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A Practical Preparation of (*Z*)-2-(5-Amino-1,2,4-thiadiazol-3-yl)-2-(methoxyimino)acetic Acid

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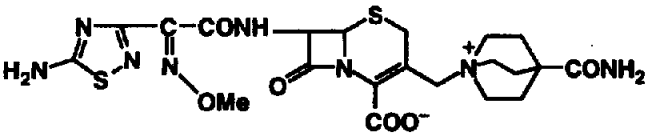
Abstract: A *Z*-isomer of 2-(5-amino-1,2,4-thiadiazol-3-yl)-2-(methoxyimino)acetic acid, which is the common acyl moiety of clinically useful cephalosporins, has been prepared from the aminoisoxazols through the thiadiazol-acetate in two pathways.

Recently, (*Z*)-7β-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2-(alkoxyimino)acetamido]cephalosporins[1] such as E1040[2](**1**) and SCE2787[3] have been reported as clinically useful antibiotics having excellent antimicrobial activities. Their common acyl moiety at the C-7 position is corresponding to the *Z*-isomer of 2-(5-amino-1,2,4-thiadiazol-3-yl)-2-(alkoxyimino)acetic acid (**10**) . The *E* isomer is not a valuable acyl portion for useful β-lactam antibiotics, so far. Consequently, it was our intention to successfully develop a general method of entry into the *Z* isomer **10** by our own strategy. Although several methods[1,4] have been known for the production of **10**, we wish to report herein a novel preparation directed toward the mass production of the methoxyimino compound **10a** through the skeletal rearrangement of the aminoisoxazols **3** or **5**, and the stereoselective O-methylation of the hydroxyimino compound **11**.[5]



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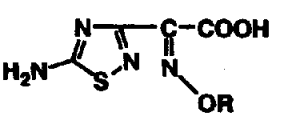

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10a: R=Me

The starting 3-amino-5-methoxyisoxazol **3** [6] have been prepared from 3,3-dimethoxy acrylonitrile **2**. A suspension of methyl chloroformate and potassium thiocyanate in acetonitrile was stirred at 70°C for 30min to give methoxycarbonylisothiocyanate *in situ*, which reacted with **3** at 5°C for 10min and 20°C for 15min to give methyl 2-(5-methoxycarbonylamino-1,2,4-thiadiazol-3-yl)acetate (**4a**)[7] [86%, mp 169°C (MeOH)] by the skeletal rearrangement [8] of the intermediary thiourea derivative such as **6**. Instead of methyl chloroformate, ethyl chloroformate, phenyl chloroformate and benzyl chloroformate were similarly used for the reaction to afford the corresponding alkoxycarbonylamino derivatives **4b**[7] [83%, mp 112°C (MeOH)], **4c**[7] [60%, mp 164°C (MeOH)] and **4d**[7] [40%, mp 123°C (MeOH)], respectively.

The methoxycarbonyl compound **4a** was also prepared from 3-aminoisoxazol (**5**), which was commercially available[9]. The aminoisoxazol **5** was treated with the aforesaid methoxycarbonylisothiocyanate in acetonitrile at 5°C for 30min and at 20 °C for 15min to give the thiourea derivative **6**[7] [58%, mp 167°C (hexane-EtOAc)], followed by warming in MeOH at 35°C for 1h to afford the thiadiazolyl-acetaldehyde **7**[7] [98%, mp 166°C (MeOH)]. Oxidation of **7** with peracetic acid in aq. t-BuOH at 20°C for 18h provided the corresponding acetic acid derivative [80%, mp 190 °C (MeOH)], which was esterified with 10%HCl-MeOH to give quantitatively the methyl ester **4a**.

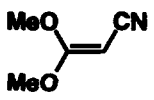
The methylene group of **4** was oxidized by SeO_2 to the keto ester **8** in high yield, but this reagent may be not adapted in the industrial scale production because of its toxicity. Many kinds of oxidation were assayed, and finally, the best result was realized by treatment of **4** (1eq) with DMSO (5eq), iodine (0.1eq) and conc.H_2SO_4 (0.1eq) in refluxing EtOAc for 3h to give the intractable keto ester **8** [**8a**[7]: 83%, foam; **8b**[7]: 78%, mp 174°C (hexane-EtOAc); **8c**[7]: 58%, foam; **8d**[7]: 69%, mp 147°C (hexane-EtOAc)].

Without isolation of the labile intermediate **8a**, the methoxyimino compound **9** was readily prepared from **4a**. After the acetate **4a** was refluxed with DMSO, iodine and conc.H_2SO_4 in EtOAc for 3h as described above, a solution of methoxyamine hydrochloride in 95%MeOH was added and the resulting mixture was stirred at 20°C for 30min. The desired *Z* isomer of the methoxyimino acetate **9**[7] was exclusively obtained in almost quantitative yield: mp 161°C(hexane-EtOAc). The *Z*-configuration of **9** was confirmed by hydrolysis (1M NaOH, 100°C, 4h) to the amino acid **10a**[7] [80%, mp 182°C(dec)], which was identical with the authentic sample in all respects.[1] The amino acid **10a** has been converted into the corresponding acid chloride in almost quantitative yield.[10]

Alternatively, **9** was prepared from **4a** through the hydroxyimino compound **11**. This procedure would provide a general preparation of other valuable alkoxyimino derivatives. Treatment of **4a** in THF containing conc.HCl with methyl nitrite (MeONO) gas,[11] which was produced by addition of 6M H_2SO_4 to a solution of $NaNO_2$ in 50%MeOH, gave the oxime **11**[7] [92%, mp 190°C ($CHCl_3$)].

In O-methylation of **11**, a large number of variables including methylating reagent [e.g., MeI and $(MeO)_2SO_2$], base [Ag_2O, K_2CO_3, BaO, $Ba(OH)_2$, CaO, Et_3N], solvent (DMSO, DMF, Me_2CO, Et_2O, dioxane) and temperature were assayed. Most of conditions gave only the *E* isomer **12**[7]: for example, reaction of **11** with MeI in DMF in the presence of BaO or $Ba(OH)_2$ gave **12** in about 80% yield [R_f 0.41(hexane-EtOAc 1 : 1); **9**: R_f 0.29]. Remarkably, the use of combined reagents BaO (5eq) and $Ba(OH)_2 \cdot 8H_2O$ (0.5-0.8eq) for **11** with MeI (1.2eq) or $(MeO)_2SO_2$ (1.1eq) in DMF-$CHCl_3$ gave exclusively the desired *Z* isomer **9** in 84% or 80% yields. Also, methylation of **11** with MeI and Ag_2O afforded the *Z* isomer **9** in 80% yield. A variety of (*Z*)-alkoxyimino compounds could be provided by these conditions.

Thus, the *Z* isomer **10a** was obtained from the aminoisoxazols **3** or **5** through the thiadiazol-acetate **4a** in two pathways.



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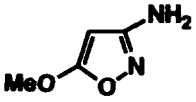

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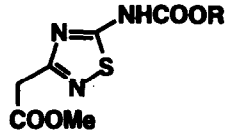

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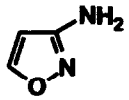
4a : R=Me
b : R=Et
c : R=Ph
d : R=Bn



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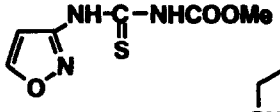

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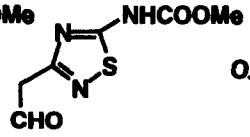

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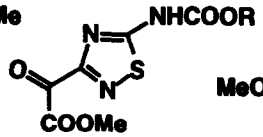

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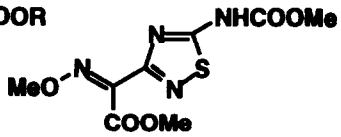
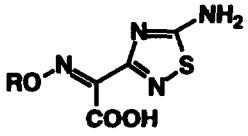


9

8a : R=Me
b : R=Et
c : R=Ph
d : R=Bn



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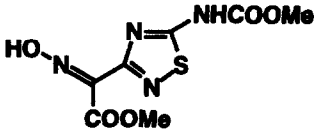
10a: R=Me



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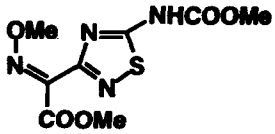

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7. All compounds were purified by recrystallization or silica-gel column chromatography, and were fully characterized by spectroscopic means and elemental analyses. Significant ^{1}H-NMR spectra data (270 MHz or 400 MHz, $CDCl_3$, δ: TMS=0 or $CHCl_3$=7.26) are the following. **4a**: δ 3.73 (3H, s), 3.95 (3H, s), 3.97 (2H, s). **4b**: δ 1.38 (3H, t), 3.73 (3H, s), 3.97 (2H, s), 4.39 (2H, q). **4c**: δ 3.66 (3H, s), 3.99 (2H, s). **4d**: δ 3.70 (3H, s), 3.85 (2H, s), 5.33 (2H, s). **6**: δ 3.85 (3H, s), 7.36 (1H, d), 8.28 (1H, d). **7**: δ 3.90 (2H, d), 3.92 (3H, s), 9.87 (1H, t). **8a**: δ 3.96 (3H, s), 4.02 (3H, s). **8b**: δ 1.40 (3H, t), 4.01 (3H, s), 4.41 (2H, q). **8c**: δ 4.00 (3H, s), 7.25-7.49 (5H, m). **8d**: δ 4.00 (3H, s), 5.35 (2H, s), 7.32-7.49 (5H, m). **9**: δ 3.94 (3H, s), 3.97 (3H, s), 4.12 (3H, s). **10a** (in DMSO-d_6): δ 3.90 (3H, s), 8.20 (2H, broad s). **11**: δ: 3.96 (3H, s), 4.02 (3H, s), 9.45 (1H, broad s), 9.92 (1H, broad s). **12**: δ: 3.63 (3H, s), 4.00 (6H, s, Me).
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