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A Novel Palladium-Catalyzed Reaction and Its Application in Preparation of Derivatives of Stilbazols

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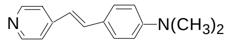
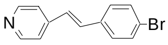
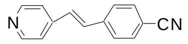
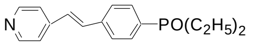
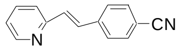
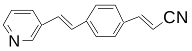
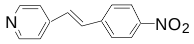
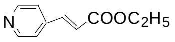
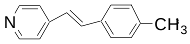
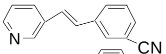
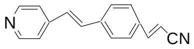
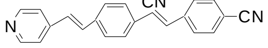
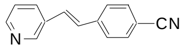
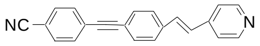
Abstract: A novel palladium-catalyzed coupling reaction for the preparation of derivatives of stilbazoles was presented. A series of stilbazoles were synthesized firstly by this highly efficient method. From this reaction it was found that reaction solvent is one of important factors in this catalytic system.

Keyword: Palladium catalyzed, preparation, stilbazole.

Many derivatives of stilbazoles have strong biological activities and pharmacological actions. For instance, β-substituent-(E)-4-styrylpyridines can be used as cytokinin analogues[1]. A series of N-substituted tetrahydro (phenylethenyl) pyridine derivatives were reported *in vitro* against both nicotinic and muscarinic receptors derived from rat cerebral cortax[2]. Therefore they can be used as candidates to develop new drugs for treatment of some diseases. On the other hand, this kind of compounds themselves is an important type of nonlinear optical materials by polymerization[3]. Also, they can coordinate with some transition metal to form super-molecular network and give rise to novel high SHG organic NLO materials that have excellent mechanic and physical performances[4]. Moreover, they can be a monomer of polymer and afford high quality liquid crystal by polymerization[5]. With the development of investigation in this field, more and more functions and uses of this kind of compounds are found and applied in many areas. However, up to now only a few classical preparations for this kind of compounds were reported. Most of them are aldol-condensation reactions[6]. The others are mainly involved in electrolysis reactions[7]. In this decade some metal-catalyzed reaction was employed for the synthesis of stilbazoles[8], but the all reported methods are unsatisfactory, since most of them should be carried out under rigorous conditions such as high temperature, sealing in bomb and long reaction time, as well as with trouble separation. Moreover, it tends to form ring opening compounds and unstable byproduct. As a result, it is necessary to develop some new methodologies for the preparation of the stilbazoles.

Herein, we report a new palladium catalyzed coupling reaction between vinyl pyridine and substituted aryl compounds to form a series of functional stilbazoles with high stereoselectivity, giving rise to *trans*-product exclusively. At first, in our laboratory general Heck reaction was employed for the synthesis of these compounds since it expands the selective range of starting materials. It was reported that derivatives of stilbazoles were prepared in the yield of about 50% by using palladium-catalyzed coupling[8a]. However, only low yield (20-30%) was observed in our laboratory, and finally the reaction reached an equilibrium while reaction time was prolonged to several days. For instance, 4-bromo-N, N-dimethyl-phenylamine coupled with vinylpyridine for three days and 10% of the target product in the yield was obtained. At first, we supposed that increase of leaving ability of halide substituents in aryl group would favor the progress of the coupling. 4-Indo-N, N-dimethyl-phenylamine was synthesized for the coupling with vinyl pyridine in order to get desired coupling product. However, the coupling reaction did not run. Second, different kinds of palladium catalysts were tested in this coupling reaction in order to obtain desired products. For instance, $Pd(dba)_2$, $Pd(PPh_3)_4$, $Pd(PPh_3)_2 Cl_2/CuI$ and $Pd(AcO)_2/PPh_3$, respectively, was used in this preparation under the same conditions. No any improvement was observed. Afterwards, different kinds of base such as $HNEt_2$, HN $(iPr)_2$, K_2CO_3/DMSO, and $CsCO_3$/DMF were employed in this coupling under the same conditions, also no coupling products were found. Finally, the catalytic system was changed into $Pd(AcO)_2$ /P(o-tolyl)$_3$ in the solvent mixture of Et_3N/DMF. At this case dramatic change of the reaction was observed. For example, the gold yellow precipitate was observed after the reaction carried out in bomb at the temperature of 120°C for only one hour. Actually, we obtained the desired coupling product. The yield was beyond 60%. Subsequently investigation indicated that if this reaction finished in two hour the isolated yield could be raised to 90%. In terms of such short reaction time and high yield, later, we tried to carry out this reaction under more moderate condition. The bomb was replaced by a flask and the reaction was allowed to reflux for 5-6 hr, affording 4-(4-N,N-dimethylamino) stylylpyridine in the same high yield. What is more, the separation of productive compounds was simple and efficient. Using the solubility difference between product and starting material in hexane, the pure product can be obtained by washing with hexane instead of fussy chromatography. By conventional methods, it takes about one week for getting less than one gram desired product. In this improving method, more than 30 g desired product can be obtained in one day.

Table 1 The data of m.p. and isolated yields of synthesized stilbazoles[9]

Compound	Yield(%)*	m.p.(^{0}C)	Compound	Yield(%)	m.p.(^{0}C)
1 	91(10)	244-245	**8** 	80	144-145
2 	92(38)	115-116	**9** 	94	55-57
3 	97(30)	120-122	**10** 	81	98-100
4 	95(35)	145-147	**11** 	89	79-81
5 	93(33)	149-151	**12** 	91	76-77
6 	95(28)	138-140	**13** 	70	223-225
7 	95(25)	116-118	**14** 	68	180-182

*The data in parentheses are yields before improvement of the reaction.

The typical procedure was as follows.

To 500 mL of three-necked flask 20.0 g (0.190 mol) of 4-vinylpyridine, 32.8 g (0.180 mol) of 4-bromonitrobenzene and 3% mol of Pd(OAc)$_2$ with a little ligand of P(*o*-tolyl)$_3$ were added. Then 260 mL of cosolvent (Et$_3$N:DMF = 2:1 in volume) was added to dissolve the starting materials. The reaction mixture was allowed to reflux for 6-8 hours. The end of the reaction was monitored by TLC and triethyl amine was removed in vacuum. The residue was washed with water to remove DMF. The crude product was washed by mixture of hexane and ethylacetate thoroughly, affording 34.2 g of pure 4-(4-nitro)styrylpyridine in the yield of 95%. The other compounds were prepared in the same way.

In conclusion the palladium-catalyzed coupling reaction between vinylpyridine and aryl halide was studied in detail. A novel method to synthesize stilbazoles was developed unprecendentedly. A series of stilbazole derivatives were prepared by this new method in high yield. However, the principle of the solvent effect is still ambiguous, study on the mechanism involved the solvent effect is in progress.

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References and notes

1. S. Nishikawa, M. Sato, H. Kojima, C. Suzuki, N. Yamada, M. Inagaki, N. Kashimura, H. Mizuno, *Proc. Plant Growth Regul. Soc. Am.*, **1996,** *3rd* , 131.
2. J. W. Beach, C. R. McCurdy, M. Gattu, K. L. Boss, O. E. Templeton, A.V. Terry, *J. Med..Chem. Res.*, **1997,** *7,* 271.
3. a) H. Nagase, H. Nemoto, F. Miyata, J. Abe, Y. Shirai, *Jpn.Kokai Tokkyo Koho, JP* **10 07, 670 [9807, 670]**
   b) N. N.emoto, J. Abe, F. Miyata, Y. Shirai, Y. Nagase, *MCLA S&T Sect. B: Nonlinear Opt.*, **1998,** *19,* 105.
4. a) W. B. Lin, O. R. Evans, R. G. Xiong, Z. Y. Wang, *J. Am. Chem. Soc.*, **1998,** *120,* 13272.
   b) W. B. Lin, Z. Y. Wang and L. Ma, *J.Am.Chem.Soc.*, **1999,** *121*, 11249.
5. H. Yan, B. Li, B. F. Li, X. L. Xie, Z. R. Pan, *Gong Neng Gao Fen Zi Xue Bao.*, **1998**, *11*, 91.
6. a) C. M. Brink and P. J. DeJager, *Natuurwetenskapp.*, **1963,** *3*, 74.
   b) A. N. Kost, A. K. Sheinkman and A. N. Rozenberg, *Zh.Obshch.Khim.*, **1964,** *34*, 4046.
   c) L. P. Nethsinghe, P. H. Plesch, D. J. Hodge, *Angew. Makromol. Chem.*, **1987,** *148*, 161.
   d) A. N. Vasil'ev, L. K. Mushkalo, *Zh.Obshch.Khim.*, **1992,** *62*, 2087.
   e) D. Hellwinkel, K. Göke and R. Karle, *Synthesis,* **1994,** 973.
7. V. A. Petrosyan and M. E. Niyazymbetov, *Izv. Akad. Nauk SSSR, Ser, Khim,,* **1991,** *5,* 1151.
8. a) V. Peesapaties, U. N. Rao, R. A. Pethrick, *J.Indian Chem.Soc.*, **1991,** *68,* 389.
   b) M. Beller, O. R. Thiel, H. Trauthwein, *Synlett.*, **1999,** *2*, 243.
   c) Y. Lim, J. Han, J. Kang, *Bull. Korean Chem. Soc.*, **1998,** *19*, 1143.
9. ^{1}H and ^{13}C NMR (CDCl$_3$, 500 MHz) spectroscopic data for: **1**: ^{1}H: δ 8.51 (d, 2H, J = 5.9Hz), 7.44 (d, 2H, J = 8.8Hz), 7.32 (d, 2H, J = 5.9Hz), 7.24 (d, 1H, J = 16.1Hz), 6.80 (d, 1H, J = 16.1Hz), 6.71 (d, 2H, J = 8.8Hz), 3.01 (s, 6H); ^{13}C: δ 151.0, 150.0, 146.0, 133.8, 128.6, 124.4, 121.3, 120.6, 112.4, 40.5. **2**: ^{1}H: δ 8.63 (d, 2H, J = 5.9Hz), 7.68 (d, 2H, J = 8.3Hz), 7.63 (d, 2H, J = 8.3Hz), 7.39 (d, 2H, J = 5.9Hz), 7.29 (d, 1H, J = 16.1Hz), 7.13 (d, 1H, J = 16.1Hz); ^{13}C: δ 150.6, 143.7, 140.7, 132.8, 131.2, 129.8, 127.6, 121.2, 118.8, 111.9. **3:**

^{1}H: δ 8.62 (d, 1H, J = 4.9Hz), 7.69 (d, 2H, J = 8.0Hz), 7.68 (t, 1H, J = 7.6, 8.6Hz), 7.65 (d, 2H, J = 8.0Hz), 7.63 (d, 1H, J = 16.2Hz), 7.38 (d, 1H, J = 8.6Hz), 7.23 (d, 1H, J = 16.2Hz), 7.19 (t, J = 4.9, 7.6, 1H); ^{13}C: δ 154.5, 149.9, 141.2, 136.7, 133.3, 132.5, 131.3, 130.6, 127.4, 122.9, 118.9, 111.2. **4**: ^{1}H: δ 8.65 (d, 2H, J = 5.9Hz), 8.26 (d, 2H, J = 8.8Hz), 7.69 (d, 2H, J = 8.8Hz), 7.41 (d, 2H, J = 5.9Hz), 7.35 (d, 1H, J = 16.1Hz), 7.18 (d, 1H, J = 16.1Hz); ^{13}C: δ 150.6, 147.7, 143.6, 142.7, 130.9, 130.7, 127.7, 124.4, 121.3. **5**: ^{1}H: δ 8.54 (d, 2H, J = 5.2Hz), 7.42 (d, 2H, J = 7.9Hz), 7.33 (d, 2H, J = 5.2Hz), 7.25 (d, 1H, J = 17.1Hz), 7.18 (d, 2H, J = 7.9Hz), 6.94 (d, 1H, J = 17.1Hz), 2.36 (s, 3H); ^{13}C: δ 150.2, 144.8, 138.8, 133.4, 133.1, 129.5, 126.9, 124.9, 120.7, 21.3. **6**: ^{1}H: δ 8.57 (d, 2H, J = 6.4Hz), 7.54 (d, 2H, J = 8.6Hz), 7.44 (d, 2H, J = 8.6Hz), 7.36 (d, 1H, J = 17.1Hz), 7.34 (d, 2H, J = 6.4Hz), 7.25 (d, 1H, J = 16.0Hz), 7.05 (d, 1H, J = 16.0Hz), 5.87 (d, 1H, J = 17.1Hz); ^{13}C: δ 150.3, 149.6, 143.9, 138.9, 133.6, 131.7, 129.5, 127.9, 127.5, 127.3, 120.9, 118.1. **7**: ^{1}H: δ 8.74 (s, 1H), 8.53 (d, 1H, J = 5.1Hz), 7.84 (d, 1H, J = 7.9Hz), 7.65 (d, 2H, J = 8.6Hz), 7.59 (d, 2H, J = 8.6Hz), 7.32 (q, 1H, J = 5.1, 7.9Hz), 7.18 (d, 1H, J = 16.5Hz), 7.13 (d, 1H, J = 16.5Hz); ^{13}C: δ 151.7, 149.5, 149.4, 148.8, 141.0, 133.0, 132.6, 132.6, 128.8, 128.6, 127.0, 118.8. **8**: ^{1}H: δ 8.59 (d, 2H, J = 5.9Hz), 7.52 (d, 2H, J = 8.3Hz), 7.41 (d, 2H, J = 8.3Hz), 7.37 (d, 2H, J = 5.9Hz), 7.24 (d, 1H, J = 16.6Hz), 7.01 (d, 1H, J = 16.6Hz); ^{13}C: δ 150.4, 144.5, 135.3, 132.2, 132.1, 128.7, 126.9, 122.9, 121.1. **9**: ^{1}H: δ 8.52 (d, 2H, J = 5.0Hz), 7.44 (d, 2H, J = 7.9Hz), 7.33 (d, 2H, J = 7.9Hz), 7.29 (d, 2H, J = 5.0Hz), 7.16 (d, 1H, J = 16.2Hz), 6.93 (d, 1H, J = 16.2Hz), 4.08 (q, 4H, J = 7.0Hz), 1.30 (t, 6H, J = 7.0Hz); ^{13}C: δ 150.0, 143.6, 139.7, 132.0, 131.7, 128.1, 126.7, 126.5, 120.7, 61.9, 16.1. **10**: ^{1}H: δ 8.74 (s, 1H), 8.52 (q, 1H, J = 4.8Hz), 7.85 (d, 1H, J = 7.2Hz), 7.31 (q, 1H, J = 4.8, 7.0Hz), 7.56 (d, 2H, J = 8.0Hz), 7.47 (d, 2H, J = 8.0Hz), 7.40 (d, 1H, J = 13.2Hz), 5.90 (d, 1H, J = 13.2Hz), 7.16 (d, 1H, J = 16.2Hz), 7.12 (d, 1H, J = 16.2); ^{13}C: δ 150.0, 149.3, 148.9, 139.7, 133.3, 133.0, 132.6, 129.7, 128.1, 127.4, 127.1, 123.8, 118.4, 96.3. **11**: ^{1}H: δ 8.66 (d, 2H, J = 5.9Hz), 7.60 (d, 1H, J = 16.1Hz), 7.37 (d, 2H, J = 5.9Hz), 6.60 (d, 1H, J = 16.1Hz), 4.29 (q, 2H, J = 7.0Hz), 1.35 (t, 3H, J = 7.0Hz); ^{13}C: δ 166.2, 150.7, 141.8, 123.0, 122.1, 122.0, 61.1, 14.4. **12**: ^{1}H: δ 8.73 (s, 1H), 8.52 (d, 1H, J = 4.7Hz), 7.82 (d, 1H, J = 8.0Hz), 7.78 (s, 1H), 7.72 (d, 1H, J = 8.0Hz), 7.55 (d, 1H, J = 7.6Hz), 7.47 (t, 1H, J = 7.6, 8.0Hz), 7.30 (q, 1H, J = 4.7, 8.0Hz), 7.11 (t, 2H, J = 16.6Hz); ^{13}C: δ 149.8, 148.5, 137.6, 135.5, 132.8, 132.0, 131.7, 130.8, 129.9, 129.2, 128.7, 123.1, 118.3, 112.6. **13**: ^{1}H: δ 8.57 (d, 2H, J = 5.8Hz), 7.63 (d, 2H, J = 7.8Hz), 7.58 (d, 2H, J = 7.8Hz), 7.54 (s, 4H), 7.36 (d, 2H, J = 5.8Hz), 7.29 (d, 1H, J = 16.5Hz), 7.20 (d, 1H, J = 15.5Hz), 7.11 (d, 1H, J = 15.5Hz), 7.04 (d, 2H, J = 16.5Hz); ^{13}C: δ 150.2, 141.6, 136.7, 136.4, 132.5, 132.4, 132.2, 131.6, 127.5, 127.4, 127.2, 126.9, 126.4, 120.8, 119.0, 110.7. **14**: ^{1}H: δ 8.56 (d, 2H, J = 6.3Hz), 7.61 (d, 2H, J = 8.8Hz), 7.58 (d, 2H, J = 8.8Hz), 7.52 (s, 4H), 7.34 (d, 2H, J = 6.3Hz), 7.28 (d, 1H, J = 16.8Hz), 7.03 (d, 1H, J = 16.8Hz); ^{13}C: δ 150.3, 136.8, 132.2, 132.0, 131.8, 128.4, 128.0, 127.4, 127.0, 122.3, 122.0, 120.8, 118.5, 111.5, 93.5, 87.3.

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