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Solid-phase synthesis of 1,2,4-triazolidine-3,5-diones

Kyung-Ho Park* and Linda J. Cox

DuPont Central Research and Development, Chemical Science and Engineering, Experimental Station, PO Box 80328, Wilmington, DE 19880-0328, USA

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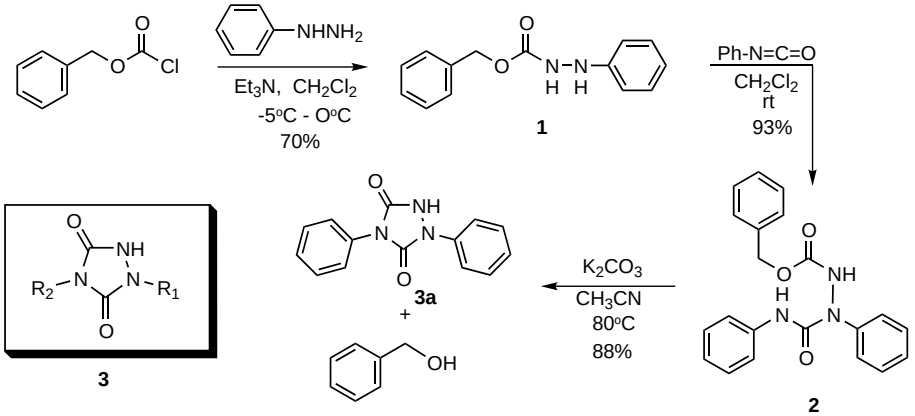
Abstract—A traceless synthesis of 1,2,4-triazolidine-3,5-diones has been achieved through *cyclo*-elimination from solid-phase. This traceless *cyclo*-elimination release step is induced by catalytic amount of base or by simply refluxing the urea carbamate intermediate.

Recently urazole and substituted urazoles (1,2,4-triazolidine-3,5-diones) have become an important structural motif both in biological systems[1] and in polymeric materials.[2] They also have been shown to exhibit some anticonvulsant[3a] or fungicidal activities[3b] as well as catalytic activity in radical polymerization.[3c] Although much attention has been directed towards solid-phase method development for the synthesis of numerous heterocycles for use in biological discovery efforts,[4] it is surprising that there are no reports of solid-phase routes to urazoles. As part of our efforts towards the preparation and biological evaluation of urazole derivatives, we disclose here an efficient route for the preparation of urazole derivatives and its synthetic strategy applicable to solid-phase combinatorial approaches.

For our solid-phase approach to the traceless 1,2,4-triazolidine-3,5-diones **3**, *cyclo*-elimination release strategies were applied.[5] Thus, a carbamate linker[6] system was introduced to release the intact target in the final step of the reaction sequence. Our preliminary solution-phase reaction to the target proved the validity of this linker system (Scheme 1). The reaction of benzyl chloroformate with phenylhydrazine in the presence of Et_3N afforded benzyl 3-phenylcarbazate **1**, which upon treatment with phenylisocyanate gave urea intermediate **2**. In the presence of base such as K_2CO_3 or Et_3N, cyclized diphenyl urazole **3a** was obtained from **2** in good yield.

Our solid-phase approach to 1,2,4-triazolidine-3,5-diones began with the coupling of hydroxymethyl polystyrene or Wang resin with *p*-nitrophenyl chloroformate to afford *p*-nitrophenyl carbonate resin **4** (Scheme 2).[7] Subsequent reaction of the carbonate resin **4** with hydrazine derivatives afforded polymer bound



Scheme 1.

* Corresponding author. Tel.: (302)-695-1784; e-mail: kyung-ho.park@usa.dupont.com

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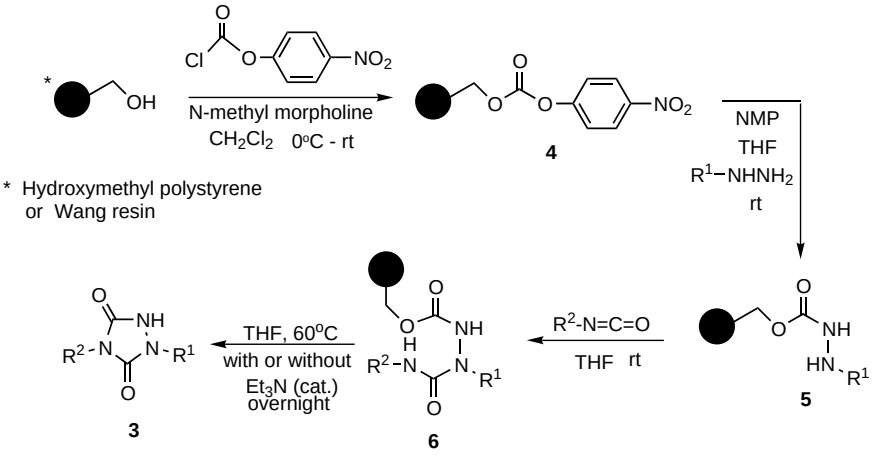

Scheme 2.

carbazate **5**. Treatment of **5** with isocyanate gave urea bound resin intermediate **6**, and subsequent *cyclo*-elimination reaction of **6** in the presence or absence of base (Et_3N) delivered 1,2,4-triazolidine-3,5-diones **3** (Table 1).

The reactivity difference of the *cyclo*-elimination step between Merrifield and Wang resin is noteworthy.[8] Thus, Merrifield-based resin **6** (R^1, R^2 = Ph) released urazole **3a** (35% overall yield) even without base; on the other hand Wang-based carbamate linker **6** needed a base (2 days of reflux) to afford **3a** (26% overall yield). Previously reported cyclization/cleavage steps of heterocycles from carbamate linkers require an excess of base (10–14 equiv.).[9] However, in the presence of base the released urazole derivatives (pK_a = 4.3–5.3)[10] are present as a salt, which necessitates an acid work-up to get the final product. Therefore, it is advantageous to employ hydroxymethyl polystyrene in the preparation of urazoles in the solid-phase reaction.

In summary, we have established a viable route for the synthesis of traceless 1,2,4-triazolidine-3,5-diones via solid-phase organic chemistry. Production of a large library of these heterocycles via parallel solid-phase synthesis and evaluation of biological activities is currently under investigation.

Table 1. 1,2,4-Triazolidine-3,5-diones (**3**) from solid-phase

Compound	R^1	R^2	% Yield[a,b] (purity)[c]
3a	C_6H_5-	C_6H_5-	35 (>95%)
3b	C_6H_5-	*p*-Cl-C_6H_4-	44 (>95%)
3c	C_6H_5-	*p*-F-C_6H_4-	37 (>95%)
3d	C_6H_5-	*m*-Cl-C_6H_4-	19 (45%)
3e	C_6H_5-	*o*-Tolyl-	20 (71%)
3f	C_6H_5-	Benzyl-	18 (>95%)
3g	CH_3-	*p*-Cl-C_6H_4-	25 (>95%)
3h	CH_3-	*p*-F-C_6H_4-	27 (>95%)

[a] Overall yield from hydroxymethyl polystyrene.
[b] Purified from column chromatography.
[c] By LC MS at 254 nm after simply removing urea impurity by short silica column.

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7. Typical procedure (Table 1, **3b**): *p*-Nitrophenyl chloroformate (0.338 g, 1.68 mmol) was added to a stirring solution of hydroxymethyl polystyrene (0.3 g, 0.84 mmol, 2.8 mmol/g) and *N*-methyl morpholine (0.17 g, 1.68 mmol) at 0°C. The reaction mixture was warmed to rt, and stirred for 2 days. The resin was filtered, washed with DCM, and dried under a vacuum to afford the resin **4** (FTIR (KBr): 1770 cm^{-1}). The resultant resin was treated with phenylhydrazine (0.45 g, 4.2 mmol) and *N*-methyl morpholine (1 mL) in NMP (*N*-methylpyrrolidinone)/THF (10 mL/10 mL) solvent. After stirring the reaction mixture for 30 h at rt under nitrogen, the resin was filtered, washed (DMF, THF), and dried under a vacuum to give the resin **5** (R^1 = Ph, FTIR (KBr): 1733 cm^{-1}).

Resin **5** (R^1 = Ph) was treated with *p*-chlorophenylisocyanate (0.258 g, 1.68 mmol) at rt overnight, filtered, washed (DMF, THF), and dried to deliver resin **6** (R^1 = Ph, R^2 = *p*-Cl-C_6H_4-, FTIR (KBr): 1746, 1715 cm^{-1}). Resin **6** (R^1 = Ph, R^2 = *p*-Cl-C_6H_4-) was stirred by reflux in the presence of Et_3N (8 mg, 0.084 mmol) in THF overnight. Filtration of the resin, concentration of the filtrate under reduced pressure, and short silica column afforded urazole **3b** (107 mg) as a white solid. Yield (overall): 44%, mp: 245°C, FTIR (KBr): 1766, 1704 cm^{-1}, ^1H NMR (300 MHz, DMF-d_7): δ 7.94–7.90 (m, 4H), 7.83–7.81 (m, 2H), 7.71–7.68 (m, 2H), 7.36 (t, 1H, J = 6.4 Hz). ^{13}C NMR (300 MHz, DMF-d_7): δ 153.1, 150.2, 137.7, 133.5, 131.7, 129.7, 129.6, 128.7, 125.6, 119.1. Anal. calcd for $C_{14}H_{10}ClN_3O_2$: C, 58.45; H, 3.50; Cl, 12.32; N, 14.61. Found: C, 58.49; H, 3.22; Cl, 12.32; N, 14.48%.

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