Synthesis and Reactivities of 1-(Isocyanomethyloxy)benzotriazole as a New Source of Isocyanomethyl Synthon

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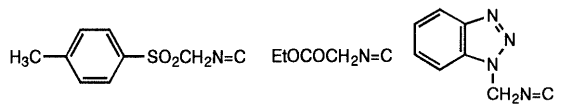
The title compound, 1-(isocyanomethyloxy)benzotriazole (6) as a new source of isocyanomethyl synthon, was synthesized in 65% yield by the dehydration of 1-(formamidomethyloxy)benzotriazole with phosphorus oxychloride in the presence of triethylamine. Under basic conditions, the reaction of 6 with aldehydes or acid chlorides gave 5-substituted oxazoles or 5-substituted 4-[(1-benzotriazolyl)oxy]oxazoles as new 4-hydroxyoxazole derivatives, respectively. The reactivities of 6 toward aldehydes are as high as those of tosylmethyl isocyanide.

Key words isocyanide; 1-(isocyanomethyloxy)benzotriazole; oxazole; 1-hydroxybenzotriazole; aldehyde; acid chloride

For the convenient one-step synthesis of five-membered heterocycles such as oxazoles, thiazoles, and imidazoles, an isocyanomethyl synthon has been widely used under basic conditions.[1] Generally, isocyanomethyl reagents, which readily produce isocyanomethyl carbanion in the presence of a base, have an isocyanomethyl group attached to an electron-withdrawing group, *i.e.*, the tosyl and ethoxycarbonyl groups of tosylmethyl isocyanide (**1**) and ethyl isocyanoacetate (**2**), respectively.[1] In a series of our studies on the reactivities of **1**,[2] 1-(isocyanomethyl)-benzotriazole (**3**) bearing an isocyanomethyl group attached at a nitrogen atom was prepared as we expected that the benzotriazolyl moiety would have a good leaving ability, like the tosyl group of **1**.[3] Katritzky and co-workers have reported that **3** could be applied for the preparation of oxazoles under basic conditions.[4]



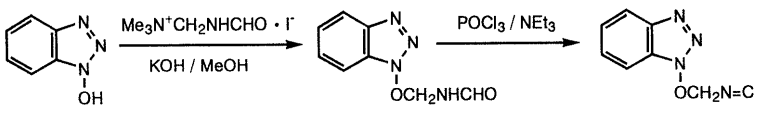
1 **2** **3**

Fig. 1.

1-Hydroxybenzotriazole (**4**), frequently used as an additive for peptide synthesis by the dicyclohexylcarbodiimide dehydration method, can also be expected to have a similar leaving ability to that of the benzotriazole moiety in **3**. This report describes the synthesis of 1-(isocyanomethyloxy)benzotriazole (**6**) as a new source of isocyanomethyl synthon and the reactivities of **6** toward aromatic and heteroaromatic aldehydes (**7**) and acid chlorides (**9**) under basic conditions. To my knowledge, compounds with an isocyanomethyl group attached at an oxygen atom have not previously been reported.

As shown in Chart 1, 1-(formamidomethyloxy)benzotriazole (**5**) was prepared as a precursor of **6** by the reaction of **4** with formamidomethyl(trimethyl)ammonium iodide[3] in the presence of KOH in refluxing methanol in 82% yield. Subsequently, the dehydration of **5** by phosphorus oxychloride in the presence of triethylamine gave **6** in 65% yield. The structure of **6** was characterized by spectral data and elemental analysis. Namely, the ^{1}H-NMR spectrum of **6** showed the methylene proton signal at 5.89 ppm as a singlet and aromatic proton signals at 7.40—8.30 ppm as a multiplet. The IR spectrum showed a characteristic isocyano group absorption at 2140 cm^{-1}. Compound **6** is obtained as stable, colorless microcrystals [mp 118—119 °C(dec.)] and has good solubility in organic solvents such as EtOAc, tetrahydrofuran (THF), ether, CH_3CN, and CH_2Cl_2.

The reactivities of **6** toward aldehydes (**7a—f**) and acid chlorides (**9a—f**) under basic conditions were investigated, as shown in Chart 2. First, in the presence of potassium *tert*-butoxide the reaction of **6** with benzaldehyde (**7a**) in dry THF afforded the corresponding 5-phenyloxazole (**8a**) in 77% yield. Similar reactions of **6** with aromatic and heteroaromatic aldehydes (**7b—f**) gave the corresponding 5-substituted oxazoles (**8b—f**) in yields of 88, 81, 77, 91, and 85%, respectively. The physical properties and the spectral data of the obtained oxazoles (**8a—f**) were identical with reported data.[2a,4,5] The most noteworthy feature of this oxazole synthesis using **6** is that the work-up is very convenient, because the only by-product **4** could be readily removed by washing with 5% sodium bicarbonate solution and the yields of **8a—f** (77—91%) are almost the same as those obtained in previous studies using tosylmethyl isocyanide (**1**)[2a,5] and better than those obtained by using 1-(isocyanomethyl)benzotriazole (**3**).[4] Next, 4-[(1-benzotriazolyl)oxy]-5-phenyloxazole (**10a**) was prepared by the reaction of **6** with benzoyl chloride (**9a**) in the presence of potassium *tert*-butoxide



4 **5** **6**

Chart 1

in dry THF at room temperature in 72% yield. The ^{1}H-NMR spectrum of **10a** showed the signal of the proton at the 2-position of the oxazole ring at 8.04 ppm and the IR spectrum showed a characteristic C–H stretching vibration due to the oxazole ring at 3100 cm^{-1}.[6] Similar reactions of **6** with acid chlorides (**9b—f**) afforded the corresponding oxazoles (**10b—f**) in moderate yields (55—74%) and the structures of **10b—f** were also confirmed by the ^{1}H-NMR and IR spectral data and elemental analyses, as listed in Table 1.

In summary, a new type of isocyanide **6** has been synthesized as a new source of isocyanomethyl synthon; it readily reacted with aldehydes (**7**) or acid chlorides (**9**) in the presence of a base to afford 5-substituted oxazoles (**8**) or 5-substituted 4-[(1-benzotriazolyl)oxy]oxazoles (**10**) as new 4-hydroxyoxazole derivatives, respectively.

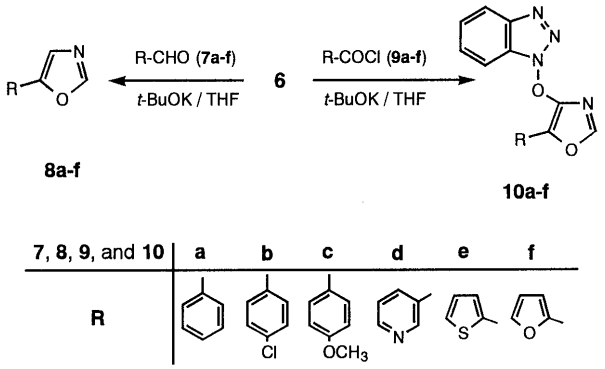


Chart 2

Experimental

All melting points were taken on a Yanagimoto micro melting point determination apparatus and are uncorrected. IR spectra were recorded on a Hitachi 270-30 infrared spectrophotometer. ^{1}H-NMR spectra were taken at 400 MHz with Bruker DPX-400 spectrometers using tetramethylsilane as an internal reference in $CDCl_3$ or dimethyl sulfoxide (DMSO)-d_6.

1-(Formamidomethyloxy)benzotriazole (5) A solution of 1-hydroxybenzotriazole (**4**, 6.8 g, 50 mmol), formamidomethyl(trimethyl)ammonium iodide (14.7 g, 60 mmol) and KOH (3.4 g, 60 mmol) in methanol (100 ml) was refluxed for 5 h with stirring. The resulting mixture was cooled to room temperature and the precipitate was collected by filtration. The crude product was purified by recrystallization from methanol. The yield was 7.9 g (82%). mp 127—128 °C, colorless prisms (methanol). IR (KBr) cm^{-1}: 3350—2900 (br), 1686, 1605, 1422, 1224, 747. ^{1}H-NMR (DMSO-d_6) δ: 5.78 (2H, d, J=6.6 Hz, –CH_2–), 7.46 [1H, m, benzotriazole(Bt)-5H], 7.73 (1H, m, Bt-6H), 7.88 (1H, m, Bt-4H), 7.96 (1H, m, Bt-7H), 8.17 (1H, d, J=1 Hz, –CHO), 9.35 (1H, m, –NH–). *Anal.* Calcd for $C_8H_8N_4O_2$: C, 50.00; H, 4.20; N, 29.15. Found: C, 49.87; H, 4.05; N, 29.24.

1-(Isocyanomethyloxy)benzotriazole (6) A solution of $POCl_3$ (5.07 g, 33 mmol) in dry THF (30 ml) was added dropwise to a suspension of **5** (5.76 g, 30 mmol) in dry THF (70 ml) at below 5 °C with stirring. After the addition of triethylamine (15.2 g, 15 mmol) the mixture was stirred for 5 h at below 5 °C on an ice-water bath. A cooled 10% aqueous NaOH solution (30 ml) was added and the mixture was concentrated under reduced pressure. EtOAc (200 ml) was poured into the residue and the organic layer was separated, washed twice with brine (20 ml), and then dried over anhydrous $MgSO_4$. The solvent was evaporated *in vacuo* to give a dark brown crude product, which was purified by reprecipitation with a mixture of acetone and hexane to give 3.4 g (65%) of **6**. This product was used in the next step without further purification. An analytical sample was obtained by recrystallization from a mixture of EtOAc and hexane (3 : 1) as colorless prisms. mp 118—119 °C (dec.). IR (KBr) cm^{-1}: 3064, 3010, 2962, 2140, 1605, 1428, 1206, 699. ^{1}H-NMR ($CDCl_3$) δ: 5.89 (2H, s, –CH_2–), 7.53 (1H, m, Bt-6H), 7.63 (1H, m, Bt-4H), 7.77 (1H, m, Bt-5H), 8.06 (1H, m, Bt-7H). *Anal.* Calcd for $C_8H_6N_4O$: C, 55.17; H, 3.47; N, 32.17. Found: C, 55.27; H, 3.26; N, 32.29.

Table 1. Yields and Physical Data for the 5-Substituted 4-[(1-Benzotriazol)oxy]oxazoles (**10a—f**)

Compd.	Yield (%)	mp (°C)	^{1}H-NMR (400 MHz, ppm, $CDCl_3$)[a]	Formula	Analysis (%) Calcd (Found) C	H	N	IR (cm^{-1})
10a	72	180—181	7.41 (3H, m, Ph-H), 7.49 (1H, m, Bt-6H), 7.59—7.68 (4H, m, Ph-H, Bt-4H, 5H), 8.04 (1H, s, Ox-2H), 8.08 (1H, m, Bt-7H)	$C_{15}H_{10}N_4O_2$	64.74 (65.00	3.62 3.71	20.13 20.36)	3100, 3008, 1506, 1464, 744
10b	58	195—196	7.40 (2H, d, J=8.9 Hz, Ph-H), 7.50 (1H, m, Bt-6H), 7.65 (2H, d, J=8.9 Hz, Ph-H), 7.66—7.74 (2H, m, Bt-4H, 5H), 8.04 (1H, s, Ox-2H), 8.08 (1H, m, Bt-7H)	$C_{15}H_9ClN_4O_2$	57.61 (57.57	2.90 3.06	17.92 17.99)	3092, 3000, 1500, 1460, 762
10c	66	78—79	3.82 (3H, s, –CH_3), 6.91 (2H, d, J=9.0 Hz, Ph-H), 7.48 (1H, m, Bt-6H), 7.58 (2H, d, J=9.0 Hz, Ph-H), 7.60—7.66 (2H, m, Bt-4H, 5H), 7.99 (1H, s, Ox-2H), 8.08 (1H, m, Bt-7H)	$C_{16}H_{12}N_4O_3$ ·3/5H_2O	60.22 (60.41	4.17 4.44	17.56 17.70)	3128, 3008, 2974, 1516, 1462, 740
10d	55	220—221	7.38 (1H, m, Py-5H), 7.52 (1H, m, Bt-6H), 7.70 (1H, m, Bt-6H), 7.70 (2H, m, Bt-5H), 7.88 (1H, m, Bt-4H), 8.08 (1H, m, Bt-7H), 8.11 (1H, s, Ox-2H), 8.14 (1H, m, Py-4H), 8.65 (1H, m, Py-6H), 8.97 (1H, m, Py-2H)	$C_{14}H_9N_5O_2$	60.21 (60.03	3.25 3.32	25.08 25.11)	3096, 3000, 1502, 1464, 760
10e	74	176—177	7.10 (1H, dd, J=5.1, 3.8 Hz, Th-4H), 7.44 (1H, dd, J=5.1, 1.2 Hz, Th-5H), 7.50 (1H, m, Bt-6H), 7.65—7.70 (2H, m, Th-3H, Bt-5H), 7.87 (1H, m, Bt-4H), 7.97 (1H, s, Ox-2H), 8.08 (1H, m, Bt-7H)	$C_{13}H_8N_4O_2S$	54.92 (54.84	2.84 2.98	19.71 19.80)	3104, 2996, 1506, 1466, 742
10f	62	160—161	6.53 (1H, dd, J=3.5, 1.8 Hz, Fu-4H), 7.18 (1H, dd, J=3.5, 0.8 Hz, Fu-3H), 7.47—7.54 (2H, m, Fu-5H, Bt-6H), 7.68 (1H, m, Bt-5H), 7.95 (1H, m, Bt-4H), 7.99 (1H, s, Ox-2H), 8.07 (1H, m, Bt-7H)	$C_{13}H_8N_4O_3$	58.21 (58.07	3.01 3.10	20.89 20.91)	3100, 2998, 1506, 1462, 728

a) The following abbreviations are used: Bt, benzotriazole; Fu, furan; Ox, oxazole; Ph, benzene; Py, pyridine; Th, thiophene.

5-Substituted Oxazoles (8a—f) General Procedure: Potassium *tert*-butoxide (1.1 g, 10 mmol) was added in one portion to a stirred solution of **6** (10 mmol) and an aldehyde **7** (10 mmol) in dry THF (40 ml) at room temperature. The mixture was stirred for 2 h at room temperature and concentrated under reduced pressure to give a light brown oil. EtOAc (100 ml) was poured onto the oil and the mixture was washed twice with 5% sodium bicarbonate solution (20 ml) and brine (20 ml). The solution was dried over $MgSO_4$, and the solvent was removed *in vacuo* to give a crude product, which was purified by recrystallization from a mixture of ether and hexane for **8a**—**e** and by distillation for **8f**. The yields of **8a**—**f**[2a,4,5] were 77, 88, 81, 77, 91, 85%, respectively.

5-Substituted 4-[(1-Benzotriazolyl)oxy]oxazoles (10a—f) General Procedure: Potassium *tert*-butoxide (560 mg, 5 mmol) was added to a solution of **6** (5 mmol) and an acid chloride **9** (5 mmol) in dry THF (20 ml). The mixture was stirred for 4 h at room temperature, then the solvent was removed *in vacuo* to give a viscous brown oil. The residue was dissolved in EtOAc (100 ml) and the mixture was washed twice with 5% sodium bicarbonate solution (20 ml) and brine (20 ml), then dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure to give the corresponding 5-substituted 4-[(1-benzotriazolyl)-oxy]oxazole (**10**), which was purified by silica gel flash column chromatography with a mixture of acetone and hexane (1 : 1). Analytical samples of **10** were obtained by recrystallization from ether for **10a**—**c** and **10f** or from EtOAc for **10d**—**e**. The physical properties, elemental analysis, and ^{1}H-NMR and IR spectral data of **10** are listed in Table 1.

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