC/HOBt/DIEA) provided **5**. Treatment of the resin **5** with excess (10 equiv.) amounts of the azomethine imine, generated in situ treatment of hydrazonyl chloride **6** ($Ar^2 = 4\text{-}MeC_6H_4$, $Ar^3 = Ph$) with base. 1,3-Dipolar cycloaddition on polymer-support smoothly proceeded under the mild conditions (r.t., 8 h) to provide the corresponding pyrazoline **7**. Subsequently, elimination of a *p*-toluenesulfonyl group with DBU (10 equiv.), followed by acid cleavage from the polymer-support (25% TFA/CH_2Cl_2) afforded the desired pyrazoles **8**. The two regioisomeric products **8a** and **8b** were detected by ^1H NMR. The major isomer was **8a** with 84% selectivity in 98% purity (Table 1, Entry 1). It should be noted that the *p*-toluenesulfonyl group plays an important role, not only as an electron-withdrawing group activating the dipolarophile and inducing regioselectivity but also as a leaving group allowing aromatization of the pyrazoline.[11]



Scheme 1. Solid-phase synthesis of pyrazoles via 1,3-dipolar cycloaddition with polymer-supported vinylsulfones.

We next investigated the synthetic diversity of pyrazoles utilizing this method by the combination of amino acids (R^1) and phenylhydrazines (Ar^2 and Ar^3). The results are shown in Table 1. The validation of the Ar^2 group afforded the corresponding pyrazoles in good purities with 76–89% regioselectivity, except 2-furyl and 1-naphthyl groups decreased purities and regioselectivity (Entries 1–11). The substituents of the Ar^3 group did not affect product purities and regioselectivity (Entries 12–18). Both the Ar^2 and Ar^3 were modified (Entries 19–22). However, a bulky substituent of the R^1 group considerably decreased regioselectivity (Entry 25).

In summary, we have demonstrated versatile and efficient solid-phase synthesis of pyrazole derivatives in good purities. The polymer-supported β-(*p*-toluenesulfonyl)acrylate can be utilized to the synthesis of various heterocycles utilizing other 1,3-dipolar cycloaddition.

Table 1. Synthesis of pyrazole derivatives by 1,3-dipolar cycloaddition on polymer-support

Entry	R^1	Ar^2	Ar^3	**8a**:**8b**[a]	Purity[b]/%	δ/ppm of Ha/Hb	Rt/min of **8a**[c]	MS[d]
1	H	4-MeC_6H_4	Ph	84:16	98 (83)[e]	7.75/8.69	7.1	335.1
2	H	4-$MeOC_6H_4$	Ph	78:22	96	7.79/8.68	6.5	351.1
3	H	4-biphenyl	Ph	76:24	96	7.96/8.74	8.4	397.2
4	H	1-naphthyl	Ph	70:30	75	7.26/8.88	7.5	371.1
5	H	4-NO_2-C_6H_4	Ph	87:13	84	7.43/8.79	7.0	366.1
6	H	4-FC_6H_4	Ph	84:16	97	7.26/8.72	6.9	339.1
7	H	4-CF_3-C_6H_4	Ph	77:23	94	7.38/8.77	8.0	389.1
8	H	4-BrC_6H_4	Ph	85:15	96	7.28/8.72	7.7	399.0
9	H	2-furyl	Ph	76:24	63	7.17/8.72	5.5	311.1
10	H	cyclohexyl	Ph	89:11	92	6.78/8.59	7.1	327.2
11	H	Ph	Ph	85:15	98 (85)[e]	7.29/8.71	6.6	321.1
12	H	Ph	4-MeC_6H_4	86:14	97	7.27/8.65	7.1	335.2
13	H	Ph	4-CN-C_6H_4	82:18	81	7.34/8.85	6.7	346.1
14	H	Ph	4-$MeOC_6H_4$	88:12	94	7.26/8.58	6.7	351.1
15	H	Ph	4-*i*-Pr C_6H_4	82:18	99	7.27/8.66	8.3	385.2[f]
16	H	Ph	4-FC_6H_4	90:10	98	7.30/8.67	6.8	339.1
17	H	Ph	4-ClC_6H_4	82:18	98	7.30/8.71	7.5	335.1
18	H	Ph	4-BrC_6H_4	87:13	98	7.30/8.72	7.6	399.0
19	H	4-MeC_6H_4	4-$MeOC_6H_4$	85:15	96	7.18/8.62	7.0	365.2
20	H	4-MeC_6H_4	4-NO_2-C_6H_4	74:26	85	7.41/8.73	7.5	380.1
21	H	4-CN-C_6H_4	4-$MeOC_6H_4$	77:23	79	7.26/8.82	6.7	376.1
22	H	4-$MeOC_6H_4$	4-NO_2-C_6H_4	87:13	95	7.40/8.66	7.1	396.1
23	Me	Ph	Ph	79:21	92	7.30/8.72	6.9	335.2
24	$CH_2C_6H_5$	Ph	Ph	82:18	88	7.13/8.56	8.5	433.2[f]
25	*i*-Bu	Ph	Ph	68:32	91	7.26/8.70	8.3	377.2

[a]The ratio of regioisomers was determined by ^{1}H NMR (270 MHz). [b]The purity of the crude product (**8a** + **8b**) after cleavage was determined by reversed-phase HPLC with peak areas detected by UV (254 nm). [c]Reversed-phase HPLC analysis was performed with a Hewlett Packard 1100 series equipped with Inertsil-ODS-3 C18 column (GL Science Inc., 4.6 × 75 mm) and a binary linear gradient (solvent A = water/0.1% formic acid, solvent B = acetonitrile/0.1% formic acid, 10%B–90%B in 10 min). [d]Electrospray-TOF Mass data were recorded as $[M + H]^+$ on an Applied Biosystems Mariner. [e]Isolated yield based on the loading amount of the resin. [f]$[M + Na]^+$ was observed.

References and Notes

1 R. G. Franzen, *J. Comb. Chem.*, **2**, 195 (2000).

2 T. D. Penning, J. J. Talley, S. R. Bertenshaw, J. S. Carter, P. W. Collins, S. Docter, M. J. Graneto, L. F. Lee, J. W. Malecha, J. M. Miyashiro, R. S. Rogers, D. J. Rogier, S. S. Yu, G. D. Anderson, E. G. Burton, J. N. Cogburn, S. A. Gregory, C. M. Koboldt, W. E. Perkins, K. Seibert, A. W. Veenhuizen, Y. Y. Zhang, and P. C. Isakson, *J. Med. Chem.*, **40**, 1347 (1997).

3 J. Li, K. M. L. DeMello, H. Cheng, S. M. Sakya, B. S. Bronk, R. J. Rafka, B. H. Jaynes, C. B. Ziegler, C. Kilroy, D. W. Mann, E. L. Nimz, M. P. Lynch, M. L. Haven, N. L. Kolosko, M. L. Minich, C. Li, J. K. Durta, B. Rast, R. M. Crosson, B. J. Morton, G. W. Kirk, K. M. Callaghan, D. A. Koss, A. Shavnya, L. A. Lund, S. B. Seibel, C. F. Petras, and A. Silvia, *Bioorg. Med. Chem. Lett.*, **14**, 95 (2004).

4 R. R. Ranatunge, M. Augustyniak, U. K. Bandarage, R. A. Earl, J. L. Ellis, D. S. Garvey, D. R. Janero, L. G. Letts, A. M. Martino, M. G. Murty, S. K. Richardson, J. D. Schroeder, M. J. Shumway, S. W. Tam, A. M. Trocha, and D. V. Young, *J. Med. Chem.*, **47**, 2180 (2004).

5 Pyrazole library on solid-phase: a) S. R. Stauffer and J. A. Katzenellenbogen, *J. Comb. Chem.*, **2**, 318 (2000). b) A. C. Spivey, C. M. Diaper, H. Adams, and A. J. Rudge, *J. Org. Chem.*, **65**, 5253 (2000). c) K. Washizuka, K. Nagai, S. Minakata, I. Ryu, and M. Komatsu, *Tetrahedron. Lett.*, **41**, 691 (2000). d) K. Washizuka, K. Nagai, S. Minakata, I. Ryu, and M. Komatsu, *Tetrahedron Lett.*, **40**, 8849 (1999).

6 E. J. Kantorowski and M. J. Kurth, *Mol. Diversity*, **2**, 207 (1997).

7 N. Fuchi, T. Doi, T. Harada, J. Urban, B. Cao, M. Kahn, and T. Takahashi, *Tetrahedron Lett.*, **42**, 1305 (2001).

8 N. Fuchi, T. Doi, B. Cao, M. Kahn, and T. Takahashi, *Synlett*, **2002**, 285.

9 M. Chiericato, P. D. Croce, G. Carganico, and S. Maiorana, *J. Heterocycl. Chem.*, **16**, 383 (1979).

10 Commercially available Fmoc–Rink amino resin (0.52 mmol/g) was treated with 20% piperidine in DMF before use.

11 Regioselective synthesis of pyrazoles: a) A. Nagarajan, G. Zepeda, and J. Tamariz, *Tetrahedron Lett.*, **37**, 6835 (1996). b) A. R. Katritzky, M. Wang, S. Zhang, M. V. Voronkov, and P. J. Steel, *J. Org. Chem.*, **66**, 6787 (2001). c) V. K. Aggarwal, J. de Vicente, and R. V. Bonnert, *J. Org. Chem.*, **68**, 5381 (2003).

Published on the web (Advance View) February 23, 2005; DOI 10.1246/cl.2005.438