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Parallel synthesis of tandem Ugi/Diels–Alder reaction products on a soluble polymer support directed toward split-pool realization of a small molecule library

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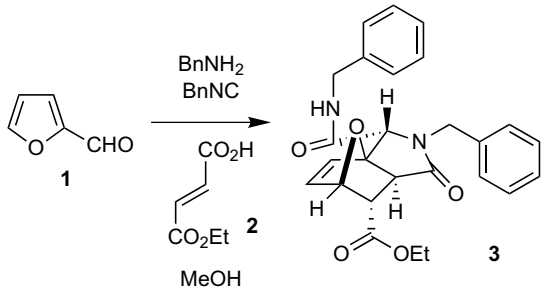
Abstract—A series of parallel reactions were carried out for the tandem Ugi/Diels–Alder reaction on our MPEG–O–CH_2- platform. Ninety-six out of a 100 entries were successful to give complex heterotricycles. The stereoselectivity was found not to be influenced by the building blocks used for amine and carboxylic acid components. An unexpected side pathway was found but was suppressed by employing appropriate reaction conditions. The reaction was also performed on solid phase, by which a larger library is potentially realized by employing the split-pool method.

Multicomponent coupling reactions are a powerful method for construction of a diverse collection of small molecules as a source for biologically interesting compounds.[1] The Ugi four-component coupling reaction[2] is representative among this class of reactions. The Ugi reaction is a coupling reaction between aldehyde, amine, isocyanide, and carboxylic acid to give α-acylamino amide in one step. Recently, efforts have been made for tandem or sequential reactions to synthesize more complex molecules in combination with the Ugi reaction.[3,4] In 1999, Paulvannan reported a tandem Ugi/Diels–Alder (UDA) reaction wherein furfural (**1**) and fumaric/maleic acid derivatives were used for the aldehyde and carboxylic acid components, respectively (Scheme 1).[4] Intramolecular Diels–Alder reaction[5] takes place after the Ugi reaction to provide a complex heterotricycle **3** in good yield with good stereoselectivity.[6] These products were further subjected to other diversity-generating reactions by Schreiber et al., to afford diverse sets of heterotricycles.[7] Though the usefulness of the heterocyclic scaffold prepared by the tandem UDA reaction as the starting point for another diversity-generation has been thus shown, no effort has been made to construct small molecule library by using the reaction. In the course of our study directed toward development of drug-like small molecules, we had been interested in the tandem UDA reaction which provides diverse sets of small molecules. Here we report the preliminary result on our attempt to construct small molecules library in both liquid and solid phase using our original platform.



Scheme 1.

Poly(ethylene glycol) monomethyl ether (MPEG–OH, av MW 5000)[8] with formylacetal linker[9] was at first used as a platform for rapid evaluation of the tandem UDA reaction.[10] 5-Hydroxymethyl-2-furfural (**4**) was immobilized onto the platform because (1) availability of building blocks for the furfural component is the poorest among components used in the tandem UDA reaction,[11] and (2) isolation of an intermediary Schiff base on the

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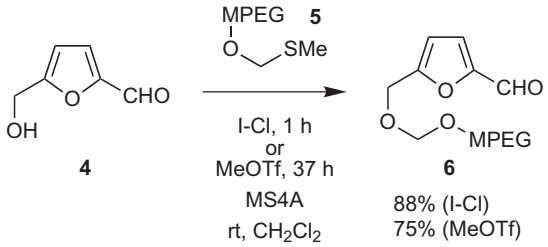
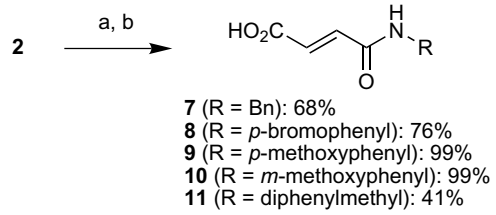


Scheme 2.

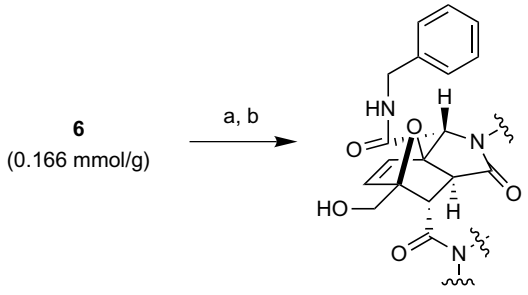


Scheme 3. Reagents and conditions: (a) $(COCl)_2$, DMF, benzene, 0 °C, 2 h, then concentration; (b) RNH_2, Cs_2CO_3, THF, rt, 12 h, then KOH, H_2O, rt, 12 h.

polymer support will potentially allow a hitherto unsuccessful, split-pool construction of the UDA multi-component coupling products library fully encoded chemically on insoluble cross-linked polymer beads. The immobilization was carried out onto MPEG–O–CH_2SCH_3 **5**[9] by using iodine monochloride in the presence of molecular sieves to give **6** in 88% yield after precipitative purification (Scheme 2). It is noteworthy that the diene moiety is inert to the electrophilic reagent used, and the reaction was rapidly completed within 1 h. Though the reaction was also effected by methyl triflate, the reaction was much slower (37 h) and the yield was lower (75%) than the former method.

Totally five fumaric acid monoamides were prepared from monoethyl fumarate (**2**) conveniently in one-pot manner (Scheme 3). Treatment with oxalyl chloride gave an acyl chloride, which was exposed to five amines in parallel in the presence of cesium carbonate. After amidation had been completed, an aqueous solution of potassium hydroxide was introduced to the reaction mixture for hydrolysis of the ester moiety. The usual aqueous work-up allowed us to isolate the fumaric acid derivatives **7**–**11** pure enough for the next tandem UDA reaction in moderate to fairly good yields (41–99%).

Twenty amines were used in combination with the carboxylic acid building blocks **7**–**11** (Scheme 4, Table 1). All reactions were carried out in parallel with 20 mg (0.0040 mmol) of immobilized furfural **6** and 20 equiv of amine, benzyl isocyanide, and fumaric acid derivative in MeOH (0.4 mL, 0.01 M) at 50 °C for 48 h. After the reaction period, the reaction mixture was directly subjected to gel permeation column chromatography



Scheme 4. Reagents and conditions: (a) R–NH_2 (×20),[9] BnNC, fumaric acid derivative (**7**–**11**), MeOH, 50 °C, 48 h, then GPC (<10 min); (b) TFA, CH_2Cl_2, rt, 4 h, then silica gel chromatography (<1 min).

Table 1. Products and yields for parallel synthesis of the tandem UDA reaction on the MPEG–O–CH_2-platform[a,b]

Amine building blocks	Fumaric acid building blocks				
	7	**8**	**9**	**10**	**11**
p-Bromophenethylamine (**a**)	**7a** (41%)	**8a** (64%)	**9a** (49%)	**10a** (>99%)	**11a** (79%)
3-Aminopropanol (**b**)	**7b** (17%)	**8b** (21%)	**9b** (0%)	**10b** (>99%)	**11b** (35%)
p-Methoxybenzylamine (**c**)	**7c** (65%)	**8c** (73%)	**9c** (15%)	**10c** (79%)	**11c** (40%)
n-Hexylamine (**d**)	**7d** (32%)	**8d** (85%)	**9d** (45%)	**10d** (>99%)	**11d** (53%)
n-Decylamine (**e**)	**7e** (67%)	**8e** (84%)	**9e** (28%)	**10e** (>99%)	**11e** (40%)
1-Phenyl-2-propylamine (**f**)	**7f** (67%)	**8f** (34%)	**9f** (11%)	**10f** (>99%)	**11f** (71%)
α-Methylbenzylamine (**g**)	**7g** (98%)	**8g** (56%)	**9g** (9%)	**10g** (59%)	**11g** (71%)
Allylamine (**h**)	**7h** (45%)	**8h** (65%)	**9h** (7%)	**10h** (97%)	**11h** (85%)
Diphenylmethylamine (**i**)	**7i** (60%)	**8i** (63%)	**9i** (38%)	**10i** (>99%)	**11i** (99%)
α-(2-Naphthyl)ethylamine (**j**)	**7j** (>99%)	**8j** (62%)	**9j** (54%)	**10j** (>99%)	**11j** (>99%)
2-Aminoethanol (**k**)	**7k** (29%)	**8k** (53%)	**9k** (0%)	**10k** (>99%)	**11k** (42%)
p-Chlorobenzylamine (**l**)	**7l** (63%)	**8l** (96%)	**9l** (46%)	**10l** (>99%)	**11l** (86%)
p-Methylbenzylamine (**m**)	**7m** (>99%)	**8m** (80%)	**9m** (63%)	**10m** (>99%)	**11m** (>99%)
3-Butoxypropylamine (**n**)	**7n** (>99%)	**8n** (64%)	**9n** (0%)	**10n** (>99%)	**11n** (70%)
2,5-Difluorobenzylamine (**o**)	**7o** (>99%)	**8o** (72%)	**9o** (81%)	**10o** (>99%)	**11o** (90%)
1-Adamantanamine (**p**)	**7p** (>99%)	**8p** (44%)	**9p** (63%)	**10p** (58%)	**11p** (0%)
p-Fluorobenzylamine (**q**)	**7q** (>99%)	**8q** (99%)	**9q** (60%)	**10q** (>99%)	**11q** (67%)
o-Methylbenzylamine (**r**)	**7r** (>99%)	**8r** (60%)	**9r** (59%)	**10r** (74%)	**11r** (92%)
Benzylamine (**s**)	**7s** (89%)	**8s** (74%)	**9s** (>99%)	**10s** (91%)	**11s** (69%)
n-Octylamine (**t**)	**7t** (90%)	**8t** (>99%)	**9t** (>99%)	**10t** (>99%)	**11t** (93%)

[a] For reaction conditions, see Scheme 4.
[b] Compound purity was >70% as judged from ^1H NMR spectra (500 MHz).

(GPC, Sephadex® G-25, ϕ 8 mm × 13 mm) using MeOH. The first elution (2.2 mL) was collected and concentrated to give the MPEG-immobilized heterotricycle. This chromatography is rapidly finished in 10 min, and allows quantitative recovery of the MPEG polymer without contamination of the small molecules.

Cleavage of the tandem UDA product from the platform was effected by trifluoroacetic acid in CH_2Cl_2 at rt for 4 h.[9] After concentration, the crude product was rapidly passed through a pad of silica gel (takes less than 1 min) to give small molecules released from the polymer. No decomposition was detected at all during these cleavage operations.

The results for a total of 100 parallel reactions are summarized in Table 1. Weight-based yields for these UDA and cleavage reactions ranged from 0% to >99%; 68 entries successfully gave the tandem UDA product in more than 60% yield, whereas four entries did not provide the product, and two entries proceeded only in less than 10% yield. In all cases the purity of the tandem UDA product was more than 70% as judged from ^{1}H NMR. The main impurity is the unreacted 5-hydroxymethyl-2-furfural (**4**). As for the stereoselectivity, all reactions apparently gave the structure shown in Scheme 4 predominantly,[12] except for the runs where sterically demanding 1-adamantanamine (**p**) was used for the amine building block, by comparing their ^{1}H NMR spectra with reported ones. Since the structure of 1-adamantanamine-derived tandem UDA products **7p**–**10p** could not be determined by the ^{1}H chemical shifts, we synthesized a heterotricycle **12** corresponding to **8b** in a solution phase and submitted it to X-ray crystallographic analysis (Fig. 1).[13] The result clearly revealed the stereochemistry of **12** was identical with the structure representatively shown in Scheme 4, and hence we concluded that the stereoselectivity is not directly affected by the amines and fumaric acid building blocks employed. It should be also noted here that the asymmetric carbon center in the amine building blocks (**f**, **g**, and **j**) did not affect the stereoselectivity notably; the possible diastereomers were produced in nearly equal amounts in all cases.

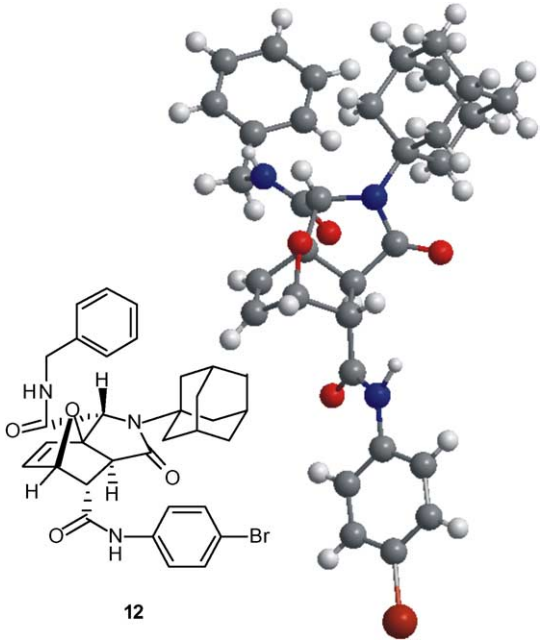
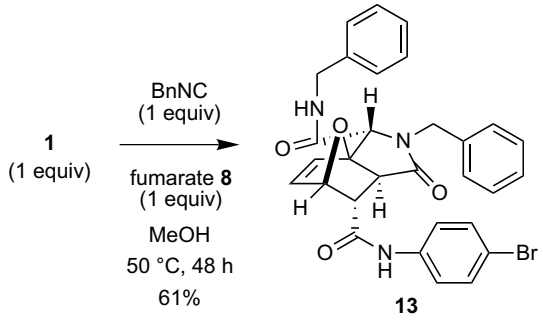


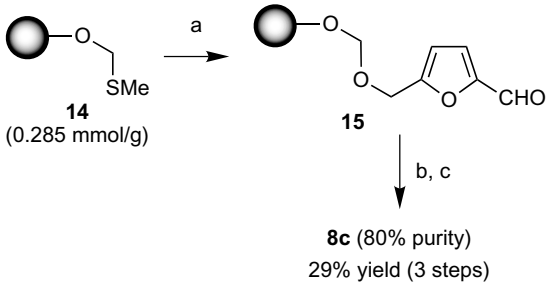
Figure 1. Chem3D representation for the X-ray crystallographic structure of 1-adamantanamine-derived tandem UDA product **12**.

During these experiments, another pathway was found to compete with the desirable tandem UDA reaction especially when sterically demanding amines such as *tert*-butylamine (data not shown) or 1-adamantanamine (**p**) were used. In these cases, unexpected **8s** was always produced partially (up to 20% yield) probably due to in situ generation of benzylamine from benzyl isocyanide (Scheme 5). In fact, **13** was found to be provided in 61% yield (based on benzyl isocyanide used) by simply mixing benzyl isocyanide, fumaric acid derivative, and furfural at 50 °C for 48 h. This side reaction competes when sterically demanding, and hence less reactive, amines are employed. After several experiments, we found raising the temperature (60 °C) and reducing the solvent amount to 0.04 M was effective to suppress such an undesirable process almost completely.

The PEG–O–CH_2-system can be constructed also on cross-linked insoluble polymer beads using TentaGel S OH resin (Scheme 6).[8,9,14] Thus, after loading furfural derivative **4** onto the platform, the tandem UDA reaction product **8c** was conveniently synthesized in 29% yield with 80% purity over three steps.[15]



Scheme 5.



Scheme 6. Reagents and conditions: (a) **4** (10 equiv), I–Cl (4 equiv), MS4A, CH_2Cl_2, rt, 3.5 h; (b) *p*-methoxybenzylamine (20 equiv), BnNC (20 equiv), fumaric acid derivative **8** (20 equiv), MeOH/THF (2:1), 50 °C, 48 h; (c) TFA/CH_2Cl_2 (3:7), rt, 2.5 h.

In summary, we have carried out 100 reactions of the tandem UDA reaction of primary amines, benzyl isocyanide, fumaric acid derivatives, and 5-hydroxymethyl-2-furfural in liquid phase by using our MPEG–O–CH_2-platform. All reactions gave the stereoisomer representatively drawn in Scheme 4. An unexpected side pathway leading to undesirable **8s** was found but was successfully suppressed by raising the temperature and concentration. In addition, cross-linked insoluble polymer beads were demonstrated to be an efficient platform for a solid phase synthesis of the heterotricycle. We are currently studying how to realize a larger-scale small molecule library by a split-pool method using TentaGel-immobilized furfural **15** towards discovery of biologically interesting compounds useful for chemical genetics studies.[16]

Acknowledgements

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References and notes

1. Armstrong, R. W.; Combs, A. P.; Tempest, P. A.; Brown, S. D.; Keating, T. A. *Acc. Chem. Res.* **1996**, *29*, 123–131; Weber, L.; Illgen, K.; Almstetter, M. *Synlett* **1999**, 366–374; Bienayme, H.; Hulme, C.; Oddon, G.; Schmitt, P. *Chem. Eur. J.* **2000**, *6*, 3321–3329; Domling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3169–3210; Domling, A. *Curr. Opin. Chem. Biol.* **2000**, *4*, 318–323; Orru, R. V. A.; de Greef, M. *Synthesis* **2003**, 1471–1499.
2. Ugi, I. *Angew. Chem., Int. Ed. Engl.* **1959**, *71*, 386.
3. Cristau, P.; Vors, J. P.; Zhu, J. P. *Tetrahedron Lett.* **2003**, *44*, 5575–5578; Naskar, D.; Roy, A.; Seibel, W. L.; West, L.; Portlock, D. E. *Tetrahedron Lett.* **2003**, *44*, 6297–6300; Portlock, D. E.; Naskar, D.; West, L.; Ostaszewski, R.; Chen, J. J. *Tetrahedron Lett.* **2003**, *44*, 5121–5124; Portlock, D. E.; Ostaszewski, R.; Naskar, D.; West, L. *Tetrahedron Lett.* **2003**, *44*, 603–605; Gracias, V.; Moore, J. D.; Djuric, S. W. *Tetrahedron Lett.* **2004**, *45*, 417–420.
4. Paulvannan, K. *Tetrahedron Lett.* **1999**, *40*, 1851–1854.
5. For intramolecular Diels–Alder reaction of furan, see; Mukaiyama, T.; Iwasawa, N. *Chem. Lett.* **1981**, 29–32; Breu, J.; Butz, T.; Range, K. J.; Sauer *Acta Cryst.* **1997**, *C53*, 515–517; Kappe, C. O.; Murphree, S. S.; Padwa, A. *Tetrahedron* **1997**, *53*, 14179–14233; Ghelfi, F.; Parsons, A. F.; Tommasini, D.; Mucci, A. *Eur. J. Org. Chem.* **2001**, 1845–1852; Wright, D. L.; Robotham, C. V.; Aboud, K. *Tetrahedron Lett.* **2002**, *43*, 943–946; Akai, S.; Naka, T.; Omura, S.; Tanimoto, K.; Imanishi, M.; Takebe, Y.; Matsugi, M.; Kita, Y. *Chem. Eur. J.* **2002**, *8*, 4255–4264.
6. A tandem UDA reaction with pyrolle has been reported recently, see; Paulvannan, K. *J. Org. Chem.* **2004**, *69*, 1207–1214.
7. Lee, D. S.; Sello, J. K.; Schreiber, S. L. *Org. Lett.* **2000**, *2*, 709–712; Sello, J. K.; Andreana, P. R.; Lee, D. S.; Schreiber, S. L. *Org. Lett.* **2003**, *5*, 4125–4127.
8. MPEG–OH and TentaGel S OH resin were purchased from Aldrich Co. (catalog No. 20251-7) and Advanced ChemTech, Inc. (catalog No. SJ6004), respectively.
9. Oikawa, M.; Tanaka, T.; Kusumoto, S.; Sasaki, M. *Tetrahedron Lett.* **2004**, *45*, 787–790.
10. For our related studies using another soluble polymer platform, MPEG–O–AAc–, for rather simple Ugi four-component coupling reaction, see: Oikawa, M.; Ikoma, M.; Sasaki, M. *Tetrahedron Lett.* **2004**, *45*, 2371–2375.
11. In contrast to our strategy, amine components were immobilized in other polymer-phase synthetic studies on the tandem UDA reaction,[4,7] where no library has been realized yet for the tandem UDA product.
12. For example, the stereoselectivities were 85% (**7a**), 91% (**7s**), 100% (**7l**), 96% (**8h**), and 81% (**11h**). These were determined by ^{1}H NMR spectra.
13. Crystallographic data for **12**: monoclinic colorless plate ($0.25 \times 0.25 \times 0.05$ mm^3, space group $P2_1/c$, unit cell constants $a = 17.484(6)$ Å, $b = 12.959(4)$ Å, $c = 6.412(9)$ Å, $\beta = 101.805(2)°$, $V = 5857(3)$Å^3, Z value = 8, $D_{calc} = 1.439$ g/m^3).
14. The usefullness of this platform will be reported elsewhere.
15. Since the loading of primary alcohols onto the resin proceeds approximately in 30% yield (data not shown), the yields for the tandem UDA and the cleavage reactions were evaluated to be 80% and >96%, respectively. The MTM group, after the loading, is supposed to be hydrolyzed and the generating hydroxy group is inert during the tandem UDA reaction followed by the cleavage. We are currently investigating a high-yield immobilization method for primary alcohols on the platform.
16. Schreiber, S. L. *Science* **2000**, *287*, 1964–1969; Burke, M. D.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 46–58.