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Urazole synthesis. Part 2: facilitating N^4 substitution

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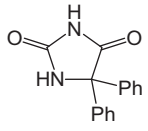
ABSTRACT

The di-*tert*-butyl-di-*p*-nitrophenyl ester of hydrazinetetracarboxylic acid was prepared and shown to be useful in the preparation of urazoles (i.e., 1,2,4-triazolidine-3,5-diones), by reaction with a primary amine using either *n*-BuLi or pyridine as base, depending on the desired N^4 substituent. With more electronegative N^4 substituents, pyridine is the preferred base. This work complements our reported urazole synthesis, which introduced the N^4 substituent early in the sequence and thus did not facilitate variation at N^4 for library synthesis.

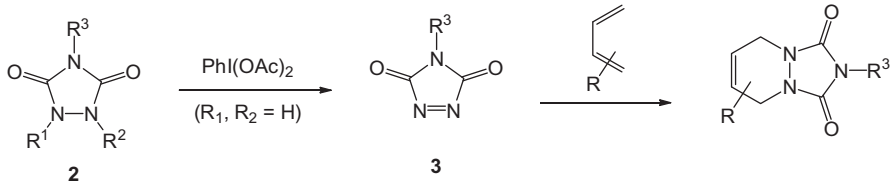
Since the synthesis of phenytoin (**1,** Fig. 1) in 1908,[1] and the subsequent recognition of its anticonvulsant properties in 1939,[2] hydantoins have served as useful scaffolds for drug discovery.[3,4] This heterocycle provides a rigid framework to which pharmacophoric groups can be attached.[5] By contrast, the five membered heterocycle with one of the hydantoin carbons replaced by nitrogen (i.e., the urazole, or 1,2,4-triazolidine-3,5-dione (**2**)) has remained under-utilized in medicinal chemistry.[6] Synthetically, urazoles (especially N^4-phenylurazole) are best known for their ability to be oxidized to the corresponding 1,2,4-triazoline-3,5-diones, which serve as super-dienophiles as shown in Scheme 1.



1

Figure 1. Phenytoin.

Contributing to their underuse has been the scarcity of methodology for the rapid preparation of diverse urazoles. The most commonly employed synthetic route to such compounds is shown in Scheme 2,[7] and involves sequential introduction of the nitrogen atoms, with relatively little capability to vary substituents as required for the preparation of a urazole library. Also, the necessity of employing strong base at the end of the sequence does not



2 3

Scheme 1. Use of urazoles (**2**) in synthesis of 1,2,4-triazoline-3,5(4*H*)-diones (**3**) and reaction with dienes.

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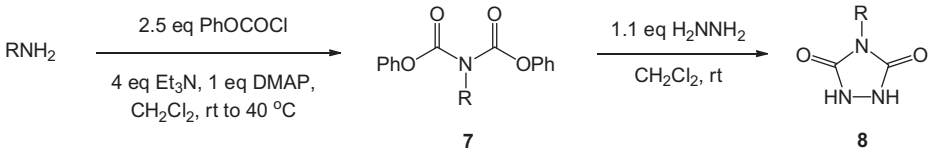
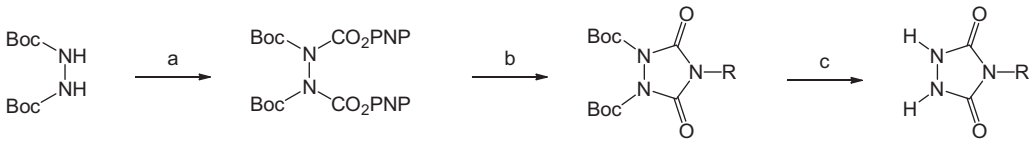
Scheme 2. Classic synthetic route to urazoles.

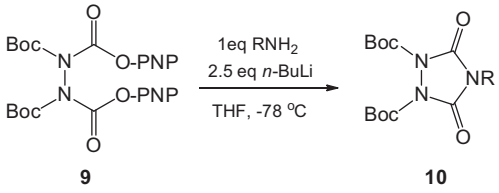


Scheme 3. Recently reported urazole synthesis.



Scheme 4. Reagents and conditions: (a) 2.2 equiv p-$NO_2C_6H_4OCOCl$, 3.0 equiv Et_3N, CH_2Cl_2 reflux overnight, yield, 92%; (b) 1 equiv RNH_2, 2.5 equiv n-BuLi, THF −78 °C, or 1 equiv RNH_2, pyridine 70–90 °C; (c) excess TFA, anhyd CH_2Cl_2, rt.

Table 1
Synthesis of N^1,N^2-di-Boc protected Urazoles Using n-BuLi[10]



Entry	Compound #	R	Yield (%)
1	**10a**	$PhCH_2$	42
2	**10b**	$PhCH_2CH_2$	28
3	**10c**	p-$MeOC_6H_4CH_2$	27
4	**10d**	Allyl	21
5	**10e**	AllylOCO	29
6	**10f**	t-Butyl	31
7	**10g**	p-$MeOC_6H_4$	11

permit the preparation of hydrolytically labile urazoles, including N^4-alkoxyurazoles and urazoles where one or more of the nitrogen atoms are protected by a carbamate (e.g., Boc) group.

We recently reported the new synthetic methodology shown in Scheme 3, which allows the preparation of some potentially hydrolytically labile urazoles, including the N^4-alkoxyurazoles (R = OR′).[8] Although this methodology avoids strong base, and permits the synthesis of numerous substituted urazoles, it suffers from the limitation that the N^4 substituent is introduced early in the sequence, thereby again posing some constrains on the facile generation of urazole libraries. Thus we desired to devise methodology which would enable expeditious modification at N^4).

After exploring numerous strategies, we were able to successfully prepare the di-*tert*-butyl-di-*p*-nitrophenyl ester of hydrazinetetracarboxylic acid (**9**) from commercially available di-*tert*-butyl hydrazodicarboxylate as shown in Scheme 4. This previously unknown compound is a crystalline solid and is readily purified by precipitation from the product mixture using diethyl ether.[9] Subsequent reaction of this intermediate with primary amines, either at −78 °C, employing n-BuLi as base, or alternatively at 75 °C in pyridine as solvent, produced N^1,N^2 protected urazoles (**10**) in acceptable yields as shown in Table 1. An X-ray structure of one of these N^1,N^2-diBoc protected urazoles (**10a**) is shown in Figure 2. The pyridine procedure seemed superior for the preparation of urazoles containing potentially anion-stabilizing substituents (e.g., aryl, alkoxy, etc.) at N^4. As shown in Table 2, the N^1, N^2 Boc groups can be removed with excess TFA in dry CH_2Cl_2. In most cases, these intermediate highly electron deficient N^1,N^2-di-Boc protected urazoles were unstable toward column chromatography and/or to washing with aqueous Na_2CO_3 (to remove p-nitrophenol) and thus, as shown in Table 3, without purification, they could directly be converted into the stable parent urazoles (**11**) by subsequent removal of the Boc protecting groups in good overall yield. The N^1,N^2 unsubstituted urazoles (**11**) are usually insoluble in CH_2Cl_2, but can be purified by column chromatography using CH_2Cl_2/MeOH mixtures or by direct precipitation from the reaction medium.

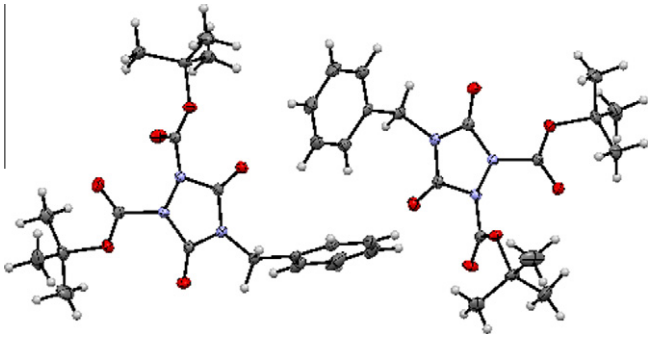
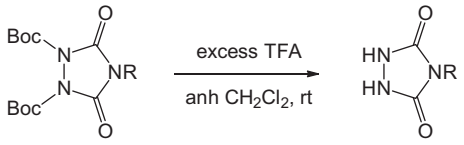


Figure 2. X-ray structure of **10a**.

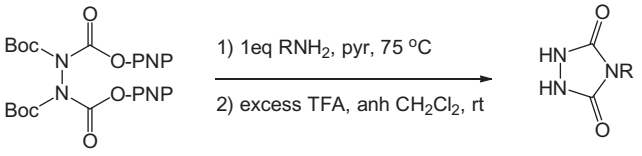
Table 2
Removal of Boc protecting groups[11]



10 **11**

Entry	Compound #	R	Yield (%)
1	**11a**	$PhCH_2$	71
2	**11b**	$PhCH_2CH_2$	80
3	**11c**	*p*-$MeOC_6H_4CH_2$	98
4	**11d**	Allyl	99
5	**11g**	*p*-$MeOC_6H_4$	93

Table 3
Synthesis of urazoles in pyridine as solvent[12]



9 **11**

Entry	Compound #	R	Yield (%)
1	**11f**	*t*-Butyl	21
2	**11g**	*p*-$MeOC_6H_4$	71
3	**11h**	$PhCH_2O$	50

Conclusions

We have devised a second new route to the urazole scaffold. This methodology complements our earlier reported urazole synthesis in that it introduces the N^4 substituent late in the sequence and thus facilitates variation at this position. The readily available crystalline intermediate **9** is useful in urazole preparation, and may be of value in the preparation of other heterocycles. Two variations of this procedure employ either *n*-BuLi or pyridine as base, with pyridine being preferred for more electronegative N^4 substituents.

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9. *Procedure for synthesis of the di-tert-butyl-di-p-nitrophenyl ester of hydrazinetetracarboxylic acid (***9***)*: To a chilled (0 °C) solution of di-*tert*-butyl hydrazodicarboxylate (2.0 g, 8.61 mmol) in dry dichloromethane (30 mL), triethylamine (2.61 g, 3.6 mL, 25.8 mmol) and *p*-nitrophenyl chloroformate (3.82 g, 18.9 mmol) were added. The reaction was stirred for 30 min at 0 °C and then was heated to reflux overnight. The resultant reaction mixture was cooled to room temperature and washed with water and then with brine. The organic layer was dried over Na_2SO_4 and the solvent evaporated in vacuo. The resultant solid was then slurried with excess diethyl ether (approx. 40 mL) and allowed to stir for 30 min. Then the precipitated white solid was filtered, washed with additional diethyl ether, and further dried under vacuum to produce 4.45 g (92%) of **9**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.32 (d, 4H, J = 9 Hz), 7.39 (d, 4H, J = 9 Hz), 1.59 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.61, 141.79, 141.20, 138.84, 118.43, 115.10, 79.61, 20.81; IR (thin film, cm^{-1}): 1820, 1781, 1593, 1528, 1490, 1371, 1348, 1281, 1198, 1146, 1110 (mp = 165.5–166.3 °C).
10. *General procedure for synthesis of Boc protected urazoles* (1). To a cold (−78 °C) solution of the di-*tert*-butyl-di-*p*-nitrophenyl ester of hydrazinetetracarboxylic acid (1.0 g, 1.78 mmol) in THF (15 mL), was added benzylamine (0.19 g, 195 μL, 1.78 mmol) and then *n*-BuLi (2.2 M solution in hexanes, 2.18 mL, 4.79 mmol). The reaction was kept at −78 °C for one hour, then quenched with acetic acid (approx. 1 mL, 16.6 mmol). The resultant reaction mixture was evaporated in vacuo and purified by flash chromatography (silica gel, CH_2Cl_2). **10c**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 (d, 2H, J = 8 Hz), 7.04 (d, 2H, J = 8 Hz), 4.81 (s, 2H), 4.02 (s, 4H), 1.72 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.63, 140.46, 139.17, 123.64, 119.32, 107.01, 79.49, 48.15, 36.22, 20.66; IR (thin film, cm^{-1}): 1762, 1513, 1253, 1149. (mp = 120.8–121.1 °C).
11. *General procedure for removing the Boc protecting groups:* To a solution of 4-methoxybenzyl-1,2-di-Boc protected urazole (0.5 g, 1.19 mmol) in anhyd CH_2Cl_2 (15 mL), TFA (1 mL, 13.1 mmol) was added. The reaction mixture was stirred for three hours at room temperature. The solvents were removed in vacuo and the residue was stirred with an ether/hexane (1:1, 5 mL) mixture for 20 min. The precipitated urazole was isolated by filtration. Alternatively, the concentrated crude reaction mixture could be purified by flash chromatography (silica gel, CH_2Cl_2/methanol). **11c**: ^{1}H NMR (400 MHz, 2% CD_3OD in $CDCl_3$): δ 7.35 (d, 2H, J = 8); 6,79 (d, 2H, J = 8); 4.59 (s, 2H); 3.71 (s, 3H); ^{13}C NMR (100 MHz, 2% CD_3OD in $CDCl_3$): δ 159.15, 155.26, 129.76, 127.82, 113.83, 55.08, 41.80; IR (thin film, cm^{-1}): 1683, 1467, 1251, 1176, 1130, 1033.
12. *General procedure for direct synthesis of* N^1,N^2 *unsubstituted urazoles using pyridine as solvent:* To a solution of di-*tert*-butyl-di-*p*-nitrophenyl ester of hydrazinetetracarboxylic acid (**9**) (1.0 g, 1.78 mmol) in dry pyridine (15 mL), *p*-anisidine (0.219 g, 1.78 mmol) was added. The reaction was heated at 75 °C for one hour. The resultant reaction mixture was evaporated in vacuo to remove pyridine. The resultant product was dissolved in anh CH_2Cl_2 (15 mL) and treated with TFA (1 mL, 13.1 mmol) and stirred for 3 h at room temp and the product isolated as above. **11g**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 (m, 2H), 7.04 (m, 2H), 3.87 (t, 3H, J = 2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.96, 158.04, 131.01, 127.23, 118.02, 59.01; IR (thin film, cm^{-1}): 1683, 1515, 1455, 1302, 1251, 1201, 1137, 1037.