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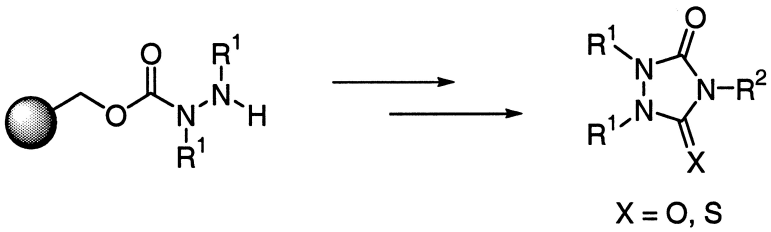

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Solid-Phase Syntheses of 1,2,4-Trisubstituted Urazole and Thiourazole Derivatives

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Solid-phase syntheses of 1,2,4-trisubstituted urazole and thiourazole derivatives have been accomplished. The synthesis began with the coupling of carbonylimidazole−Wang resin with a disubstituted hydrazine. The resultant carbazate was coupled with an isocyanate or isothiocyanate. Subsequent heating of the resin in the presence of triethylamine or potassium *t*-butoxide induced cyclization and released the desired (thio)-urazole into solution. Most of the products were obtained in high yields and purities. Structural diversity can be further expanded at the R^2 substituent by performing the palladium-mediated Suzuki coupling reaction.

Introduction

Combinatorial chemistry has emerged as an important component in the drug discovery program. Given the fact that heterocycles are essential moieties in a wide range of biologically active molecules, it is hardly surprising that considerable effort has been channeled to the development of combinatorial synthetic methodologies for the preparation of heterocyclic libraries.[1] The quest for more biologically active compounds has placed a huge demand for more heterocyclic and natural-product-like molecules.[2] Despite the increased repertoire of combinatorial syntheses of heterocycles, solid-phase syntheses of urazole and thiourazole derivatives still have not been attempted.

Urazoles were reported to possess herbicidal activity against weeds.[3] A thiourazole compound, derived from its isourazole precursor after isomerization by glutathione *S*-transferase, also exhibited herbicidal activity.[4] In addition, urazoles were shown to be useful as insecticides.[3b,5] The effectiveness of urazoles as antifungal agents against *Pellicularia sasakii* and *Cocliobolus miyabeanus* strains has also been described.[6]

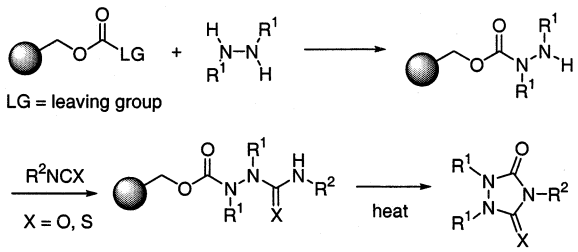
In biomedical research, urazole has been employed as a template for the syntheses of triazaprostaglandin analogues. These analogues were shown to have a bronchodilatory effect of a similar magnitude compared to the natural prostaglandins.[7] Research efforts, mainly from Hall and co-workers, have also demonstrated the antineoplastic activity, hypolipidemic, antiinflammatory, and antidepressant effects of the urazole derivatives.[8]

Further exploration of urazoles and thiourazoles as useful therapeutic agents requires ready access to these classes of heterocycles. In view of this, we initiated solid-phase syntheses of urazole and thiourazole derivatives. Reported herein are the findings of our synthetic studies.

Results and Discussions

As depicted in Scheme 1, our approach involves the initial coupling of an activated carbonate resin with a disubsitituted hydrazine. The resin-bound carbazate is reacted with either an isocyanate or an isothiocyanate, and the resultant resin is then heated to induce cyclization and concomitant cleavage of the product from the solid support. This approach allows only the completely assembled linear precursor to undergo cyclization and give the desired product.

Scheme 1. Our Synthetic Strategy



An activated carbonate resin that fulfills the following criteria is required for the synthesis: (i) it should be sufficiently activated to allow facile displacement of the leaving group by disubstituted hydrazine derivatives; (ii) it must be reasonably stable for ease of handling and storage. The solid support chosen for our study was carbonylimidazole resin. Previous studies showed that compounds bearing an amino functionality such as amino acids, amino alcohols, and diamines could easily displace the imidazole group.[9] We prepared this activated carbonate resin **1** by treating Wang resin with 1,1′-carbonyldiimidazole in the presence of pyridine. The resin can be stored in a desiccator for at least 6 months with no sign of degradation as revealed by gel-phase ^{13}C NMR spectroscopy.[10]

The coupling of carbonylimidazole−Wang resin **1** with disubstituted hydrazine derivatives **2** was investigated (Scheme 2). Our preliminary study indicated that the addition of an equivalent amount of 4-(dimethylamino)pyridine (DMAP) was needed to ensure the complete displacement of the imidazole group by diethylhydrazine. In the case of dimethylhydrazine, the reaction proceeded to completion without DMAP.[11] However, a more bulky substituent such as diisopropylhydrazine required not only DMAP but also

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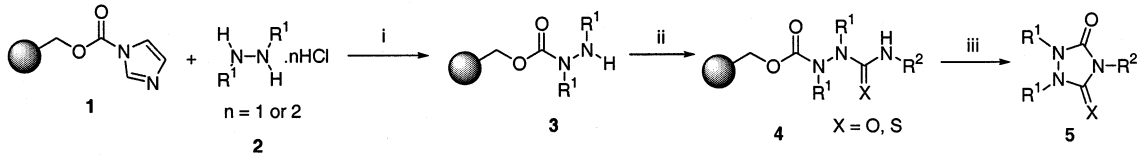
Scheme 2. Solid-Phase Syntheses of Urazoles and Thiourazoles[a]



[a] Reagents and conditions: (i) DMAP, diisopropylethylamine, anhydrous DMA, room temp (for R^1 = Me, Et) or 50 °C (for R^1 = *i*-Pr), 18 h; (ii) R^2NCX, anhydrous 1,2-dichloroethane, 60 °C, 18 h; (iii) triethylamine−anhydrous toluene (3:20), 110 °C, 18 h or KO*t*-Bu, anhydrous THF, 60 °C, 18 h.

Table 1

entry	R^1	R^2	X	yield[a] (%)	purity[b] (%)
5a	Me	4-MeOPh	O	66	72
5b	Me	cyclohexyl	O	60	95
5c	Et	4-MeOPh	O	68 (28)	72 (36)
5d	Et	2-NO_2Ph	O	57 (41)	74 (56)
5e	Et	*n*-Pr	O	36	54
5f	Et	cyclohexyl	O	36	67
5g	*i*-Pr	4-MeOPh	O	22	76
5h	*i*-Pr	2-NO_2Ph	O	31	63
5i	*i*-Pr	Bn	O	9	57
5j	Ph	4-MeOPh	O	0	−
5k	Ph	Bn	O	0	−
5l	Me	CH_2CH_2Ph	S	61	96
5m	Me	cyclohexyl	S	39	75
5n	Et	4-MeOPh	S	41	97
5o	Et	4-NO_2Ph	S	43	94
5p	Et	Bn	S	50	94

[a] Overall yields based on the loading of Wang resin as specified by the supplier. [b] Purities as assessed by HPLC, monitored at 254 nm for entries **5a**,**c**,**d**,**g**,**h**,**l**−**p** and at 220 nm for entries **5b**,**e**,**f**,**i**. The yields and purities quoted in parentheses are of the products obtained from the carbonylimidazole−hydroxymethyl resin.

heating at 50 °C for complete reaction as shown by gel-phase ^{13}C NMR spectroscopy.[12] The displacement of imidazole by an aromatic-group-substituted hydrazine, such as diphenylhydrazine, could be achieved at room temperature in the presence of DMAP.

The resin-bound carbazate **3** was then treated with a variety of aliphatic and aromatic isocyanates. When the reaction was performed at room temperature, there was no conversion after a period of 1−2 days, as monitored by gel-phase ^{13}C NMR spectroscopy. At an elevated temperature of 60 °C, the desired product **4** was successfully obtained in 18 h, even with the bulky cyclohexyl isocyanate.

Cyclization of the linear precursor **4** was carried out in refluxing toluene in the presence of triethylamine for 18 h to afford the corresponding urazole derivatives **5**. Our results indicate that the extent of cyclization is dependent on the nature of both the hydrazine and the isocyanate substituents. Most of the products bearing the dimethyl- and diethylhydrazine substituents (**5a**,**c**,**d**) were obtained in satisfactory yields and purities (Table 1).

The yields for the more bulky diisopropyl-substituted urazoles (**5g**,**h**) were lower. It was thought that the cyclization was incomplete. Hence, the postcyclized resin was treated with TFA−CH_2CH_2 (1:1), but mass spectrometry of the crude cleavage mixture did not detect any uncyclized precursor, indicating that the cyclization had proceeded to completion. Furthermore, there was no additional product being cyclized off the resin by extending the heating period. To account for the low product yields, the loading of diisopropylhydrazine was examined. The resin-bound diisopropylcarbazate was subjected to TFA cleavage, and the cleaved product was weighed.[13] The level of loading was determined to be 54%. This shows that the carbonyl group was probably dislodged at the elevated temperature during the loading step and led to the decreased yields of the final cyclized products.

Although the cyclitive cleavage condition using triethylamine worked well with most of the substrates, it did not provide any product for carbazates **4b**,**f**,**i**−**k**. A stronger base, such as potassium *t*-butoxide, was sought and successfully delivered the desired products (**5b**,**f**,**i**). However, when this latter cleavage condition was applied to the diphenylhydrazine-containing substrates, it failed to afford any product (**5j**−**k**). Gel-phase ^{13}C NMR spectroscopy revealed the existence of the linear precursors; the failure of product formation was attributed to the resistance of the substrates to undergo cyclization.[14]

Our synthetic methodology for urazoles was then extended to the preparation of thiourazole derivatives. The resin-supported carbazate **3** was reacted with isothiocyanates to provide resin **4**, which was then heated under basic conditions to induce cyclization and cleavage of the thiourazole derivatives **5l**−**p** from the support. The yields of the cyclized products were moderate, but the HPLC purities were generally higher than those of their urazole counterparts (Table 1).

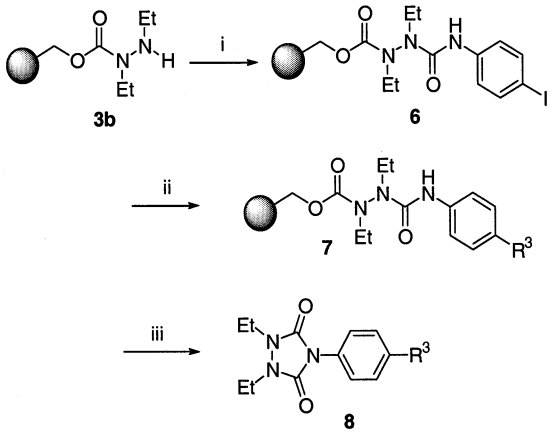
The syntheses of diethyl-substituted urazoles (**5c**,**d**) were also carried out using a carbonylimidazole−hydroxymethyl resin. This solid support was prepared by treating hydroxymethyl resin with 1,1′-carbonylimidazole in anhydrous CH_2Cl_2−pyridine (9:1). However, this route was abandoned because of lower product yields and purities.

To further expand the structural diversity at the R^2 substituent, the resin-bound diethylcarbazate was reacted with 4-iodophenyl isocyanate. The resultant resin **6**, which possessed an iodo functionality, provided a reactive site for palladium-mediated Suzuki reactions (Scheme 3). The transformation was carried out with slight heating in the presence of $Pd(PPh_3)_4$ and triethylamine.[15] A variety of boronic acids having different stereoelectronic demands were reacted to furnish resins **7**. Resins **7** were then subjected to heating to release the corresponding urazoles **8** (Table 2).[16] The use of Na_2CO_3 as base in the Suzuki reaction was not successful because only trace amounts of the products **8** were obtained. This is probably due to the insolubility of the inorganic base in the solvent.

Conclusion

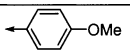
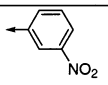
In conclusion, we have demonstrated a short synthetic route to access the 1,2,4-trisubstituted urazole and thiourazole

Scheme 3. Incorporation of Additional Diversity via Suzuki Coupling Reaction[a]



[a] Reagents and conditions: (i) 4-iodophenyl isocyanate, anhydrous 1,2-dichloroethane, 60 °C, 18 h; (ii) $R_3B(OH)_2$, $Pd(PPh_3)_4$, triethylamine, anhydrous DMA, 40 °C, 18 h; (iii) triethylamine−anhydrous toluene (3:20), 110 °C, 18 h.

Table 2

Entry	R^3	Yield (%)[a]
8a		11
8b		25
8c		9
8d		27

[a] Isolated yields after purification by preparative TLC, based on the loading of Wang resin as specified by the supplier.

derivatives. The cyclitive cleavage of products is influenced by both the hydrazine and iso(thio)cyanate substituents. The synthesis made use of a carbonylimidazole resin, which is easily derived from Wang resin. Further diversity can also be added by performing Suzuki coupling. This methodology provides a valuable route to urazole- and thiourazole-containing libraries.

Experimental Section

Materials and General Procedures. Anhydrous THF was freshly distilled before use. Chemical reagents and other anhydrous solvents were purchased from Aldrich and Fluka. Resins were purchased from Novabiochem. The drying of resins was carried out in a desiccator connected to a vacuum line. Preparative thin-layer chromatography was performed using precoated silica gel plates (1 mm thickness) from Aldrich. All HPLC analyses were carried out on a Hewlett-Packard Hypersil ODS reverse-phase column (200 mm × 2.1 mm): gradient elution with 0.1% TFA/MeCN and 0.1% TFA/H_2O starting at 10:90 and ending at 100:0; flow rate of 0.3 mL/min over 20 min. ^1H and ^{13}C NMR spectra were recorded on a 400 MHz spectrometer at the frequencies indicated. Signals were quoted as δ values (in ppm) and described as follows: s (singlet), d (doublet), t (triplet), q (quartet), sx (sextet), sp (septet), m (multiplets). Gel-phase ^{13}C NMR spectra were obtained in 15−30 min of experimentation time (AQ = 0.1 s, zero delay). The dried resins (75−100 mg) were packed into NMR sample tubes (5 mm o.d.) and then swelled with chloroform-*d*. High-resolution mass spectra were recorded using a ESI-TOF mass spectrometer.

Preparation of (Thio)urazoles 5. To a suspension of carbonylimidazole−Wang resin **1** (0.71 mmol/g; 100 mg, 0.071 or 1.0 mmol/g; 100 mg, 0.1 mmol for entries **5b**,**e**,**f**,**i**,**l**,**m**,**p**) containing disubstituted hydrazine hydrochlorides **2** (10 equiv) and DMAP (10 equiv) in anhydrous *N*,*N*′-dimethylacetamide (DMA) (1.5 mL) was added distilled *N*,*N*′-diisopropylethylamine (10 or 20 equiv). The suspension was stirred gently at room temperature for 18 h and then filtered. Resin **3** was washed with CH_2Cl_2 (5 × 2 mL) and dried under vacuum. In the case of diisopropylhydrazine, the suspension was heated at 50 °C for 18 h. Carbazate resin **3** was suspended in anhydrous 1,2-dichloroethane (DCE) (2 mL), and iso(thio)cyanate (10 equiv) was added. The suspension was heated at 60 °C for 18 h with gentle stirring and then filtered. Resin **4** was washed successively with DMF (5 × 2 mL) and CH_2Cl_2 (5 × 2 mL) and was dried under vacuum. When 2-nitrophenyl isocyanate was used, resin **4** was washed extensively with DMSO (15 × 2 mL) and CH_2Cl_2 (5 × 2 mL). Anhydrous toluene (1 mL) and triethylamine (150 μL) were added to dried resin **4**. The suspension was stirred gently with heating at 110 °C for 18 h, cooled to room temperature, and then filtered. For the preparation of (thio)urazoles **5b**,**f**,**i**,**m**, anhydrous THF (2 mL) and potassium *t*-butoxide (0.5 mmol, 56 mg) were added, and the suspension was heated at 60 °C with stirring for 18 h, cooled to room temperature, and then filtered. The cleaved resin was washed with CH_2Cl_2 (3 × 1 mL). The filtrate and washings were combined and concentrated under reduced pressure to afford the (thio)urazoles.

1,2-Dimethyl-4-(4-methoxyphenyl)urazole (5a). ^1H NMR (400 MHz, $CDCl_3$) δ 3.25 (6H, s), 3.82 (3H, s), 6.97 (2H, dt, J = 9.0, 2.2 Hz), 7.37 (2H, dt, J = 9.0, 2.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.4, 55.5, 114.4, 124.0, 127.0, 153.8, 159.3; *m*/*z* (ESI) $C_{11}H_{14}N_3O_3$ (MH^+) calcd 236.1035, found 236.1037.

1,2-Dimethyl-4-cyclohexylurazole (5b). ^1H NMR (400 MHz, $CDCl_3$) δ 1.14−1.36 (3H, m), 1.62−1.73 (3H, m), 1.80−1.84 (2H, m), 2.10 (2H, qd, J = 12.4, 3.4 Hz), 3.16 (6H, s), 3.86 (1H, tt, J = 12.4, 3.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.9, 25.7, 29.3, 32.2, 52.0, 154.7; *m*/*z* (ESI) $C_{10}H_{18}N_3O_2$ (MH^+) calcd 212.1399, found 212.1395.

1,2-Diethyl-4-(4-methoxyphenyl)urazole (5c). ^1H NMR (400 MHz, $CDCl_3$) δ 1.22 (6H, t, J = 7.1 Hz), 3.69 (4H, q, J = 7.1 Hz), 3.82 (3H, s), 6.97 (2H, dt, J = 9.1, 2.2 Hz), 7.39 (2H, dt, J = 9.1, 2.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.5, 40.1, 55.5, 114.4, 124.1, 126.9, 153.8, 159.2; *m*/*z* (ESI) $C_{13}H_{18}N_3O_3$ (MH^+) calcd 264.1348, found 264.1341.

1,2-Diethyl-4-(2-nitrophenyl)urazole (5d). ^1H NMR (400 MHz, $CDCl_3$) δ 1.27 (6H, t, J = 7.1 Hz), 3.72 (4H, q, J = 7.1 Hz), 7.56 (1H, dd, J = 8.0, 1.4 Hz), 7.61 (1H, td, J = 8.0, 1.4 Hz), 7.76 (1H, td, J = 8.0, 1.4 Hz), 8.16 (1H, dd, J = 8.0, 1.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.6, 40.2,

124.9, 125.8, 129.9, 130.5, 134.1, 145.2, 152.6; *m/z* (ESI) $C_{12}H_{14}N_4O_4Na$ (MNa^+) calcd 301.0913, found 301.0915.

1,2-Diethyl-4-propylurazole (5e). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (3H, t, J = 7.3 Hz), 1.12 (6H, t, J = 7.1 Hz), 1.68 (2H, sx, J = 7.3 Hz), 3.50 (2H, t, J = 7.3 Hz), 3.59 (4H, q, J = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.0, 11.4, 21.2, 39.9, 41.0, 155.2; *m/z* (ESI) $C_9H_{18}N_3O_2$ (MH^+) calcd 200.1399, found 200.1395.

1,2-Diethyl-4-cyclohexylurazole (5f). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.11 (6H, t, J = 7.1 Hz), 1.16−1.37 (3H, m), 1.63−1.72 (3H, m), 1.80−1.86 (2H, m), 2.12 (2H, qd, J = 12.4, 3.3 Hz), 3.56 (4H, q, J = 7.1 Hz), 3.86 (1H, tt, J = 12.4, 3.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.3, 24.9, 25.7, 29.4, 39.9, 52.0, 154.9; *m/z* (ESI) $C_{12}H_{22}N_3O_2$ (MH^+) calcd 240.1712, found 240.1711.

1,2-Diisopropyl-4-(4-methoxyphenyl)urazole (5g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.45 (12H, d, J = 6.9 Hz), 3.82 (3H, s), 3.98 (2H, sp, J = 6.9 Hz), 6.95 (2H, dt, J = 9.0, 2.2 Hz), 7.34 (2H, dt, J = 9.0, 2.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.2, 52.5, 55.5, 114.3, 124.0, 127.1, 155.0, 159.1; *m/z* (ESI) $C_{15}H_{22}N_3O_3$ (MH^+) calcd 292.1661, found 292.1662.

1,2-Diisopropyl-4-(2-nitrophenyl)urazole (5h). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.48 (12H, d, J = 6.9 Hz), 4.01 (2H, sp, J = 6.9 Hz), 7.50 (1H, dd, J = 7.9, 1.4 Hz), 7.59 (1H, td, J = 7.9, 1.4 Hz), 7.74 (1H, td, J = 7.9, 1.4 Hz), 8.14 (1H, dd, J = 7.9, 1.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.4, 52.8, 124.8, 125.8, 129.8, 130.5, 134.0, 145.3, 153.6; *m/z* (ESI) $C_{14}H_{19}N_4O_4$ (MH^+) calcd 307.1406, found 307.1407.

1,2-Diisopropyl-4-benzylurazole (5i). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36 (12H, d, J = 6.9 Hz), 3.87 (2H, sp, J = 6.9 Hz), 4.62 (2H, s), 7.28−7.37 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.2, 42.7, 52.4, 127.8, 128.1, 128.7, 135.9, 156.0; *m/z* (ESI) $C_{15}H_{22}N_3O_2$ (MH^+) calcd 276.1712, found 276.1711.

1,2-Dimethyl-4-(2-phenylethyl)thiourazole (5l). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.04 (2H, m), 3.33 (3H, s), 3.63 (3H, s), 4.07 (2H, m), 7.22−7.33 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.6, 33.3, 33.4, 43.9, 126.7, 128.5, 129.0, 137.6, 152.7, 169.8; *m/z* (ESI) $C_{12}H_{16}N_3OS$ (MH^+) calcd 250.1014, found 250.1013.

1,2-Dimethyl-4-cyclohexylthiourazole (5m). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.13−1.42 (3H, m), 1.65−1.76 (3H, m), 1.82−1.86 (2H, m), 2.23 (2H, qd, J = 12.4, 3.4 Hz), 3.31 (3H, s), 3.62 (3H, s), 4.53 (1H, tt, J = 12.4, 4.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.9, 25.8, 28.5, 31.2, 33.7, 56.0, 152.4, 169.6; *m/z* (ESI) $C_{10}H_{18}N_3OS$ (MH^+) calcd 228.1171, found 228.1177.

1,2-Diethyl-4-(4-methoxyphenyl)thiourazole (5n). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (3H, t, J = 7.1 Hz), 1.34 (3H, t, J = 7.1 Hz), 3.84 (3H, s), 3.88 (2H, q, J = 7.1 Hz), 4.24 (2H, q, J = 7.1 Hz), 7.01 (2H, dt, J = 9.0, 2.2 Hz), 7.33 (2H, dt, J = 9.0, 2.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.6, 12.7, 40.5, 42.0, 55.5, 114.5, 125.3, 129.0, 153.0, 160.0, 171.1; *m/z* (ESI) $C_{13}H_{18}N_3O_2S$ (MH^+) calcd 280.1120, found 280.1120.

1,2-Diethyl-4-(4-nitrophenyl)thiourazole (5o). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30 (3H, t, J = 7.1 Hz), 1.35 (3H, t, J = 7.1 Hz), 3.91 (2H, q, J = 7.1 Hz), 4.26 (2H, q, J = 7.1 Hz), 7.76 (2H, dt, J = 9.1, 2.1 Hz), 8.36 (2H, dt, J = 9.1, 2.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.6, 12.8, 40.6, 42.0, 124.2, 128.6, 138.0, 147.4, 151.7, 169.3; *m/z* (ESI) $C_{12}H_{15}N_4O_3S$ (MH^+) calcd 295.0865, found 295.0861.

1,2-Diethyl-4-benzylthiourazole (5p). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.16 (3H, t, J = 7.1 Hz), 1.24 (3H, t, J = 7.1 Hz), 3.78 (2H, q, J = 7.1 Hz), 4.14 (2H, q, J = 7.1 Hz), 5.04 (2H, s), 7.26−7.34 (3H, m), 7.48 (2H, d, J = 7.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.6, 12.6, 40.3, 41.9, 45.9, 128.0, 128.5, 128.6, 135.3, 153.5, 171.0; *m/z* (ESI) $C_{13}H_{18}N_3OS$ (MH^+) calcd 264.1171, found 264.1172.

Procedure for the Preparation of Urazoles 8. To a suspension of carbazate resin **3b** (300 mg) in anhydrous DCE (4 mL) was added 4-iodophenyl isocyanate (257 mg, 1.05 mmol). The suspension was heated at 50 °C for 18 h with gentle stirring and then was filtered. Resin **6** was washed successively with DMF (5 × 5 mL) and CH_2Cl_2 (5 × 5 mL) and was dried under vacuum. To dried resin **6** (100 mg) and $Pd(PPh_3)_4$ (69 mg, 0.06 mmol) contained in a dry round-bottom flask was added anhydrous DMA (2 mL). The system was flushed profusely with argon. After the mixture was stirred for 10 min at room temperature, $R_3B(OH)_2$ (0.6 mmol) and triethylamine (42 μL, 0.3 mmol) were introduced. The mixture was subjected to further flushing with argon and then was heated at 40 °C for 18 h with gentle stirring. Following that, the suspension was cooled to room temperature and then was filtered. Resin **7** was washed successively DMF (3 × 2 mL), THF−H_2O 3:2 (3 × 2 mL), THF (3 × 2 mL), and CH_2Cl_2 (3 × 2 mL) and was dried under vacuum. Anhydrous toluene (1 mL) and triethylamine (150 μL) were added to dried resin **7**. The suspension was stirred gently with heating at 110 °C for 18 h, cooled to room temperature, and then filtered. The resin was washed with CH_2Cl_2 (3 × 1 mL). The filtrate and washings were combined and concentrated under reduced pressure to afford the urazoles **8**. The crude products were purified by preparative TLC (hexane−EtOAc 1:1).

1,2-Diethyl-4-(4-biphenyl)urazole (8a). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (6H, t, J = 7.1 Hz), 3.73 (4H, q, J = 7.1 Hz), 7.38 (1H, dt, J = 7.4, 1.3 Hz), 7.43−7.47 (2H, m), 7.58−7.62 (4H, m), 7.68 (2H, dt, J = 8.8, 2.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.6, 40.1, 125.5, 127.2, 127.6, 127.8, 128.8, 130.6, 140.3, 141.0, 153.5; *m/z* (ESI) $C_{18}H_{20}N_3O_2$ (MH^+) calcd 310.1556, found 310.1554.

1,2-Diethyl-4-[4-(4-methoxyphenyl)phenyl]urazole (8b). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (6H, t, J = 7.1 Hz), 3.72 (4H, q, J = 7.1 Hz), 3.86 (3H, s), 6.99 (2H, dt, J = 8.8, 2.1 Hz), 7.51−7.58 (4H, m), 7.63 (2H, dt, J = 8.8, 2.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.6, 40.1, 55.4, 114.3, 125.6, 127.3, 128.2, 130.1, 132.8, 140.6, 153.6, 159.4; *m/z* (ESI) $C_{19}H_{22}N_3O_3$ (MH^+) calcd 340.1661, found 340.1661.

1,2-Diethyl-4-[4-(3-nitrophenyl)phenyl]urazole (8c). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (6H, t, J = 7.1 Hz), 3.74 (4H, q, J = 7.1 Hz), 7.64 (1H, t, J = 8.4 Hz), 7.69−7.74 (4H, m), 7.92 (1H, dt, J = 8.4, 1.0 Hz), 8.23 (1H, ddd, J = 8.4, 2.1, 1.0 Hz), 8.46 (1H, t, J = 2.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.6, 40.1, 122.0, 122.4, 125.7, 127.8, 129.9, 132.0, 133.0, 138.2, 141.9, 148.8, 153.2; *m/z* (ESI) $C_{18}H_{19}N_4O_4$ (MH^+) calcd 355.1406, found 355.1407.

1,2-Diethyl-4-[4-(2-thienyl)phenyl]urazole (8d). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (6H, t, J = 7.1 Hz), 3.72 (4H, q, J = 7.1 Hz), 7.09 (1H, dd, J = 5.1, 3.6 Hz), 7.31 (1H, dd, J = 5.1, 1.1 Hz), 7.33 (1H, dd, J = 3.6, 1.1 Hz), 7.56 (2H, dt, J = 8.8, 2.1 Hz), 7.69 (2H, dt, J = 8.8, 2.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.6, 40.1, 123.7, 125.4, 125.5, 126.5, 128.1, 130.6, 134.1, 143.3, 153.3; *m*/*z* (ESI) $C_{16}H_{18}N_3O_2S$ (MH^+) calcd 316.1120, found 316.1118.

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Supporting Information Available. ^{1}H NMR spectra of the crude products **5a**,**b**,**e**,**o**,**p**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Diagnostic peaks of carbonylimidazole−Wang resin in gel-phase ^{13}C NMR spectrum (100 MHz, $CDCl_3$): δ 69.2, 116.5, 130.1, 136.5.

(11) For substitution by hydrazine without the use of DMAP, see the following. Lee, A.; Huang, L.; Ellman, J. A. General Solid-Phase Method for the Preparation of Mechanism-Based Cysteine Protease Inhibitors. *J. Am. Chem. Soc.* **1999**, *121*, 9907−9914.

(12) The displacement was confirmed by the disappearance of all the peaks of the imidazole group and the existence of peaks associated with the diisopropylhydrazine moiety at δ 20.1, 21.2, 50.0, 51.0.

(13) The resin (64 mg) was treated with TFA−CH_2CH_2 1:1 (2 mL) at room temperature for 3 h and then was filtered and washed further with CH_2Cl_2 (3 × 1 mL). The filtrate and washings were concentrated under reduced pressure to afford the TFA salt of diisopropylhydrazine. To this salt was added CH_2Cl_2 (5 mL) and concentrated HCl (2 drops). The solvent was removed. To the residue was added chloroform (5 mL), and the solution was transferred to another flask. The addition of chloroform and the transfer of solution were carried out again. The combined solutions were then concentrated under reduced pressure to give the pure diisopropylhydrazine monohydrochloride (3.5 mg), which showed ^{1}H NMR signals identical to the signals of the authentic sample available commercially (Sigma-Aldrich Rare Chemicals). The above procedure was repeated with a smaller amount of resin (33 mg) and gave the diisopropylhydrazine monohydrochloride (1.9 mg). On the basis of the initial loading of Wang resin (0.76 mmol/g) as specified by the supplier, the average loading of diisopropylhydrazine resin was calculated to be 54%.

(14) Diagnostic peaks of resin **4j** (100 MHz, $CDCl_3$): δ 55.5 (CH_3O−), 66.7, 70.1. Diagnostic peaks of resin **4k** (100 MHz, $CDCl_3$): δ 45.1 (CH_2Ph), 66.8, 70.1.

(15) After the Suzuki coupling reaction was performed, the filtrate was subjected to mass spectrometric analysis. There was no prematurely cyclized product detected, similar to that involving the use of Na_2CO_3.

(16) Mass spectrometry of the crude cyclized mixture did not detect any iodo-containing urazole, indicating that all of the iodo groups had been reacted during the Suzuki reaction.

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