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A convenient solution and solid-phase synthesis of Δ^5-2-oxopiperazines via *N*-acyliminium ions cyclization

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Abstract—An extremely efficient synthesis of Δ^5-2-oxopiperazines in solution phase and on solid support has been established via a Ugi four-component condensation reaction (U-4CC) followed by *N*-acyliminium ion cyclization between the aldehyde (acetal) functionality and the newly formed amide bond. The desired Δ^5-2-oxopiperazines are obtained in excellent yields and purity.

Construction of heterocyclic ring systems on solid support is of considerable interest in combinatorial organic synthesis.[1] One of the major challenges in this field is the need for highly efficient protocols for the heterocyclic ring formation and elaboration of diversified substitutions around the core structure. As part of our program to develop conformationally restricted peptidomimetic libraries using solid-phase organic synthesis (SPOS), we are interested in a general solid-phase synthesis of Δ^5-2-oxopiperazines (Fig. 1). Piperazine and substituted piperazines are important pharmacophores that have been incorporated in a number of drugs or drug candidates.[2] The formation of such ring structures has been an important field of study. However, current methodology for construction of 2-oxopiperazine system is limited to solution phase synthesis and a lengthy transformation sequence is usually needed.[3] Strategically, Ugi four-component condensation (U-4CC)[4] is an attractive reaction for us to start with since it gives dipeptide-like products that can be tailored to our need for making the piperazine ring system using *N*-acyliminium ion cyclization.[5] Post Ugi modifications, leading to the formation of interesting heterocyclic compounds, such as piperazines,[2] diketopiperazines,[6a,b] imidazoles,[6c] and 1,4-benzodiazepine-2,5-diones,[6d] have been reported. There are, however, few reports dealing with the newly formed amide bond derived from the isocyanide moiety.[7] Herein we describe a novel tandem Ugi condensation–*N*-acyliminium ion cyclization reaction to form a Δ^5-2-oxopiperazines ring system.

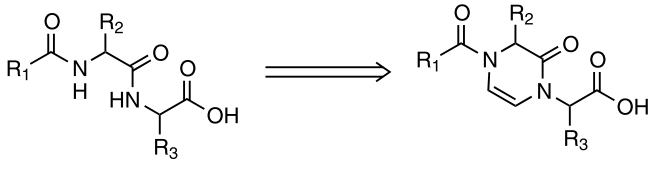

Figure 1. Δ^5-2-Oxopiperazine as dipeptidomimetic.

The test reaction using this tandem Ugi-*N*-acyliminium ion cyclization strategy is demonstrated in the solution phase as shown in Scheme 1. Thus, a carboxylic acid (**2**), an aldehyde (**3**), aminoacetaldehyde diethyl acetal (**4**) and an isocyanide (**5**) are mixed together in methanol and chloroform and stirred for 24 h at room temperature. After the reaction is completed as indicated by TLC, the solvents are removed under reduced pressure. The intermediate product **6**, which is identified spectroscopically, is treated with 50% TFA in dichloromethane without further purification. The cyclization completes within 2–4 h at room temperature. Removal of solvents and purification of the residue with preparative silica gel TLC affords the desired product **1a** in 75% yield. Either aromatic or aliphatic acids give the desired products in similar yields. However, aliphatic aldehydes generally give better reaction yields than the aromatic aldehydes.

A number of strategies for solid-phase Ugi four-component condensation have been reported.[8,9] Due to the greater availability of aldehydes and carboxylic acids relative to isocyanides, we chose to adapt a strategy involving immobilization of isocyanides on solid support.[6c,9b] Wang resin bound isocyanides **7** (e.g. R = *p*-CH_2PhO-) are prepared according to the literature procedure. The isocyanide resin thus prepared is mixed with a carboxylic acid **8**, an aldehyde **9** and aminoaldehyde diethyl acetal (**4**) at room temperature to furnish the intermediate Ugi product **10**. Treatment of the resin

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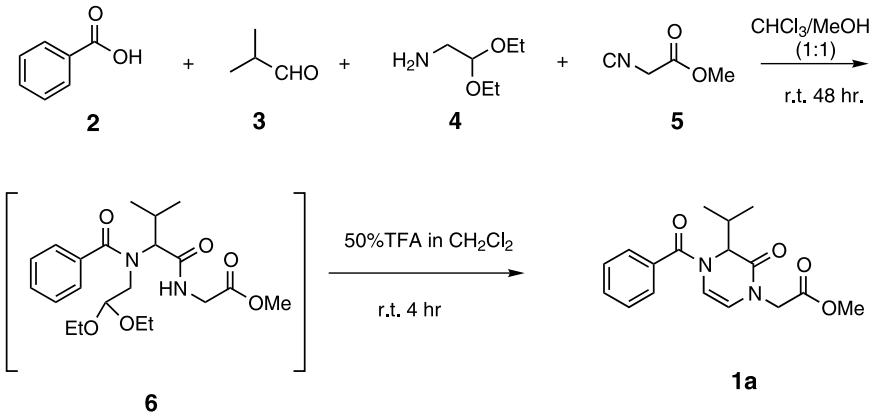
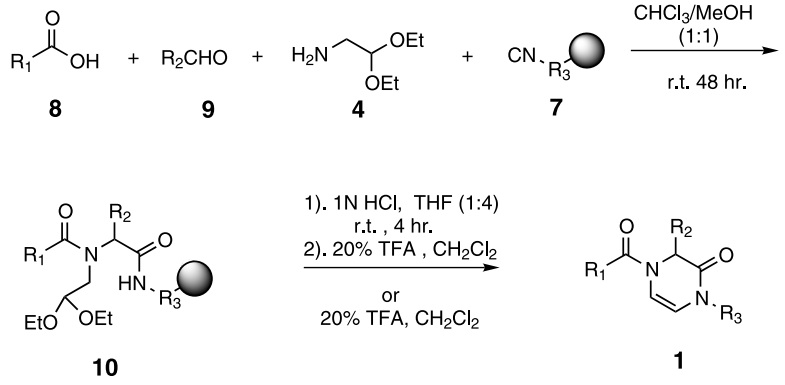


Scheme 1. One-pot solution-phase synthesis of Δ^5-2-oxopiperazines.

bound intermediate **10** with 1N HCl in THF followed by 20% TFA in CH_2Cl_2 gives the desired Δ^5-2-oxopiperazines **1** in good yields and purity.[10] It is found that the HCl treatment prior to TFA cleavage is not necessary and direct treatment of the resin **10** with TFA provides the same product in almost identical yield and purity. The cyclization apparently involves an *N*-acyliminium ion intermediate formed from aldehyde (or acetal) functionality and the newly formed amide bond, which upon deprotonation leads to the unsaturated products (Scheme 2, Table 1).

In summary, the preparation of Δ^5-2-oxopiperazines in solution phase as well as on a solid support has been demonstrated for the first time using simple and efficient procedures. The reaction has been used for library synthesis and gives high quality products. It is possible to introduce an additional site of diversity into this oxopiperazine ring or another ring by using the more complex aminoacetal derivatives or by trapping the *N*-acyliminium ion intermediate with internal or external electrophiles. These results will be reported in due course.



Scheme 2. Solid-phase synthesis of 2-oxopiperazines.

Table 1. One-pot synthesis of Δ^5-2-oxopiperazines

Compounds	R_1	R_2	R_3	Yield[a]
1a	Phenyl	*n*-Propyl	CH_2COOMe	75[b]
1b	*n*-Butyl	*i*-Propyl	CH_2COOMe	72[b]
1c	4-Methoxylphenyl	Phenyl	CH_2COOMe	68[b]
1d	Phenyl	Isopropyl	1,1,3,3-tetramethylbutyl	85[b]
1e	3-Nitrophenyl	Isopropyl	p-$(CH_2)_2C_6H_4OH$	92
1f	4-Methoxycarbonylphenyl	Isopropyl	p-$(CH_2)_2C_6H_4OH$	94
1g	4-Methoxycarbonylphenyl	Cyclohexyl	p-$(CH_2)_2C_6H_4OH$	97
1h	4-Fluorophenylmethyl	Cyclohexyl	p-$(CH_2)_2C_6H_4OH$	97

[a] Isolated yields based on the resin loading (**b**–**g**: 0.95 mmol/g by gravimetric measurement).
[b] Solution-phase reaction (cf. Scheme 1).

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10. **Typical reaction procedure**: In a 5 mL glass filter tube, resin bound isocyanide **7** (150 mg, 0.1 mmol) is suspended in a mixed solvent of chloroform and methanol (1:1; 3 mL), aminoaldehyde diethyl acetal (5 equiv.) and an aliphatic aldehyde (5 equiv.) are added and the mixture is shaken for 30 min before a carboxylic acid (3–5 equiv.) is added. The resin is shaken at room temperature for 48 h. The solvent is drained and the resin is washed with DMF (3×3 mL), MeOH (3×3 mL) and CH_2Cl_2 (3×3 mL) to give the product resin **10**. After drying under vacuum overnight, the resin **10** is suspended in 3 mL of 1N HCl in THF (1:2) and shaken for 4 h at room temperature. The solvent is drained and the resin is washed with THF (3×3 mL), MeOH (3×3 mL) and CH_2Cl_2 (3×3 mL) and dried under vacuum. The dried resin is treated with 20% TFA in CH_2Cl_2 to give the desired products after removal of the solvents. The product is typically >90% pure by TLC and HPLC. The baseline impurities, if any, are removed by preparative TLC using 16% CH_3CN in CH_2Cl_2 to give the pure product. The yield is calculated based on the loading of the isocyanide resin precursor. Compound **1e**: EI MS m/z 423 (M+H); ^{1}H NMR (CD_3CN): δ 8.15 (d, J=8 Hz, 2H), 7.62 (d, J=8.4 Hz, 2H), 7.16 (d, J=8 Hz, 2H), 6.84 (d, J=8.4 Hz, 2H), 5.82 (dd, J=1.6 and 5.6 Hz, 1H), 5.65(d, J=5.6 Hz, 1H), 4.80 (dd, 1.6 and 9.2 Hz, 1H), 4.00 (s, 3H), 3.80 (m, 2H), 2.90 (m, 2H), 2.05 (m, 1H), 1.05 (d, J=7.2 Hz, 3H), 1.03 (d, J=6.8 Hz, 3H); ^{13}C NMR (CD_3CN) δ 19.5, 20.2, 30.3, 34.3, 48.3, 53.3, 62.1, 110.4, 116.3 (2C), 117.1, 118.6 (2C), 129.4, 130.5 (2C), 130.7, 131.3 (2C), 133.0, 140.1, 156.8, 165.2 (CON), 167.3 (CON), 169.0 (COO).