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# Convenient Synthesis of Bis(oxazoline) Dicarboxylate Derivatives.

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**Abstract:** The synthesis of bis(oxazoline) dicarboxylate derivatives was investigated. Diethylaminosulfur trifluoride (DAST) was used as a convenient cyclization reagent in the synthesis of bis(oxazoline) dicarboxylate derivatives, which can not be obtained by the general method using MsCl and $Et_3N$ as dehydrating cyclization reagent.

**Keywords:** Bis(oxazoline), synthesis, diethylaminosulfur trifluoride (DAST).

Bis(oxazoline) as versatile ligand has been found widespread use in many kinds of asymmetric catalytic reactions[1]. Many different methods have been developed for synthesizing the bis(oxazoline) ligands[1-4]. The effective method explored by Denmark[3] and Ikeda[4] is as follows: the diacid chloride or diacid ester reacted with amino alcohol to afford dihydroxyamide, which was treated with MsCl and $Et_3N$ to give the intermediate bismesylate, then bismesylate was treated with methanolic solution of NaOH to furnish the bis(oxazoline).

We utilized the aformentioned Denmark's method to synthesize the ligands **1**. When MsCl was used for the cyclization of dihydroxy diamides**,** bis(oxazoline) **1b~1f** were successfully obtained[5], however **1a** can not be obtained from **3** with MsCl and $Et_3N$ (**Scheme 1**), instead a new compound **4** was obtained[6]. The reason of formation of compound **4** may be that the adjacent carboxy ester group accelerate the leaving group methanesulfonyl to leave, and the more stable conjugated compound **4** was formed. Consequently, only when the substitute of the bismesylate is alkyl or phenyl, they can be cyclized to give the bis(oxazoline) (such as **1b-1f**).

According to the reports of Williams[7] and Knight[8], diethylaminosulfur trifluoride (DAST) has been successfully used for the cyclization of β-hydroxy amide. So we tried to use DAST in our reaction system. We treated the dihydroxy diamide **3** with a slight excess (1.1 equiv.) of DAST at –78 °C in $CH_2Cl_2$, after addition of $K_2CO_3$, the temperature of the reaction mixture was risen to room temperature. The target bis(oxazoline) biscarboxylate **1a** was afforded in high yield (86%) (**Scheme 1)**.

In addition, DAST was also employed to the cyclization of biphenyl dihydroxy diamide **5** and phenyl hydroxylamide **7** (**Scheme 2**). Bis(oxazoline) **6** and oxazoline **8**

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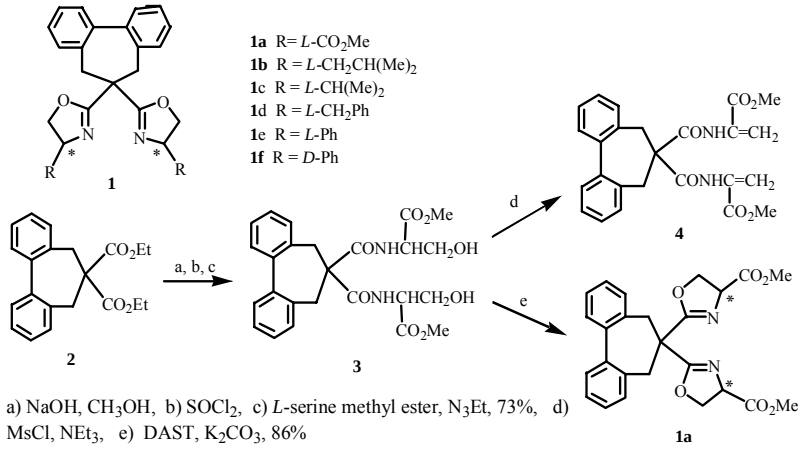
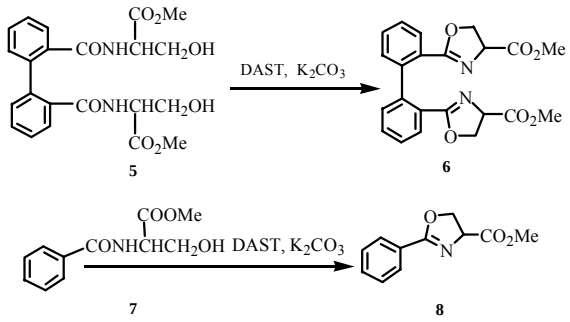
were obtained in 82% and 85% yield, respectively. Ikeda[9] reported that the bis(oxazoline) **6** could be synthesized with the Burgess' reagent [(methoxyCarbonylsulfanoyl) Triethylammonium hydroxide inner salt] in THF in 56%-69% overall yields based on 2,2'-binaphthyldicarboxylic acid. The preparation of Burgess' reagent is troublesome, in contrast, DAST is commercial readily available. Moreover, the reaction is very effective and the experimental condition is mild.

**Scheme 1**




**Scheme 2**




In summary, although the general method for the synthesis of bis(oxazoline) **1b~1f** using MsCl and $Et_3N$ was effective, it was unsuccessful for the synthesis of **1a**. In this case DAST can be a good cyclization reagent instead of MsCl.

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6. Spectral data (200 MHz for $^{1}$H NMR and 50 MHz for $^{13}$C NMR in $CDCl_3$, δ ppm): **4:** $^{1}$H NMR 8.59 (s, 2H, CONH), 7.50-7.25 (m, 8H, ArH), 6.63 (d, 2H, *J* =5.6 Hz, $=CH_2$), 5.91 (d, 2H, *J* =2.0 Hz, $=CH_2$), 3.87 (s, 6H, $CO_2Me$), 3.48 (s, 2H, $ArCH_2$), 2.85 (s, 2H, $ArCH_2$). $^{13}$C NMR: 172.99, 164.44, 140.41, 136.24, 130.76, 129.19, 128.17, 127.56, 127.24, 106.74, 52.77, 52.53, 34.05. MS (EI): *m/z* 448 ($M^+$, 30), 320 (18), 219 (100), 191 (60). HRMS (EI): calcd. for $C_{25}H_{24}N_2O_6$ 448.1634; found: 448.1631.
   **3:** $^{1}$H NMR: 7.40-7.26 (m, 8H, ArH), 6.97 (s, 2H, NH), 4.63 (t, 2H, *J* = 3.4 Hz, $CHCO_2Me$), 4.06-3.95 (m, 4H, $CH_2OH$), 3.79 (s, 6H, $CO_2Me$), 3.52-2.80 (m, 6H, $ArCH_2$ + OH). $^{13}$C NMR: 171.36, 170.63, 140.30, 135.17, 130.18, 127.93, 127.51, 65.50, 61.93, 55.16, 52.69, 36.71. MS(FAB): *m/z* 485(M+1). Anal. calcd. for $C_{25}H_{28}N_2O_8$: C, 61.98; H, 5.78; N, 5.78. Found: C, 62.11; H, 5.92; N, 5.70.
   **1a:** $^{1}$H NMR: 7.41-7.12 (m, 8H, ArH), 4.76 (dd, 2H, *J* = 7.2, 7.4 Hz), 4.68-4.40 (m, 4H), 3.73 (s, 6H, $CO_2Me$), 3.40-2.90 (m, 4H, $ArCH_2$). $^{13}$C NMR: 171.04, 169.15, 140.79, 135.12, 130.02, 127.94, 127.51, 127.15, 70.00, 68.02, 53.35, 52.51, 52.45, 37.58, 37.44. MS(EI): *m/z* 448 ($M^+$, 35), 389 (M-59, 21), 320(M-128, 100); HRMS (EI) calcd. for $C_{25}H_{24}N_2O_6$ 448.1634. Found: 448.1633.
   **8:** $^{1}$H NMR: 7.98 (m, 2H, ArH), 7.49-7.36 (m, 2H, ArH), 4.96 (dd, 2H, *J* = 6.2, 12.0 Hz), 4.73-4.52 (m, 4H), 3.82 (s, 3H, $CO_2CH_3$); $^{13}$C NMR: 171.2, 169.6, 140.7, 139.0, 130.9, 127.7, 127.2, 126.9, 52.7. HRMS (EI): calcd. for $C_{11}H_{11}NO_3$ 205.0739. Found: 205.0735.
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