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# The universal Rink-isonitrile resin: applications in Ugi reactions†

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**Abstract**—The Rink-isonitrile resin provides a new universal platform for Ugi multi-component reactions. Applications were demonstrated by the traceless synthesis of diketopiperazines, benzodiazepines, and 5-substituted 1*H*-tetrazoles. © 2002 Published by Elsevier Science Ltd.

Recently we introduced the Universal Rink–isonitrile resin **1** (Fig. 1),[1] an odorless and stable polymer-bound isonitrile that can be easily prepared in two steps from commercial Rink resin. We have demonstrated, with the synthesis of 2-acylamino imidazopyridines, that the resin can serve as a universal platform for isonitrile-based non-classical multiple component reactions (MCR).[1] Our recent studies suggested that this platform is also amenable to classical MCRs such as Ugi and Passerini reactions.[2] Intriguingly, if nucleophilic elements were carefully positioned in the reagent inputs, **1** could behave as those universal isonitriles such as Armstrong's 1-isocyanocyclohexene.[3,4] The acid-labile Rink linkage is, therefore, the pivotal point for post-MCR modifications, which lead to heterocyclic structures not readily accessible via commercial isonitriles.

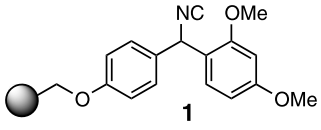
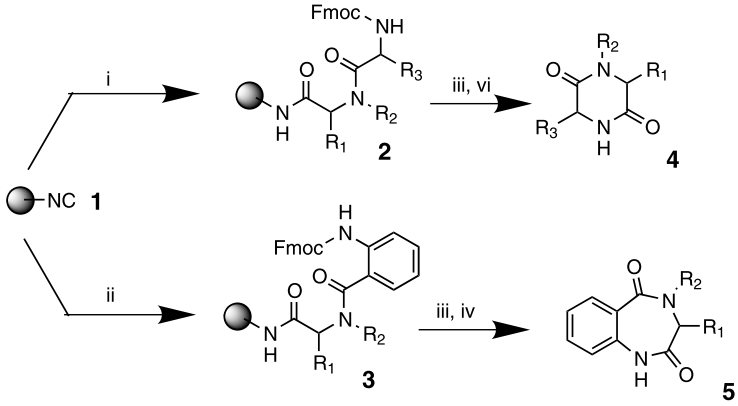



**Figure 1.** Universal Rink-isonitrile resin.

The application was examined by the solid-phase synthesis of diketopiperazines and benzodiazepine-2,5-diones (Scheme 1 and Table 1).[5] The MCR of resin **1**, aldehyde, amine and Fmoc-protected amino acid or 2-aminobenzoic acid (2-Abz) provided resin-bound dipeptide intermediate **2** or **3**. Treatment with 20% piperidine/*N*,*N*-dimethyl formamide (DMF) exposed the amino terminus for ring closure. Three approaches (the first three entries in Table 1) were found to effect




**Scheme 1.** (i) Fmoc-protected amino acid, $R_1CHO$, $R_2$-$NH_2$, MeOH/THF (1/1), 16 h; (ii) *N*-Fmoc-2-Abz-OH, $R_1CHO$, $R_2$-$NH_2$; MeOH/THF (1/1), 16 h; (iii) 20% piperidine/DMF; (iv) 10% HOAc/DCE, 60°C, 16 h.

*Keywords*: solid-phase synthesis; isonitrile resin; multi-component reactions; 5-substituted 1*H*-tetrazoles.

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† Dedicated to the memory of Professor Henry Rapoport.

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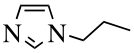
**Table 1.** Diketopiperazines and benzodiazepines prepared on the Rink-isonitrile resin

| Product | $R_1$ | $R_2$ | $R_3$ (amino acid) | Purity (%)[a] | Yield (%)[b] |
|---|---|---|---|---|---|
| **4a**[c] | *t*-Bu | 3-MeO-Bn | Gly | 50 | – |
| **4a**[d] | *t*-Bu | 3-MeO-Bn | Gly | 40 | – |
| **4a** | *t*-Bu | 3-MeO-Bn | Gly | 86 | 33 |
| **4b** | *i*-Bu | Bn | Gly | 94 | 78 |
| **4c**[e] | *i*-Bu | Bn | Aib | 100 | 48 |
| **4d**[e] | *i*-Bu | Bn | Pro | 88 | 23[f] |
| **5a** | $PhCH_2CH_2$ | 4-MeO-Bn | – | 81 | 64 |
| **5b** | *i*-Bu | 4-MeO-Bn | – | 100 | 91 |
| **5c** | $PhCH_2CH_2$ | *i*-Bu | – | 74 | 64 |
| **5d** | $PhCH_2CH_2$ | Bn | – | 88 | 42 |
| **5e** | $PhCH_2CH_2$ |  | – | 87 | 29 |
| **5f** | $PhCH_2CH_2$ | 3-MeO-Bn | – | 66 | 38 |

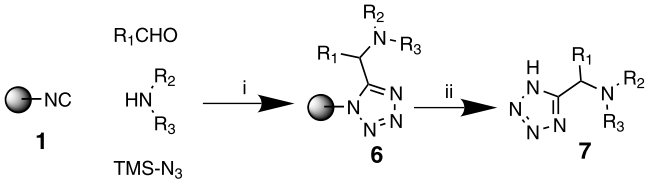
[a] Purity of the crude products after cleavage, judged by LC–MS at 220 nm. Products were cleaved by overnight heating in 10% AcOH/DCE at 50°C unless otherwise specified.
[b] Overall yields from Rink-isonitrile resin. Formed as racemic mixtures.
[c] Prepared using Boc-Gly-OH. Cyclized with 10% AcCl/MeOH at 50°C.
[d] 15% TFA cleavage followed by heating the product with 10% AcOH/*i*PrOH.
[e] See Ref. 6 for the structures of **4c** and **4d**.
[f] Formed as a 1:1 diastereomeric mixture.

the cyclization: (1) 10% acetyl chloride (AcCl)/MeOH at 50°C; (2) 15% TFA cleavage followed by heating the product with 10% acetic acid/isopropanol (AcOH/*i*-PrOH); (3) heating in 10% AcOH/dichloroethane (DCE) at 50°C overnight. Our experiments suggested that the AcCl/MeOH and TFA-AcOH/*i*PrOH methods generated significant amount of linear dipeptides, while heating in 10% AcOH/DCE provided clean *cyclo*-eliminated products with good to moderate purities and overall yields. We did not observe uncyclized products with this method.

After the successes with diketopiperazines and benzodiazepines, we further extended the applications to Ugi tetrazole synthesis.[7,8] As depicted in Scheme 2, the reaction of resin **1**, aldehyde, amine and trimethylsilyl azide furnished resin-bound product **6**, which then yielded tetrazole **7** after traceless TFA cleavage. Unlike the original Ugi chemistry that generates 2,5-disubstituted products,[7] the preparation on resin **1** provided 5-substituted 1*H*-tetrazoles.[9] To our knowledge, this is the first time this class of compounds was synthesized using an MCR approach. Some results of this study are summarized in Table 2.

In summary, we have demonstrated that Rink-isonitrile resin can be employed as a universal platform for classical Ugi reactions. As a novel addition to the collection of universal isonitriles, this resin appears to be a more practical alternative since it is stable, easy to prepare, and odor free. We are continuously exploiting its synthetic potentials and will report the results in due course.

**Preparation of diketopiperazine (**Table 1, **4a)**: Trimethylacetaldehyde (0.1 ml, 0.88 mmol), 3-methoxybenzyl amine (0.11 ml, 0.88 mmol) and Fmoc-Gly-OH (0.26 g, 0.88 mmol) were mixed in THF/MeOH (1/1) for 5 h. The mixture was then added to the resin **1** (0.5g, 0.35 mmol). The suspension was agitated overnight at room temperature. The resin was washed with MeOH and DMF. The resin was treated with 20% piperidine/DMF (2×15 min), and then washed with DMF, MeOH and DCE. 10% HOAc/DCE was added to the resin and the suspension was agitated at 60°C for 16 h. The cleavage filtrate was collected and the resin was extracted with MeOH/THF. All extracts were combined and evaporated to dryness. The crude product was further purified by HPLC to yield 33 mg of the product (33% after three steps from Rink isonitrile resin).[10]




**Scheme 2.** (i) THF/MeOH (1/1), 16 h; (ii) 15% TFA/DCM, 30 min.

**Table 2.** Tetrazoles prepared on the Rink-isonitrile resin

| Entry | $R_1$ | $R_2R_3NH$ | % Purity[a] | Yield %[b] |
|---|---|---|---|---|
| **7a** | $PhCH_2CH_2$ | Piperidine | 100 | 67 |
| **7b** | $PhCH_2CH_2$ | Morpholine | 100 | 76 |
| **7c** | Ph | Piperidine | 100 | 89 |
| **7d** | Bn | Morpholine | 79 | 25 |
| **7e** | 4-MeO-Ph | Morpholine | 100 | 75 |

[a] Purity of the crude products after cleavage, judged by LC–MS at 220 nm.
[b] Formed as racemic mixtures.

**Preparation of tetrazole (**Table 2**, 7c)**: Benzaldehyde (0.10 ml, 0.9 mmol) and piperidine (0.11 ml, 1.26 mmol) were mixed in THF/MeOH (1/1) for 5 h. TMS-$N_3$ (0.12 ml, 0.9 mmol) was added. The solution was then added to the resin **1** (0.2 g, 0.18 mmol) and the suspension was agitated for 16 h. The resin was washed with MeOH, DMF, MeOH and dichloromethane (DCM), followed by cleavage with 15% TFA/DCM (2×15 min). The cleavage filtrate was collected and evaporated to dryness. The crude product was purified on preparative HPLC to yield 39 mg of the product (89%).[11]

## Acknowledgements

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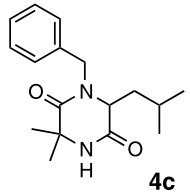
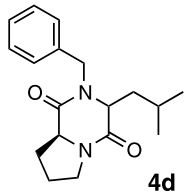
6. The structure of **4c** and **4d**:



**4c**



**4d**

7. (a) Ugi, I. *Angew. Chem., Int. Ed. Engl*. **1962**, *1*, 8; (b) Nixey, T.; Kelly, M.; Hulme, C. *Tetrahedron Lett*. **2000**, *41*, 8729–8733.
8. For recent progress on tetrazole chemistry, see: Butler, R. N. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V., Eds; Pergamon: Oxford, UK, 1996; Vol. 4.
9. There are only few practical routes to 5-substituted 1*H*-tetrazoles, see: Demko, Z. P.; Sharpless, K. B. *J. Org. Chem*. **2001**, *66*, 7945–7950, and references cited therein.
10. Spectral data for **4a**: $^1$H NMR (300 MHz, $CD_3OD$, $\delta$) 7.68 (m, 2H), 8.10 (m, 1H), 7.52 (m, 3H), 7.93 (m, 1H), 6.03 (s, 1H), 3.89 (s, 3H), 3.80 (m, 4H) 3.12 (m, 4H). $^{13}C\{^1H\}$ (150 MHz, $CD_3OD$, $\delta$) 28.1, 39.8, 46.3, 51.6, 55.5, 69.1, 113.4, 113.8, 120.0, 130.3, 137.5, 160.3, 166.1, 168.5. MS (DCI): $m/z$ 291 $[M+H]^+$.
11. Spectral data for **7c**: $^1$H NMR (300 MHz, $CD_3OD$, $\delta$) 7.69 (m, 2H), 7.52 (m, 3H), 6.04 (s, 1H), 3.25 (m, 4H), 1.87 (m, 4H) 1.66 (m, 2H). $^{13}C\{^1H\}$ (150 MHz, $CD_3OD$, $\delta$) 21.5, 22.8, 52.6, 65.6, 129.6, 130.1, 130.6, 130.7. MS (DCI): $m/z$ 244 $[M+H]^+$.