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Solid phase synthesis of highly substituted 2,4-dioxopiperidines

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Abstract

A convenient solid phase synthesis of (*E*)-*N*-substituted-acetyl-*N*-(2-methoxycarbonyl-3-(aryl)-prop-2-enyl)amino acids and the condensation of their esters to highly substituted 2,4-dioxopiperidines are described.

2,4-Dioxopiperidines have been shown to possess biological activity in a number of therapeutic areas. Recently, various 2,4-dioxopiperidines were found to be potent as therapeutic or prophylactic agents for hepatic disease, for bacterial and viral infections and for diseases including AIDS.[1] But the synthesis of a novel highly substituted 2,4-dioxopiperidine **7** which has potential to be further functionalized has never been reported. Herein a general method was developed to synthesize various highly substituted 2,4-dioxopiperidines **7** via solid-phase synthesis of (*E*)-*N*-substituted-acetyl-*N*-(2-methoxycarbonyl-3-(aryl)-prop-2-enyl)amino acids **5**.

The solid phase synthesis was initiated with Fmoc-protected amino acid-Wang resin **1** (Scheme 1). Various commercially available Fmoc-amino acid-Wang resin units provide the first diversity element in $\mathbf{R^1}$ of 2,4-dioxopiperidines **7**. After removal of the Fmoc group of **1**, alkylation of the free amines **2** was accomplished by Pd(0) catalyzed reaction with methyl 2-(*Z*)-(bromomethyl)-3-aryl-prop-2-enoates **3**[2,3] in DMF.

The bromides **3** were synthesized in two steps. The first step is a DABCO catalyzed Baylis–Hillman reaction of methyl acrylate with the appropriate aldehyde.[2] The second step involves a Corey–Kim bromination using NBS–DMS (Scheme 2).[3] The alkylation with the bromide **3** gives the second element of diversity ($\mathbf{R^2}$) to the 2,4-dioxopiperidines **7**.

The subsequent amidation step generates the third diversity element ($\mathbf{R^3}$)[4] of **7** by the use of different amidating reagents (Scheme 1, Table 1): (1) compound **4** reacted with ethyl malonyl chloride, pyridine, and DMAP in CH_2Cl_2 providing *N*-ethoxycarbonylacetyl amides **5**;[5,6] (2) compound **4** reacted with cyanoacetic acid, and DIC in DMF giving *N*-cyanoacetyl amide **5**;[7] (3) compound **4** reacted with diketene, and NEt_3 in CH_2Cl_2 generating *N*-methylcarbonylacetyl amide **5**.[8]

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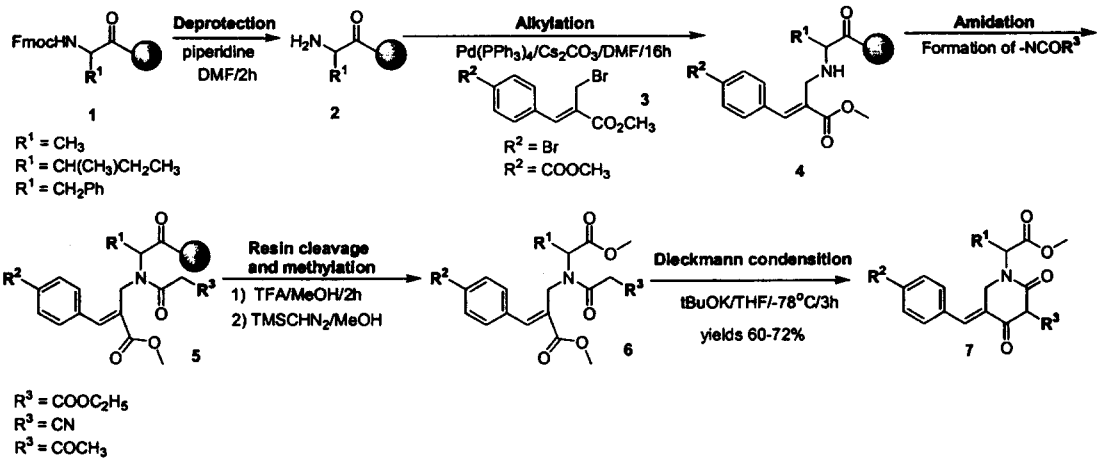
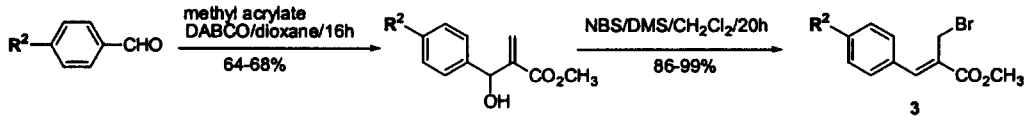
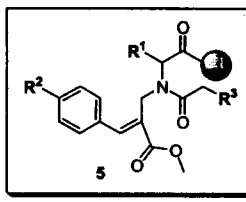


Scheme 1.



Scheme 2.

Table 1
The reaction conditions of amide formation for compound **5**



5	Amidation	R^3
(1)	ethyl malonyl chloride pyridine/DMAP/CH_2Cl_2/16h	$COOC_2H_5$
(2)	cyanoacetic acid DIC/DMF/50h	CN
(3)	diketene/NEt_3/CH_2Cl_2/50h	$COCH_3$

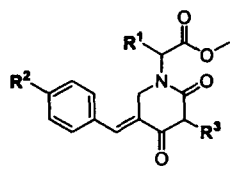
After resin cleavage with CF_3COOH/MeOH, and methylation with $TMSCHN_2$ in MeOH, the methyl esters **6** were obtained. Three diversities ($\mathbf{R^1}$, $\mathbf{R^2}$, and $\mathbf{R^3}$) were generated. The isolated yields for pure **6** are 28–31% after five step reaction from **1**.[9] Finally, Dieckmann condensation of **6** with *t*BuOK in THF at –78°C provided different highly substituted 2,4-dioxopiperidines **7** in 60–72% yields (Table 2).[10–13]

In summary, solid phase synthesis of (*E*)-*N*-substituted-acetyl-*N*-(2-methoxycarbonyl-3-(aryl)-prop-2-enyl)amino acids **5** is accessible from commercially available Fmoc-protected aminoacids on Wang resin. The synthesis requires an alkylation and subsequent amidation step. This approach can be used to generate number compound libraries of **5** with three diversity elements ($\mathbf{R^1}$, $\mathbf{R^2}$ and $\mathbf{R^3}$). The methyl ester **6** can be further elaborated to various 2,4-dioxopiperidines **7**.

1. Typical experimental procedures

Compound **4a**: To the Fmoc-Ala-Wang resin **1a** (Novabiochem, 0.74 mmol/g) (1 g, 0.74 mmol) was added a solution containing 5 mL each of DMF and piperidine at room temperature. The suspension was allowed to mix at room temperature for 2 h. Then the supernatant was removed. The resin was washed with DMF, MeOH, CH_2Cl_2, and dried in vacuo. To the dried resin were added methyl (bromomethyl)-3-(4-methoxycarbonylphenyl)prop-2-enoate **3**[2,3] (231 g, 0.74 mmol), $Pd(PPh_3)_4$ (8.6 mg, 0.0074 mmol),

Table 2
The yields for Dieckmann condensation



7

7	R^1	R^2	R^3	%Yields
a	CH_3	$COOCH_3$	$COOC_2H_5$	64
b	$CH(CH_3)CH_2CH_3$	$COOCH_3$	$COOC_2H_5$	60
c	$CH(CH_3)CH_2CH_3$	Br	$COOC_2H_5$	72
d	$CH(CH_3)CH_2CH_3$	Br	CN	60
e	CH_2Ph	$COOCH_3$	$COCH_3$	65

Cs_2CO_3 (241 mg, 0.74 mmol) and DMF (10 mL) at room temperature. The suspension was allowed to mix at room temperature for 16 h. After 16 h, the supernatant was removed. The resin was washed with DMF, MeOH, and CH_2Cl_2 and then dried in vacuo.

Compound **5a**: A mixture of the above resin, pyridine (120 μL, 1.48 mmol), DMAP (0.9 mg, 0.0074 mmol) in CH_2Cl_2 (10 mL) was stirred at 0°C for 20 min. Ethyl 3-chloro-3-oxopropionate (188 uL, 1.48 mmol) was added. The suspension was stirred for 16 h at 25°C before the supernatant was removed. The resin was washed with MeOH, and CH_2Cl_2 and dried in vacuo.

Compound **6a**: To the above resin, TFA (10 mL) was added. The suspension was stirred for 2 h at 25°C. Then the supernatant was removed, and the resin was washed with MeOH (3×8 mL). The combined supernatants were concentrated and dried in vacuo. The residue was redissolved in MeOH (10 mL), and (trimethylsilyl)diazomethane (2.0 M solution in hexanes) was added dropwise until the yellow color stayed. After concentration, chromatography (EtOAc/hexane) of the crude yellow oil afforded **6a** 100 mg (total yield 30% from **1a** to **6a**): ^{1}H NMR (CD_3OD, 500 MHz) δ 8.10–8.08 (d, 2H, *J*=8.2 Hz), 7.96 (d, 1H,), 7.50–7.48 (d, 2H, *J*=8.2 Hz), 4.60–4.56 (d, 1H, *J*=15.5 Hz), 4.48–4.45 (d, 1H, *J*=15.5 Hz), 4.17–4.12 (m, 2H), 3.93 (s, 3H), 3.87 (s, 3H), 3.80–3.60 (m, 3H), 3.57 (s, 3H), 1.26–1.23 (t, 3H, *J*=6.9 Hz), 1.18–1.16 (d, 3H, *J*=6.9 Hz); ^{13}C NMR (CD_3OD, 500 MHz) δ 172.8, 169.3, 169.1, 168.4, 167.9, 143.6, 140.2, 132.0, 131.5, 131.0, 130.6, 62.6, 56.2, 53.0, 52.9, 52.7, 46.0, 42.1, 14.5, 13.9; EIMS *m/z* 472 ($M+Na^+$).

Compound **7a**: The above **6a** (83 mg, 0.185 mmol) in THF (10 mL) was cooled down to −78°C. Potassium *tert*-butoxide (1.0 M solution in 2-methyl-2-propanol) (0.5 mL, 0.5 mmol) was added. The mixture was stirred for 3 h at −78°C. The reaction mixture was quenched by saturated NH_4Cl solution (10 mL). The organic layer was removed. The aqueous layer was extracted by EtOAc (2×10 mL). The combined organic layers were washed by saturated NaCl solution (20 mL), dried over Na_2SO_4, and concentrated. Chromatography (CH_2Cl_2/MeOH) of the crude yellow oil afforded **7a** 50 mg (64%): ^{1}H NMR (CD_3OD, 500 MHz) δ 8.04–8.02 (d, 2H, *J*=7.5 Hz), 7.81 (s, 1H), 7.60–7.58 (d, 2H, *J*=7.5 Hz), 5.10 (1H, overlapped with water peak), 4.17–4.13 (m, 3H), 3.90 (s, 3H), 3.80 (s, 3H), 3.34 (s, 1H), 3.30–3.28 (broad, 1H), 1.29–1.23 (t, 3H, *J*=6.0 Hz), 1.24–1.23 (d, 3H, *J*=6.1 Hz); ^{13}C NMR (CD_3OD, 500 MHz) δ 196.5, 175.4, 169.5, 168.2, 167.7, 141.6, 140.9, 132.4, 131.4, 130.9, 130.7, 90.7, 59.4, 53.0, 52.9, 49.3, 37.3, 16.8, 15.2; EIMS *m/z* 418 ($M+H^+$), 440 ($M+Na^+$).

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4. $\mathbf{R^3}$ demonstrated here are all acidifying groups. Certainly this is not a requirement. For example, R^3 can be an alkyl group, this type of cyclization was reported in Ref. 12b.
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9. NMR and LCMS of crude sample **6** show good efficiency (yields greater than 80%). Compounds **6** are highly functionalized molecules. Low isolation yields are due to the loss of resin washing and transferring (flasks and Buchner funnel were used for the reactions and workup, no special solid phase apparatus) in the five step reaction sequence, purification process and compound stability.
10. Various reaction conditions for the Dieckmann condensation of **6** to **7** were utilized: the room temperature reaction resulted in decomposition. Low reaction temperature (−78°C) and good purity of starting material **6** provided good yields of **7**.
11. No epimerization of $\mathbf{R^1}$ was observed in this Dieckmann condensation. This might be due to very low reaction temperature (−78°C). In the transformation of **6b** to **7b**, **6c** to **7c**, and **6d** to **7d**, the α-CH of the isoleucine group is always shown as a simple doublet, no other doublet was seen for the other diastereomer in the ^{1}H NMR spectra.
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13. Compounds **6** and **7** were characterized by ^{1}H, ^{13}C NMR, and ESMS. (*E*)/(*Z*) Configurations were determined by NOE.