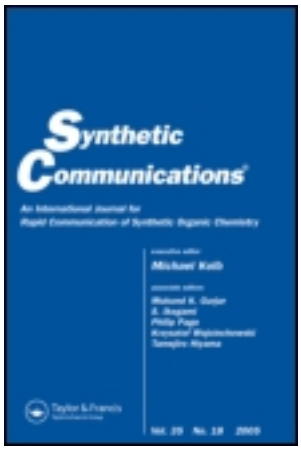

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EFFICIENT SYNTHESIS OF NOVEL 4-SUBSTITUTED URAZOLES

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EFFICIENT SYNTHESIS OF NOVEL 4-SUBSTITUTED URAZOLES

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ABSTRACT

The efficient synthesis of several new and novel 4-substituted triazolidindiones (urazoles) starting from isocyanates, amines, anilines and carboxylic acids is reported.

Recently we have reported our work in the area of synthesis of β-strand mimetic libraries using our most recent triazolopyridazine-based β-strand mimetic.[1] Our approach to the synthesis of the β-sheet mimetic template, on solid phase, is depicted in Scheme 1.

The triazolopyridazine template is synthesized by a highly efficient hetero-Diels-Alder in a key diversity-introducing step. This is a convergent synthesis that involves reaction of a resin-linked diene[2] with the hetero Diels-Alder dienophile, in this case the 1,2,4-triazoledione[3] obtained by *bis*(trifluoroacetoxy)iodobenzene ($PhI(OTFA)_2$)-mediated oxidation of the corresponding 4-substituted 1,2,4-triazolidindione (urazole).

An important component in the synthesis of these templates is the 4-substituted-urazoles. However there are only few commercially available

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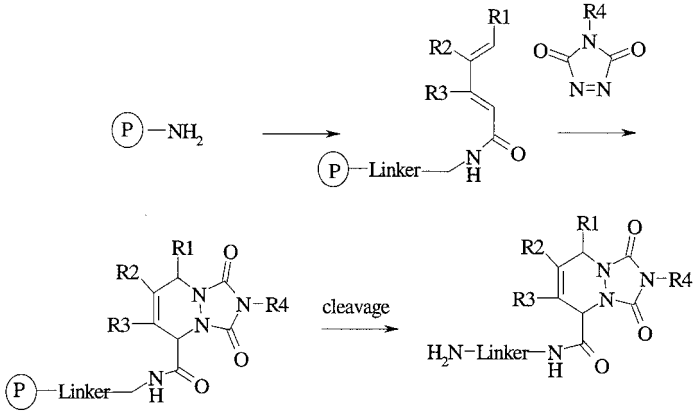


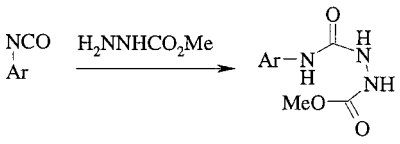
Scheme 1.

urazoles. In this communication, we disclose the efficient synthesis of a wide range of novel and synthetically useful urazoles.

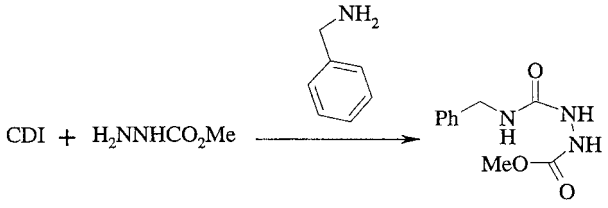
In general, substituted urazoles were prepared starting with an isocyanate, an amine or an aniline. Reaction of an isocyanate with methyl carbazate in tetrahydrofuran at room temperature overnight led to the precipitation of the intermediate substituted hydrazino carboxylate, which was usually isolated by filtration (Scheme 2). On occasions where the product did not precipitate, the product was simply obtained upon solvent evaporation. Most of the time this intermediate was pure enough to take to the next step without further manipulation.

Alternatively, if the starting material is an amine or aniline, methyl carbazate was first treated with carbonyldiimidazole followed, after 15 min, by the addition of the amine or aniline to furnish the hydrazino carboxylate (Scheme 3). If the product did not precipitate, simple flash chromatography afforded the pure intermediate.

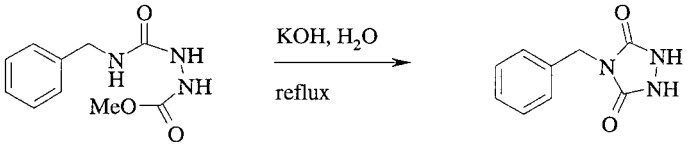
The typical method for closing the ring to prepare the urazole is to treat the substituted hydrazino carboxylate with potassium hydroxide in water at reflux (Scheme 4).[4]



Scheme 2.



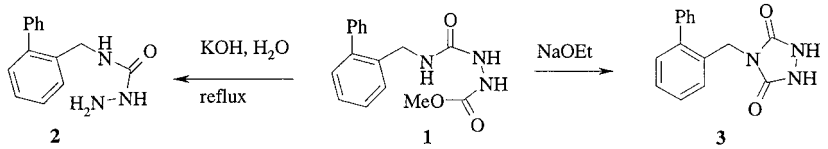
Scheme 3.



Scheme 4.

The product is then isolated by acidification of the aqueous layer with concentrated hydrochloric acid to pH~1 to precipitate the urazole and filtration. Although this method works well with most urazoles, we found that in some cases it did not lead to product formation. For example, treatment of compound **1** with KOH in water at reflux led mainly to the formation of the hydrazino derivative **2** and not to the expected product **3** (Scheme 5). It seems that under this condition decarboxylation proceeds faster than cyclization.

However, we found that cyclization can be affected by treatment of the substituted hydrazinocarboxylate with freshly made sodium ethoxide in ethanol at reflux. The desired product was then obtained following acidification with concentrated HCl as described above. A more general and milder protocol calls for the treatment of the substituted hydrazinocarboxylate with potassium carbonate in an aqueous or alcoholic solvent (MeOH or tBuOH) at reflux.[5] Although the reaction is slower under these conditions, it is cleaner and sometimes the yield is better.



2 **1** **3**

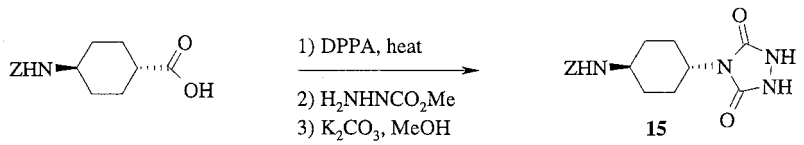
Scheme 5.

The practicality of this chemistry afforded us many of these urazoles in 100-g scale in a short period of time with no chromatographic purification involved. When working on a large scale, however, we found it more convenient not to isolate the intermediate hydrazinocarboxylate, but rather to expose the crude, after solvent evaporation, to the cyclization conditions.

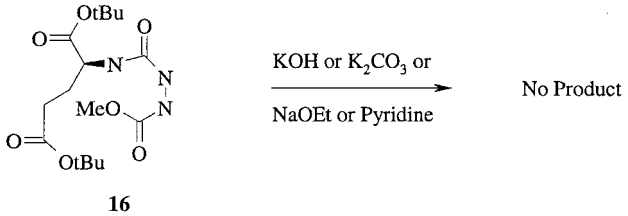
At occasions when neither amine nor isocyanate were available, a carboxylic acid derivative was employed. The carboxylate group was easily transformed into an isocyanate using the standard procedure.[6] Treatment with methyl carbazate (Scheme 6, racemic starting material), as described above, afforded the hydrazinocarboxylate and subsequently the corresponding urazole.

It is noteworthy that protected α-amino acids also undergo the cyclization to the urazoles (see Table 1).[7] However amino acids such as glutamic acid did not yield any desired product, as exemplified by hydrazinocarboxylate **16** (Scheme 7). Instead decomposition and/or recovery of starting material were the predominant outcomes.

We applied two easy and convenient methods to quickly verify the formation of the urazole. In one test (a colormetric test) we treated the urazole in dichloromethane with iodosobenzene diacetate ($PhI(OAc)_2$ or $PhI(OTFA)_2$) reagent, which oxidizes urazole to the triazolinedione. If a red or purple color is obtained, then the urazole has been formed.[8] In the second (a spectroscopic) we've recorded the HNMR in deuterated DMSO. In this solvent, the urazole ring hydrogens appear consistently at ~10 ppm and integrate to two hydrogens.



Scheme 6.



Scheme 7.

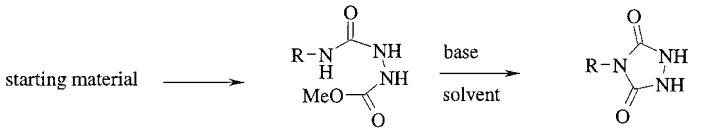


Table 1.

Entry	Starting Material	Solvent	Base	Urazole (Yield)
1	4-Nitrophenylisocyanate	H_2O	K_2CO_3	**4** (74%)
2	4-Aminomethyl pyridine	H_2O	KOH	**5** (66%)
3	2,4-Dichlorobenzylamine	H_2O	KOH	**6** (67%)
4	4-(Trifluoromethoxy)aniline	H_2O	K_2CO_3	**7** (97%)
5	1-Aminomethylnaphthalene	MeOH	K_2CO_3	**8** (64%)
6	2-Butylaniline	H_2O	KOH	**9** (94%)
7	4-*t*-Butylaniline	H_2O	KOH	**10** (100%)
8	3-Aminopropanoicacid *t*-butyl ester	*t*BuOH	K_2CO_3	**11** (55%)
9	Phenylalanine-OH	EtOH	K_2CO_3	**12** (91%)
10	*t*Bu-glutamic acid	EtOH	K_2CO_3	**13** (0%)
11	Phenyl-2-aminoethyl sulfone	MeOH	$NaOCH_3$	**14** (58%)

Inspection of the table indicates that a wide variety of urazoles could be prepared in moderate to excellent yields (55–100%). Furthermore, several of the urazoles incorporate additional functionality (see Entries 1, 8 and 9 in Table 1 and Scheme 6) that permit further derivatization on solid phase. This is a key feature to introduce diversity at that end of the molecule in our templated libraries.

In summary, by using the above-mentioned simple and convenient protocols, we have prepared many new and novel urazoles (numerous urazoles were not disclosed) on a large scale (several urazoles were prepared on 100+ g scale) and in high purity and yield. This allowed the preparation of libraries of tens of thousands of compounds based on our β-strand template.

EXPERIMENTAL SECTION

General

THF was freshly distilled. MeOH (certified ACS) and DMF (Omnisolv) were used as is. The ^{1}H and ^{13}C NMR spectra were recorded

on a Varian Unity 500 spectrometer, and the DMSO peaks at δ 2.5 ppm (^{1}H NMR) and 39.5 ppm (^{13}C NMR) served as an internal standard. The mass spectra were obtained using a Fisons VG Quattro spectrometer. Flash column chromatography was done using Merck's silica gel 60. Analytical thin layer chromatography was done on silica gel 60 F254. Melting points (m.p.) are uncorrected and were recorded using an electrothermal digital melting point apparatus model IA9100.

General Procedure for Substituted Hydrazinocarboxylates

From isocyanates (1–120 g scale): Methyl hydrazinocarboxylate (1.0 equiv.) was dissolved in anhyd. THF (approx. 1.0 ml/mmol) with stirring under an inert atmosphere. The isocyanate (1.0 equiv.) was gradually added over 1 min and the mixture stirred at room temp. overnight. The product was collected by filtration or by simple evaporation to dryness.

From amines and anilines (1–120 g scale): Methyl hydrazinocarboxylate (1.0 equiv.) was dissolved in anhyd. THF (approx. 1.0 ml/mmol) or DMF (when using HCl salts) with stirring under an inert atmosphere. Carbonyldiimidazole (1.0 equiv.) was added in portions over 2–3 min and this mixture was stirred at room temp. for 15 min. The amine or aniline (1.0 equiv.) was added followed by triethyl amine (1.0 equiv. for when HCl salts are used) and this mixture was stirred at room temp. overnight. The product was collected by filtration or by evaporation to dryness followed by column chromatography using 2–10% MeOH/CH_2Cl_2 as the mobile phase.

From carboxylic acids (1–20 g scale): The starting material was dissolved in CH_2Cl_2 with stirring. Diphenylphosphorylazide (1.0 equiv.) and triethyl amine (1.0 equiv.) were added and the mixture stirred for 2 h at room temp. Following evaporation to dryness, the mixture was refluxed in 1,2-dichloroethane for 30 min and cooled to room temp. Methyl hydrazinocarboxylate (1.0 equiv.) was added and the mixture was refluxed for an additional 30 min. After cooling to room temp., the product was collected by filtration or by evaporation to dryness followed by column chromatography.

General Procedure for 4-Substituted-1,2,4-triazolidine-3,5-diones

Method A: The substituted hydrazinocarboxylate was refluxed in aqueous 4N KOH (approx. 0.5 ml/mmol) for 2.0 h. After cooling to room temp., the mixture was stirred in ice water bath and the pH was adjusted

to approx. 1–2 with the slow addition of conc. HCl. The product was collected by filtration, washed with H_2O and dried.

Method B: The substituted hydrazino carboxylate was stirred in the appropriate solvent followed by the addition of 2.0 equiv. of K_2CO_3 or sodium ethoxide. This mixture was refluxed from 30 min to 16 h until TLC indicated the reaction was complete. The mixture was evaporated to dryness and the residue dissolved in H_2O and cooled in an ice water bath. The pH was adjusted to approx. 1–2 with the slow addition of conc. HCl. The product was collected by filtration, washed with H_2O and dried.

Method C (One pot procedure): Methyl hydrazino carboxylate (1.0 equiv.) was dissolved in THF with stirring under an inert atmosphere. CDI (1.0 equiv.) was added in portions over a 2–3 min period and this mixture was stirred at room temp. for 15 min. The amine (1.0 equiv.) was added and stirring was continued at room temp. overnight. After evaporation to dryness, the residue was either refluxed in 4N KOH or $MeOH/K_2CO_3$ until the reaction was complete. It was then worked up in the usual manner.

Note: In instances where the product has basic (ex. pyridyl) or acid sensitive (ex. Boc) functionalities the pH was adjusted to 6.5–7.0. In certain cases when the reaction mixture was acidified the product oiled out of solution. The reaction mixture was then extracted with 3 volumes of ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4 and evaporated to dryness. CH_2Cl_2 was added and the product was collected by filtration and dried. In cases where the product is not of sufficient purity, recrystallization from a minimal amount of hot ethyl acetate or stirring in CH_2Cl_2 with filtration can be used.

4-[2-(Phenyl)benzyl]-1,2,4-triazolidine-3,5-dione (3): (>97% pure) m.p. = 185–187; ^{1}H NMR (DMSO-d_6) δ 4.49 (s 2H), 7.08 (dd, 1H), 7.21 (dd, 1H), 7.3–7.5 (m, 7H), 10.22 (s, 2H); ^{13}C NMR (DMSO-d_6) δ 39.2, 125.9, 127.2, 127.3, 127.7, 128.4, 129.2, 130.0, 133.7, 139.9, 140.5, 154.8; IR (cm^{-1}) 3060, 1771, 1678, 1475.

4-(4-Nitrophenyl)-1,2,4-triazolidine-3,5-dione (4): (>93% pure) m.p. = 265–267; ^{1}H NMR (DMSO-d_6) δ 7.87 (d, 2H), 8.32 (d, 2H), 10.78 (s, 2H); ^{13}C NMR (DMSO-d_6) δ 124.1, 125.4, 138.0, 145.4, 152.1; IR (cm^{-1}) 3184, 1782, 1685, 1343.

4-(4-Pyridinylmethyl)-1,2,4-triazolidine-3,5-dione (5): (>98% pure) m.p. = 268–270 (dec); ^{1}H NMR (DMSO-d_6) δ 4.57 (s, 2H), 7.21 (d, 2H), 8.51 (d, 2H), 10.34 (s, 2H); ^{13}C NMR (DMSO-d_6) δ 40.4, 122.1, 145.4, 149.8, 154.4; IR (cm^{-1}) 2783, 1766, 1708, 1211

4-(2,4-Dichlorobenzyl)-1,2,4-triazolidine-3,5-dione (6): (>95% pure) m.p. = 227–229; ^{1}H NMR (DMSO-d_6) δ 4.59 (s, 2H), 7.17 (d, 1H), 7.42 (dd, 1H), 7.64 (d, 1H), 10.34 (s, 2H); ^{13}C NMR (DMSO-d_6)

δ 38.8, 127.5, 128.8, 129.9, 132.7, 132.9, 154.3; IR (cm^{-1}) 3048, 1766, 1680, 1467.

4-[4-(Trifluoromethoxy)phenyl]-1,2,4-triazolidine-3,5-dione (7): (>98% pure) m.p. = 224–226; ^{1}H NMR δ (DMSO-d_6) δ 7.47 (d, 2H), 7.60 (d, 2H), 10.58 (s, 2H); ^{13}C NMR (DMSO-d_6) δ (117.0, 119.0, 121.1, 123.1, quartet CF_3), 121.5, 127.7, 131.0, 147.0, 153.0; IR (cm^{-1}) 3106, 1692, 1510, 1432.

4-(1-Naphthylmethyl)-1,2,4-triazolidine-3,5-dione (8): (>98% pure) m.p. = 201–204; ^{1}H NMR (DMSO-d_6) δ 5.00 (s, 2H), 7.32 (d, 1H), 7.46 (m, 1H), 7.52–7.58 (m, 2H), 7.87 (d, 1H), 7.94 (d, 1H), 8.27 (d, 1H), 10.27 (s, 2H); ^{13}C NMR (DMSO-d_6) δ 39.6, 123.3, 125.3, 125.7, 126.0, 126.5, 128.0, 128.6, 130.5, 131.6, 133.3, 154.8; IR (cm^{-1}) 3052, 1665, 1487, 1109.

4-(2-Butylphenyl)-1,2,4-triazolidine-3,5-dione (9): (>98% pure) m.p. = 173–175; ^{1}H NMR (DMSO-d_6) δ 0.83 (t, 3H), 1.20–1.45 (m, 2H), 1.40–1.45 (m, 2H), 2.43 (t, 2H), 7.19 (dd, 1H), 7.27–7.31 (m, 1H), 7.27–7.29 (m, 2H), 10.4 (s, 2H); ^{13}C NMR (DMSO-d_6) δ 13.7, 22.0, 30.5, 31.8, 126.7, 129.2, 129.5, 129.9, 130.1, 140.9, 153.9; IR (cm^{-1}) 3040, 1747, 1677, 1463.

4-(4-*tert*-Butylphenyl)-1,2,4-triazolidine-3,5-dione (10): (>98% pure) m.p. = 282–284; ^{1}H NMR (DMSO-d_6) δ 1.29 (s, 9H), 7.32 (d, 2H), 7.47 (d, 2H), 10.40 (s, 2H); ^{13}C NMR (DMSO-d_6) δ 31.1, 34.5, 125.6, 125.7, 129.3, 150.1, 153.5; IR (cm^{-1}) 3075, 1774, 1685, 1363.

***tert*-Butyl 3-(3,5-dioxo-1,2,4-triazolidin-4-yl)propanoate (11):** (>98% pure) m.p. = 178–179; ^{1}H NMR (DMSO-d_6) δ 1.36 (s, 9H), 2.48 (t, 2H), 3.54 (t, 2H), 10.06 (s, 2H); ^{13}C NMR (DMSO-d_6) δ 27.6, 33.2, 34.4, 80.2, 154.6, 169.6; IR (cm^{-1}) 3125, 1770, 1692, 1475.

(2S)-2-(3,5-Dioxo-1,2,4-triazolidin-4-yl)-3-phenylpropanoic acid (12): (>98% pure) m.p. = 227–229; ^{1}H NMR (DMSO-d_6) δ 3.22–3.38 (m, 2H overlapping H_2O), 4.74 (dd, 1H), 7.16–7.29 (m, 5H), 10.04 (s, 2H); ^{13}C NMR (DMSO-d_6) δ 33.1, 53.1, 126.6, 128.3, 128.8, 137.3, 154.4, 170.2; IR (cm^{-1}) 3192, 1724, 1677, 1471.

4-[2-(Phenylsulfonyl)ethyl]-1,2,4-triazolidine-3,5-dione (14): (>98% pure) m.p. = 183–186; ^{1}H NMR (DMSO-d_6) δ 3.63–3.68 (m, 4H), 7.66–7.93 (m, 5H), 10.2 (s, 2H); ^{13}C NMR (DMSO-d_6) δ 32.6, 51.2, 127.8, 129.5, 134.1, 138.3, 154.0; IR (cm^{-1}) 3048, 1719, 1677, 1486.

Benzyl-*trans*-4-(3,5-dioxo-1,2,4-triazolidin-4-yl)cyclohexyl carbamate (15): (>90% pure contains <10% of the cis isomer; this ratio of t:c reflects the ratio of the isomers in the commercial precursors) ^{1}H NMR (DMSO-d_6) δ 1.35–1.38 (m, 2H), 1.44–1.51 (m, 2H), 1.87–1.89 (m, 2H), 2.27–2.34 (m, 2H), 3.55 (s, 1H), 3.64–3.70 (s, 1H), 5.00 (s, 2H), 7.24–7.37 (m, 6H), 9.92 (s, 2H); ^{13}C NMR (DMSO-d_6) δ 23.7, 28.9, 44.8, 50.0, 65.2, 127.7, 127.9, 128.3, 137.2, 154.8, 155.7; IR (cm^{-1}) 3176, 1763, 1681, 1456.

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7. Various β-amino acids also undergo this cyclization with minor variation on the synthetic protocol (Mark Blaskovich and Jean-Laurent Paparin manuscript in preparation)
8. The formation of the triazoledione can also be quantified by UV/VIS spectroscopy measurement.

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