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Methyl 3-Substituted-Isoxazole-5-Carboxylates Syntheses on Solid Supports via Wang Resin-Bound 2,3-Dibromopropionate

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ABSTRACT: *A novel Wang resin-bound 2,3-dibromopropionate reagent has been developed and used as a potential dipolarophile for the facile preparation of methyl 3-substituted-isoxazole-5-carboxylates through triethylamine, promoting a sequence of reactions involving the in situ generation of 2-bromoacrylate resin and nitrile oxide, regioselective 1,3-dipolar cycloaddition, and loss of hydrogen bromide in one pot, and then cleavage from the resin with sodium methoxide. The advantages of this method include simple operation and mild conditions with good yield and high purity of the products.* © 2012 Wiley Periodicals, Inc. Heteroatom Chem 00:1–5, 2012; View this article online at wileyonlinelibrary.com. DOI 10.1002/hc.21035

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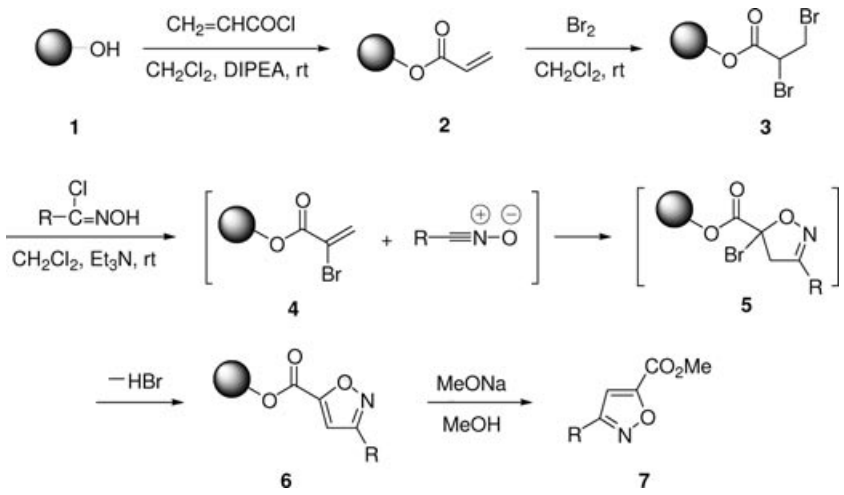
INTRODUCTION

The solid-phase organic synthesis (SPOS) is a method in which molecules are bound on a bead and synthesized step by step in a reactant solution; compared with normal synthesis in a liquid state, it is easier to remove excess reactant or by-product from the product [1]. Now, SPOS has become a central feature in the synthesis of organic materials with repetitive units. It is an attractive approach for the rapid preparation of a large number of compounds and for discovering new active molecules [2,3]. The isoxazole skeleton is present in a variety of natural products and represents useful synthetic building blocks [4]. In addition, they have shown considerable anti-inflammatory [5], antiviral [6], as well as antitubulin [7] activities. Therefore, the preparation of this family of heterocycles continues to be of interest [8, 9]. Although several groups have studied the synthesis of isoxazoles by using the SPOS technology [10] by the condensation of 1,3-dicarbonyl compounds with hydroxylamine [11,12], the addition of nitrile oxides to the supported alkynes [13–16], the anchoring of a nitrile oxide precursor onto the solid phase [17,18], and with polymer-supported vinyl ethers as chameleon catches [19], as well as using polymeric selenium reagent [20–22], the facile preparation of functionalized isoxazole libraries for lead discovery is highly desirable. Herein, we wish to report our preliminary study on the solid-phase synthesis of methyl isoxazole-5-carboxylates using



SCHEME 1 SPOS route to methyl 3-substituted-isoxazole-5-carboxylate.

a novel Wang resin-bound 2,3-dibromopropionate reagent, as shown in Scheme 1.

RESULTS AND DISCUSSION

In this study, Wang resin-bound 2,3-dibromopropionate (**3**) was chosen because it appears to facilitate the generation of 2-bromoacrylate as a dipolarophile promoted by base, which would have sufficient activity to react with nitrile oxides via 1,3-dipolar cycloaddition for the construction of functional bromosubstituted isoxazolines, whose hydrogen bromide can be eliminated easily with base to form a double bond in the final products. Besides, in the recent study of the synthesis of functionalized 5,5-disubstituted isoxazolines, isoxazoles were obtained as the sole products instead of bromoisoxazolines between 1,3-dipolar cycloaddition reactions of 2-bromoacrylic acid methyl ester with various aromatic nitrile oxides in the presence of triethylamine [23]. Encouraged by these results, we tried to carry out our idea to synthesize functionalized methyl 3-substituted-isoxazole-5-carboxylates on the basis of this new polymeric reagent **3**.

Wang resin, 4-benzyloxybenzyl alcohol resin, is the most popular support for SPOS. As a standard support, it can be used for the solid-phase immobilization of acids and phenols for SPOS. The ester linkage may be achieved, which has good stability to a variety of reaction conditions, but can be readily removed with trifluoroacetic acid or sodium methoxide [1]. So, Wang resin has been selected as support for our investigation. Initially, acryloyl chloride was quantitatively anchored to Wang resin **1** loaded with 1.20 mmol/g via an ester linkage in the presence of *N*, *N*-diisopropylethylamine (DIPEA). The resin-bound acrylate **2** was characterized by FTIR microscopy [24], which showed complete disappearance of the hydroxyl stretch and the appearance of a C=O stretch at 1725 cm^{-1} and a C=C stretch at 1651 cm^{-1}. The 2,3-dibromopropionate resin **3** was obtained efficiently by treatment of resin **2** with bromine in dichloromethane after stirring for 1 h. Conversion of **2** to **3** seemed to be quantitative, because FTIR of **3** revealed the appearance of a new strong carbonyl absorption at 1742 cm^{-1}, a moderate strong C—Br band at 572 cm^{-1}, and the complete disappearance of absorptions at 1725 and 1651 cm^{-1}. It should be noted that this new resin-bound 2,3-dibromopropionate reagent **3** is stable and can be stored at room temperature for a long time without diminution of capacity.

In the next step, subjecting **3** to the dehydrobromination and cycloaddition reaction with hydroximoyl chlorides in the presence of triethylamine afforded the resin-bound isoxazole-5-carboxylates **6** (no bromine was found by microanalysis of resin **6**), which was evidenced by their FTIR spectra, featuring a strong carbonyl absorption near 1725 cm^{-1}, and with the complete disappearance of C—Br (572 cm^{-1}) absorption. In fact, Wang resin-bound 2-bromoacrylate (**4**) could be easily obtained from the resin **3** through the loss of hydrogen bromide through triethylamine promotion. After isolation and washing, the resin **4** could react with nitrile oxides and then dehydrobrominated to generate resin **6** almost with the same results as the above procedure. However, we have found it most convenient to carry out this conversion from **3** to **6** in one pot.

TABLE 1 Yields and Purity of Methyl 3-Substituted-isoxazole-5-carboxylates (**7a–7i**)

Entry	*R*	*Product*	*Yield (%)*[a]	*Purity (%)*[b]
1	C_6H_5	**7a**	90	98
2	4-$CH_3C_6H_4$	**7b**	87	97
3	4-$MeOC_6H_4$	**7c**	88	95
4	4-ClC_6H_4	**7d**	85	94
5	2,6-$Cl_2C_6H_3$	**7e**	72	92
6	4-$NO_2C_6H_4$	**7f**	80	93
7	4-FC_6H_4	**7g**	81	95
8	2-Furyl	**7h**	85	96
9	$CH_3CH_2CH_2$	**7i**	82	95

[a]Overall yields based on Wang resin-bound 2,3-dibromopropionate **3** (1.86 mmol Br/g).
[b]Determined by HPLC of a crude cleavage product.

Eventually, cleavage of the product from isoxazole-5-carboxylate resins **6** was achieved readily by transesterification (NaOMe, MeOH/THF (1:4), reflux for 18 h) to provide methyl 3-substituted-isoxazole-5-carboxylates **7** in good yields and purity (Table 1). Besides, this process also exhibited excellent regioselectivity. Methyl isoxazole-5-carboxylates **7** were formed exclusively, indicating that the cycloaddition of resin **4** with nitrile oxides occurred with complete regioselectivity. On the other hand, as observed from Table 1, the present method was effective for reaction substrates, hydroximoyl chlorides derived from both aromatic (either with electron-withdrawing or electron-donating group) and aliphatic aldehydes. However, compound **7e** (Table 1, entry 5) showed a decrease in yield of 72%, which might have resulted from the steric hindrance of two chlorosubstituents in the ortho position of a benzene ring of the corresponding hydroximoyl chloride.

CONCLUSIONS

In summary, a novel strategy for the facile solid-phase synthesis of methyl 3-substituted-isoxazole-5-carboxylates has been developed from Wang resin-bound 2,3-dibromopropionate reagent through a sequence of reactions involving in situ generating of resin-bound 2-bromoacrylate and nitrile oxide, regioselective 1,3-dipolar cycloaddition, and loss of hydrogen bromide to form the corresponding Wang resin-bound isoxazole-5-carboxylate, followed by cleaving from resin with sodium methoxide. A simple workup procedure replaces the time-consuming isolation and purification steps in the corresponding solution-phase synthesis. Further investigations based on this novel polymeric reagent are now in progress.

EXPERIMENTAL

General

Melting points were uncorrected. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Bruker AVANCE (400 MHz) spectrometer (Billerica, MA), using $CDCl_3$ as the solvent and TMS as an internal standard. Mass spectra (EI, 70 eV) were recorded on a HP5989B mass spectrometer (Palo Alto, CA). FTIR spectra were taken on a Perkin-Elmer SP One FTIR spectrophotometer (Waltham, MA). Microanalyses were performed with a Carlo Erba 1106 elemental analyzer (Milan, Italy). HPLC was performed on an Agilent 1100 high-performance liquid chromatograph (Santa Clara, CA). Wang resin (1.20 mmol/g) and other starting materials were purchased from commercial suppliers and used without further purification. 1,2-Dichloroethane was refluxed with phosphorous pentoxide, and distilled. THF was distilled from sodium-benzophenone immediately prior to use.

*Preparation of Wang Resin-Bound 2,3-Dibromopropionate (**3**)*

Wang resin **1** (1.0 g, 1.2 mmol, loading 1.20 mmol/g) was swollen in CH_2Cl_2 (10 mL), DIPEA (0.65 g, 5.0 mmol) acryloyl chloride (0.45 g, 5.0 mmol) was added, and the reaction mixture was shaken at room temperature for 4 h. After which, the mixture was filtered and the resin was washed sequentially with DMF (2 × 10 mL), H_2O (2 × 10 mL), MeOH (2 × 20 mL), CH_2Cl_2 (2 × 10 mL), and ether (2 × 10 mL) and dried overnight in a vacuum oven at 40°C to afford resin **2**. To the resultant resin **2** swollen in CH_2Cl_2 (10 mL) for 30 min, bromine (1.5 mmol) was added. After 1 h of shaking the mixture at room temperature, the resin was collected on a filter and washed successively with CH_2Cl_2 (2 × 10 mL), H_2O (2 × 10 mL), THF (2 × 10 mL), and ether (2 × 10 mL) and then dried under vacuum overnight to afford a white resin **3** with a loading value of 1.86 Br mmol/g by elementary analysis. FTIR (KBr): ν = 3042, 2927, 1742, 1595, 1455, 1248, 1180, 1106, 995, 965, 826, 765, 572 cm^{-1}.

*General Procedure for the Preparation of Methyl 3-Substituted-Isoxazole-5-Carboxylates (**7a–7i**)*

Under a positive pressure of nitrogen, to a suspension of the swollen resin **3** (1.0 mmol, 1.08 g) in CH_2Cl_2 (15 mL), hydroximoyl chloride (2.0 mmol) was added and shortly thereafter triethylamine (0.63 mL, 4.5 mmol) was also added. After shaking the mixture for 10 h at room temperature, resin **6**

was collected by filtration, washed successively with THF/H_2O (1:1) (2 × 10 mL), DMF (2 × 10 mL), THF (2 × 10 mL), MeOH (2 × 10 mL), and CH_2Cl_2 (2 × 10 mL). Then, resin **6** was cleaved in a mixture of THF (8 mL) and MeOH (2 mL) in the presence of 45 mg of sodium methoxide at 70°C for 18 h. After cooling, the resin was filtered and washed with THF/H_2O (1/1) (3 × 10 mL), MeOH (3 × 5 mL), and Et_2O (3 × 5 mL). Evaporation of the solvent from the filtrate afforded crude products **7a**–**7i** with 92%–98% purity determined by HPLC, which were further purified by passing the crude product through a silica gel chromatographic column (ethyl acetate–hexane as the eluent, 1:4), affording the pure products for their structure analyses. All of the isolated products for this study were unambiguously characterized by ^{1}H NMR, ^{13}C NMR, IR, and for regiochemical assignment. All analytical data are consistent with the literature data.

Methyl 3-phenylisoxazole-5-carboxylate (**7a**). Colorless solid, mp 107–108°C (107–109°C [23]); ^{1}H NMR: δ = 7.85–7.81 (m, 2H), 7.49–7.44 (m, 3H), 7.26 (s, 1H), 3.98 (s, 3H); ^{13}C NMR: δ = 163.0, 160.5, 157.1, 130.5, 129.0, 128.2, 126.8, 107.4, 52.8; IR (KBr): ν = 3425, 2982, 1745, 1450, 1294, 1245, 1025, 770 cm^{-1}.

Methyl 3-(4-methylphenyl)isoxazole-5-carboxylate (**7b**). Colorless solid, mp 112–113 °C; ^{1}H NMR: δ = 7.73 (d, J = 8.4 Hz, 2H), 7.36 (d, J = 8.4 Hz, 2H), 7.27 (s, 1H), 3.95 (s, 3H), 2.40 (s, 3 H); ^{13}C NMR: δ = 163.3, 161.1, 157.2, 141.0, 129.8, 127.5, 127.0, 107.7, 52.7, 21.5; IR (KBr): ν = 3430, 2985, 1730, 1447, 1294, 1248, 1021, 820, 766 cm^{-1}; EIMS: m/z(%) = 217 (M$^+$); Anal. Calcd for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.10; N, 6.45. Found: C, 66.28; H, 5.18; N, 6.38.

Methyl 3-(4-methoxyphenyl)isoxazole-5-carboxylate (**7c**). Colorless solid, mp 117–119°C (118–119°C [23]); ^{1}H NMR: δ = 7.75 (d, J = 8.8 Hz, 2H), 7.21 (s, 1H), 7.02 (d, J = 8.8 Hz, 2H), 3.99 (s, 3H), 3.84 (s, 3H); ^{13}C NMR: δ = 162.5, 161.4, 160.2, 157.2, 128.2, 120.1, 114.6, 107.2, 55.5, 52.8; IR (KBr): ν = 3062, 2981, 1735, 1445, 1295, 1245, 1026, 765 cm^{-1}.

Methyl 3-(4-chlorophenyl)isoxazole-5-carboxylate (**7d**). Colorless solid, mp 120–122°C; ^{1}H NMR: δ = 7.78 (d, J = 8.4 Hz, 2H), 7.38 (d, J = 8.4 Hz, 2H), 7.27 (s, 1H), 4.00 (s, 3H); ^{13}C NMR: δ = 163.3, 161.2, 157.0, 136.5, 126.3, 129.3, 128.1, 107.1, 52.9; IR (KBr): ν = 3440, 2982, 1730, 1448, 1285, 1246, 1025, 925, 825 cm^{-1}; EIMS: m/z(%) = 237 (M$^+$); Anal. Calcd for $C_{11}H_8ClNO_3$: C, 55.60; H, 3.39; N, 5.89. Found: C, 55.51; H, 3.47; N, 5.82.

Methyl 3-(2,6-dichlorophenyl)isoxazole-5-carboxylate (**7e**). Colorless solid, mp 115–117°C (lit. 114–116°C [25]); ^{1}H NMR: δ = 7.48–7.35 (m, 3H), 7.06 (s, 1H), 4.02 (s, 3H); ^{13}C NMR: δ = 160.5, 159.2, 157.0, 135.6, 131.5, 128.2, 127.0, 111.2, 53.1; IR (KBr): ν = 3062, 2981, 1750, 1445, 1295, 1245, 1026, 765 cm^{-1}.

Methyl 3-(4-nitrophenyl)isoxazole-5-carboxylate (**7f**). Yellow solid, mp 168–169°C; ^{1}H NMR: δ = 8.20 (d, J = 8.6 Hz, 2H), 7.60 (d, J = 8.6 Hz, 2H), 7.30 (s, 1H), 4.02 (s, 3H); ^{13}C NMR: δ = 163.4, 161.2, 156.8, 135.8, 127.6, 126.1, 123.8, 107.8, 53.2; IR (KBr): ν = 3440, 2961, 1735, 1550, 1520, 1385, 1246, 1080, 928, 858 cm^{-1}; EIMS: m/z(%) = 248 (M$^+$); Anal. Calcd for $C_{11}H_8N_2O_5$: C, 53.23; H, 3.25; N, 11.29. Found: C, 53.35; H, 3.37; N, 11.22.

Methyl 3-(4-fluorophenyl)isoxazole-5-carboxylate (**7g**). Colorless oil; ^{1}H NMR: δ = 7.85–7.80 (m, 2H), 7.27–7.23 (m, 2H), 7.25 (s, 1H), 3.92 (s, 3H); ^{13}C NMR: δ = 164.0, 163.2, 161.2, 156.8, 129.4, 124.3, 116.8, 107.2, 52.8; IR (film): ν = 3443, 3133, 2982, 1731, 1448, 1284, 1246, 1023, 925, 830, 762 cm^{-1}. EIMS: m/z(%) = 221 (M$^+$); Anal. Calcd for $C_{11}H_8FNO_3$: C, 59.73; H, 3.65; N, 6.33. Found: C, 59.61; H, 3.77; N, 6.39.

Methyl 3-(2-furyl)isoxazole-5-carboxylate (**7h**). Colorless oil; ^{1}H NMR: δ = 7.48 (d, J = 7.5 Hz, 1H), 7.37–7.42 (m, 1H), 6.71 (d, J = 3.0 Hz, 1H), 7.28 (s, 1H), 3.95 (s, 3H); ^{13}C NMR: δ = 163.0, 160.1, 156.5, 151.0, 126.5, 114.7, 110.5, 102.8, 52.8; EIMS: m/z(%) = 193; IR (film): ν = 3058, 2933, 1722, 1435, 1385, 1225, 1205, 1170, 1031, 770 cm^{-1}; Anal. Calcd for $C_9H_7NO_4$: C, 55.96; H, 3.65; N, 7.25. Found: C, 55.90; H, 3.74; N, 7.18.

Methyl 3-(n-propyl)isoxazole-5-carboxylate (**7i**). Colorless oil; ^{1}H NMR: δ = 7.20 (s, 1H), 3.88 (s, 3H), 2.65 (t, J = 7.5 Hz, 2H), 2.12–1.50 (m, 2H), 0.98 (t, J = 7.5 Hz, 3H); ^{13}C NMR: δ = 163.5, 156.3, 154.8, 107.2, 52.1, 29.2, 22.1, 13.7; IR (film): ν = 3060, 2985, 1725, 1445, 1295, 1375, 1242, 1165, 1023, 760 cm^{-1}; EIMS: m/z(%) = 169 (M$^+$); Anal. Calcd for $C_8H_{11}NO_3$: C, 56.80; H, 6.55; N, 8.28. Found: C, 56.86; H, 6.63; N, 8.37.

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