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An efficient synthesis of α -aryl β -(*N*-tosyl)amino phosphonate derivatives from α -diazophosphonate

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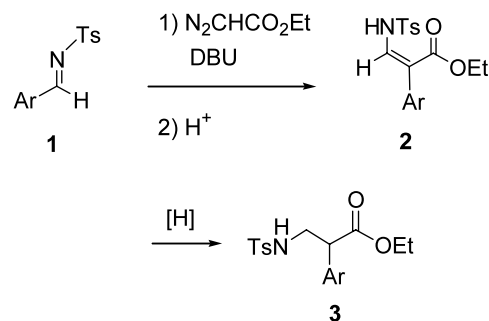
Abstract—The α -diazophosphonate was added to aryl (*N*-tosyl)imine to give β -aryl β -(*N*-tosyl)amino α -diazophosphonates, which were further subjected to TsOH-catalyzed diazo decomposition to yield α -aryl β -(*N*-tosyl)enaminophosphonates through 1,2 aryl migration. The α -aryl β -(*N*-tosyl)enaminophosphonates were hydrogenated to give α -aryl β -(*N*-tosyl)amino phosphonates.

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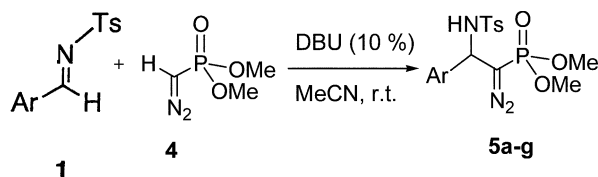
α - Or β -amino phosphonic acid derivatives have attracted considerable attention in recent years because of their involvement in certain biologically important processes.¹ For example, amino phosphonic acid derivatives have been served as the transition state analog in drug design and as haptens in the development of catalytic antibody enzymes.² Consequently, it is desirable to develop efficient approach to synthesize racemic or optically active amino phosphonates.^{1a,3}

We have recently reported the base-catalyzed addition of ethyl diazoacetate to aryl (*N*-tosyl)imines **1** and the subsequent 1,2 aryl migration reaction of the resulting β -(*N*-tosyl)amino α -diazo carbonyl products under Rh(II) complex- or TsOH-catalysis condition.⁴ This two-step reaction sequence transforms ethyl diazoacetate to α -aryl β -(*N*-tosyl)enaminophosphonates **2**, which can be further hydrogenated to give α -aryl β -(*N*-tosyl)amino esters **3** (Scheme 1).⁵ We conceived that this highly efficient reaction sequence may be similarly applied to the corresponding α -diazophosphonate to give the corresponding β -amino phosphonate derivatives. The results of our investigation are described herein.

The α -diazophosphonate **4** was prepared according to the literature procedure.⁶ The DBU-catalyzed addition of α -diazophosphonate **4** to aryl *N*-tosylimine **1a–g** was carried out at room temperature and the β -aryl β -(*N*-tosyl)amino α -diazophosphonates **5a–g** were obtained in 54–89% isolated yields (Scheme 2).⁷



Scheme 1.

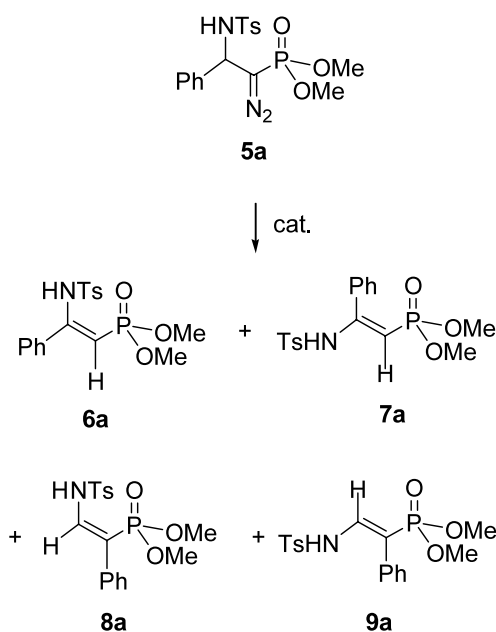


- a** Ar = C₆H₅, 75 %
b Ar = *p*-ClC₆H₄, 76 %
c Ar = *p*-FC₆H₄, 52 %
d Ar = *p*-MeOC₆H₄, 65 %
e Ar = 4-Ph-C₆H₄, 54 %
f Ar = *m*-CF₃C₆H₄, 89 %
g =

Scheme 2.

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The decomposition of the diazo compounds **5a–g** was expected to give 1,2-hydride and 1,2-aryl migration products. The effect of the catalytic system on the migratory aptitude was studied in some detail with transition metal catalysts, Lewis acids and TsOH. The β -(*N*-tosyl)amino α -diazo phosphonate **5a** was taken as the substrate and the product distribution are summarized in Scheme 3 and Table 1. In all cases, the diazo decomposition was highly efficient and 1,2 phenyl migration predominated. These results are similar to the corresponding reaction with phenyl α -diazo β -(*N*-tosyl)amino ester.^{4,5} However, the *E*:*Z* ratio of the 1,2 phenyl migration products varies under different catalytic condition. Most catalysts gave rather low *E*:*Z* ratio, TsOH being the only exception, which gave only the *Z* product. It is worthwhile to note that the *Z* product is thermodynamically more stable relative to the *E* isomer due to the intramolecular hydrogen bonding. It is conceivable that some initially formed *E* product isomerizes to the more stable *Z* isomer under the TsOH-catalyzed reaction condition.



Scheme 3.

Table 1. Product distribution in the decomposition of **5a** using different catalysts

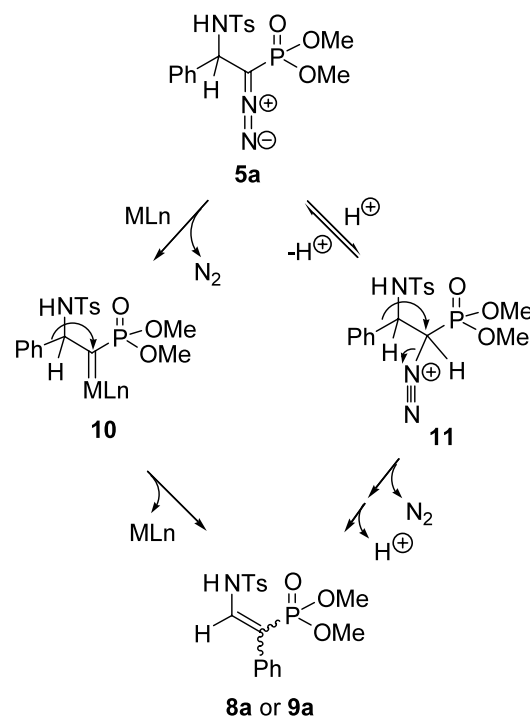
Entry	Catalyst	6a : 7a : 8a : 9a ^a	Yield ^b
1	Rh ₂ (OAc) ₄	12:0:33:55	97
2	Rh ₂ (O ₂ CCF ₃) ₄	23:0:34:43	89
3	Cu(MeCN) ₄ PF ₆	0:0:42:58	88
4	PhCO ₂ Ag	3:0:78:19	87
5	BF ₃ ·Et ₂ O	0:0:63:37	89
6	SnCl ₂ ·2H ₂ O	0:0:46:54	89
7	TsOH	0:0:100:0	97

^a Product ratio was determined by ¹H NMR (300 or 400 MHz).

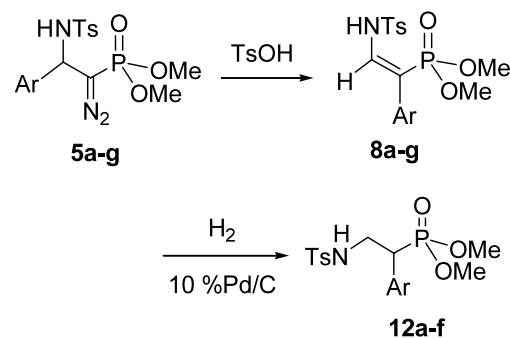
^b Yields after a rapid filtration through silica gel.

The similar reaction mechanism for β -phenyl β -(*N*-tosyl)amino α -diazoesters^{4c} may be applied to the transition metal- or acid-catalyzed reaction of **5a** (Scheme 4). The diazo compound **5a** is first converted to metal carbene **10** with Rh(II) or Cu(I) catalyst, or was protonated to give **11** in the acid-catalyzed reaction. From **10** or **11**, migration of the phenyl group synchronizes with catalyst dissociation or nitrogen expulsion, respectively, leading to the formation of **8a** or **9a**.

Since the TsOH-catalyzed reaction gave single product in excellent yield, this condition was applied to the other diazo substrates **5b–g**.^{7,8} The results are summarized in Scheme 5 and Table 2. The diazo decomposition gave the (*Z*)- α -aryl β -(*N*-tosyl)enaminophosphonates **8a–g** in excellent yields. These β -(*N*-tosyl)-enamino phosphonates seemed to decompose slowly on silica gel column; they were rapidly filtrated through silica gel and were further subjected to hydrogenation over 10% Pd/C.⁹ The α -aryl β -(*N*-tosyl)amino phosphonates **12a–f** were obtained in high yields, except in one



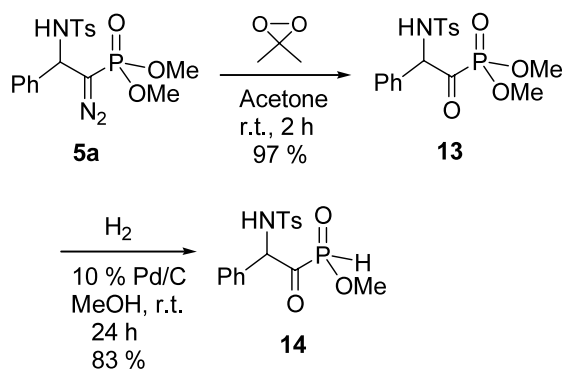
Scheme 4.



Scheme 5.

Table 2. Products from TsOH-catalyzed diazo decomposition of **5a–g** and products from hydrogenation of **8a–g**

Entry	5 (Ar=)	Yield (%), 8 ^a	Yield (%), 12 ^b
1	a , C ₆ H ₅	97	95
2	b , <i>p</i> -ClC ₆ H ₄	89	75
3	c , <i>p</i> -FC ₆ H ₄	89	94
4	d , <i>p</i> -MeOC ₆ H ₄	82	96
5	e , <i>p</i> -PhC ₆ H ₄	94	93
6	f , <i>m</i> -CF ₃ C ₆ H ₄	96	81
7	g , 2-Furyl	80	— ^c

^a Yields after a rapid filtration through silica gel.^b Yields after silica gel column separation.^c Hydrogenation gave unidentified complex mixture.**Scheme 6.**

case when the aryl group is 2-furyl, which gave unidentified complex mixture.

Thus, the above three-step reaction sequence can efficiently transform the α -diazophosphonate to α -aryl β -(*N*-tosyl)aminophosphonates. Moreover, the diazo group in the α -diazophosphonate can be subjected to other synthetically useful transformations. For example, we found that the diazo group could be oxidized with dimethyl dioxirane to give α -oxo β -(*N*-tosyl)amino phosphonate **13**, which was hydrogenolyzed to give α -oxo β -(*N*-tosyl)amino phosphinate **14** in good yield (Scheme 6).

Acknowledgements

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- Typical procedure for DBU-catalyzed addition of α -diazophosphonate **4** to aryl *N*-tosylimine **1a–g**.** To a solution of α -diazophosphonate **4** (1.0 mmol) in anhydrous CH₃CN (2 mL), at room temperature under N₂, was added successively a solution of DBU (0.2 mmol) in anhydrous CH₃CN (1 mL) and imine **4** (1.2 mmol) in anhydrous CH₃CN (2 mL) via a syringe. After stirring at room temperature for 12 h, the reaction was quenched with saturated aqueous NaHCO₃, and then extracted with CH₂Cl₂ (15×2 mL). The solvent was removed by evaporation under reduced pressure, and the crude product was purified by flash chromatography to give β -aryl β -(*N*-tosyl)amino α -diazophosphonate **5a–g**. The structures of the products were confirmed by IR and ¹H NMR (300 or 200 MHz) spectral data. Dimethyl [1-diazo-2-(*N*-tosylamino)-2-(*p*-phenylphenyl)ethyl] phosphonate (**5e**): ¹H NMR (300 MHz, CDCl₃) δ 2.40 (s, 3H), 3.54 (d, 6H, *J*_{HP}=8.0 Hz, 3H), 3.64 (d, *J*_{HP}=7.6 Hz, 3H), 5.23 (dd, *J*=12.6, 6.9 Hz, 6H), 5.67 (d, *J*=6.9 Hz, 1H), 7.25–7.74 (m, 13H). ¹³C NMR (75 MHz, CDCl₃) δ 21.5, 30.9, 53.1, 53.2 (d, *J*_{CP}=10.4 Hz), 54.7 (d, *J*_{CP}=5.8 Hz) 126.8, 126.9, 127.2, 127.4, 127.6, 128.8, 129.6, 137.1, 137.2, 140.1, 141.2, 143.6. IR (KBr): ν 2098, 1595 cm⁻¹. FAB-MS (*m/z*, relative intensity) 492 (M+Li)⁺. Anal. calcd for C₂₃H₂₄PO₅SN₃: C, 56.90; H, 4.98; N, 8.66. Found: C, 56.90; H, 4.90; N, 8.67.
- General procedure for the TsOH-catalyzed diazo decomposition of **5a–g**.** To a solution of TsOH (4.6 mg) in anhydrous CH₂Cl₂ (2 mL) at 0°C under N₂, was added dropwise a solution of individual diazo compounds **5a–g** in anhydrous CH₂Cl₂ (10 mL). The reaction was complete within 30 min as monitored by TLC. Solvent was removed by evaporation, and the residue was purified by quick flash column chromatography over silica gel to give α -aryl β -enaminophosphonates **8a–g**, which were subjected to subsequent hydrogenation without further purification. Dimethyl [1-(*p*-phenylphenyl)-2-(*N*-tosylamino)ethenyl]phosphonate (**8e**): ¹H NMR (200 MHz, CDCl₃) δ 2.41 (s, 3H), 3.62 (d, *J*_{HP}=6.2 Hz, 3H), 3.65 (d, *J*=6.2 Hz, 6H), 7.21–7.80 (m, 14H), 10.51 (d, *J*=11.6 Hz, 1H). ¹³C NMR (75 MHz, CDCl₃) δ 21.4, 52.3, 52.4, 126.7, 126.9, 127.3, 127.6, 127.8, 128.0, 127.9, 128.7, 129.6, 129.9, 130.0, 137.2, 142.0, 142.1, 144.1. IR (film): ν 2947, 1611 cm⁻¹.

9. **General procedure for the hydrogenation of α -aryl β -enamino phosphonates 8a–g.** To a solution of α -aryl β -enamino phosphonate (0.1 mmol) in absolute MeOH (15 mL) was added 10% Pd/C catalyst (10 mg). The reaction mixture was stirred for 24 h under 1 atm hydrogen atmosphere. Then catalyst was removed by filtration and solvent was evaporated to give a residue, which was purified by flash column chromatography. Dimethyl[1-(*p*-phenylphenyl)-2-(*N*-tosylamino)ethyl]phosphonate (**12e**):

^1H NMR (200 MHz, CDCl_3) δ 2.34 (s, 3H), 3.43–3.52 (m, 1H), 3.54 (d, $J_{\text{HP}}=8.4$ Hz, 3H), 3.67 (d, $J_{\text{HP}}=11.4$, 1H), 5.28 (t, $J=9.0$ Hz, 1H), 6.90–7.80 (m, 14H). ^{13}C NMR (50 MHz, CDCl_3) δ 21.4, 42.8 (d, $J_{\text{CP}}=45.2$ Hz), 45.1, 52.9 (d, $J_{\text{CP}}=7.2$ Hz), 53.6 (d, $J_{\text{CP}}=6.8$ Hz), 126.9, 127.5, 127.5, 127.9, 129.4, 129.5, 129.7, 129.9, 136.9, 140.2, 140.7, 143.4; IR (film): ν 2954, 1607 cm^{-1} . Anal. calcd for $\text{C}_{23}\text{H}_{26}\text{NO}_5\text{PS}$: C, 60.12; H, 5.70; N, 3.05. Found: C, 60.09; H, 5.62; N, 2.83.