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Preparation of Tricyclic Nitrogen Heterocycles via Tandem Four-Component Condensation/ Intramolecular Diels-Alder Reaction

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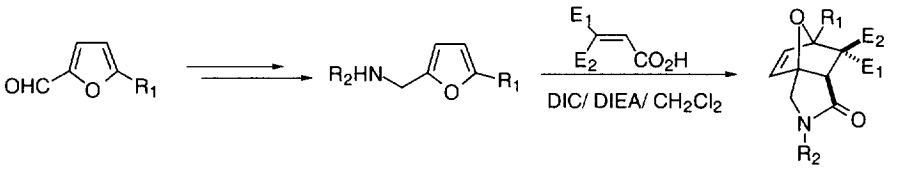
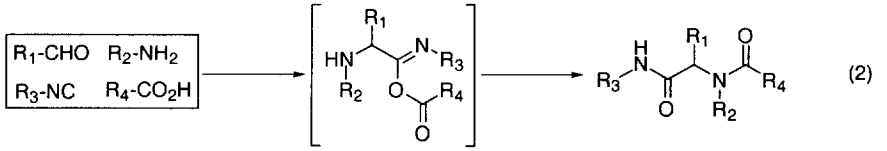
Abstract: Preparation of highly substituted rigid tricyclic nitrogen heterocycles via a tandem four-component condensation (4CC)/ intramolecular Diels-Alder (IMDA) reaction has been studied both in solution and solid phase. Influence of electronic and steric effects on the product formation has also been investigated.

We have recently studied an efficient high yield synthesis of highly substituted rigid tricyclic nitrogen heterocycles from *N*-alkyl furylamine and activated dienophile acids, such as maleic (E_1=H, E_2= CO_2Et) and fumaric (E_1= CO_2Et, E_2=H) acid derivatives under standard acylation conditions (eq 1).[1] The cycloaddition product is formed *via* an initial *N*-acylation followed by intramolecular Diels-Alder reaction. During our investigation to increase the structural diversity around the tricyclic lactam core, we were intrigued by the elegant synthetic approaches used to generate chemical diversity in short reaction sequences through multiple component condensation reactions.[2] In recent years, both three-component and four-component condensation reactions have received considerable attention in the scientific community.[2,3] Condensation of appropriately functionalized four components and post-condensation modification strategy has been successfully used for the preparation of a wide range of nitrogen heterocycles. We report herein a novel approach for the preparation of tricyclic nitrogen heterocycles through a tandem four-component condensation/ intramolecular Diels-Alder reaction (4CC/IMDA).



(1)

The four-component condensation reaction (4CC), known as the Ugi reaction, involves the condensation of an amine, an aldehyde, an isocyanide and an acid to provide an α-acylamino amide in a single step (eq 2).[2] We envisioned that by using furaldehyde **1** and maleic or fumaric acid derivative **4** as the aldehyde and acid components, respectively, the 4CC reaction would provide the triene **5**, which would immediately undergo IMDA reaction to yield tricyclic lactam **6** (Scheme 1). This approach would eliminate the necessity to prepare *N*-alkyl furylamine precursors, and also provide an additional diversity.



(2)

Condensation of furaldehyde **1**, benzylamine **2**, benzyl isocyanide **3** and activated dienophile acid **4** in MeOH at room temperature for 24-36 h provided, after purification, the cycloaddition product **6** as a diastereomeric mixture in high to excellent yield. As shown in Table 1 (entries a-c), the 4CC/IMDA reaction showed good diastereoselectivities (86:14 to 92:8). The isomer ratios were determined by integration of the ^1H

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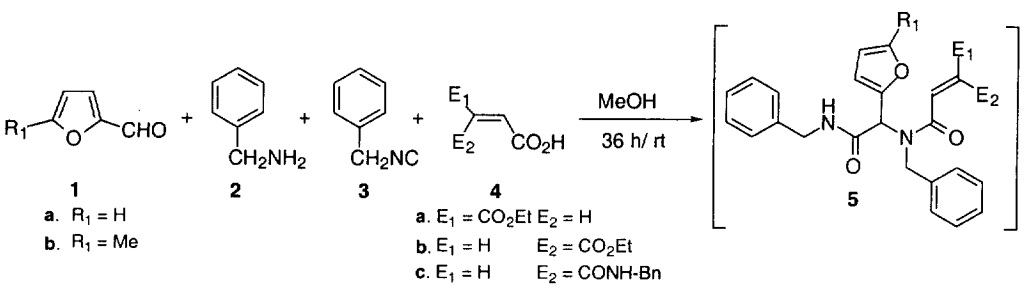
NMR spectra of the crude reaction mixture. Since the IMDA reaction involving furan as diene is known to proceed exclusively in an exo fashion, the relative stereochemistry at C-3 and C-4 is dictated by the stereochemistry of the dienophile acid **4**. Accordingly, fumaric acid derivative **4a** gave the trans product **6a** in 89% yield, whereas maleic and maleamic acid derivatives **4b** and **4c** provided the cis products **6b** and **6c** in 70% and 85% yields, respectively. The relative stereochemistry at C-3 and C-4 of **6** was assigned based on the coupling constants of H_3 and H_4 in the ^1H NMR (trans **6a** $J_{3,4}$= 3.7 Hz: cis **6b** $J_{3,4}$=9.2 Hz). At this time no effort was made to determine the stereochemistry at C-9.

To examine the substituent effect on the 4CC/ IMDA reaction, 5-methylfuraldehyde **1b** was condensed with **2**, **3** and **4a-c** using the above condensation conditions to provide the corresponding cycloaddition products **6d-f** as a mixture of diastereoisomers (Table 1, entries d-f). Irrespective of the methyl substituent on the furan ring, the products **6d-f** were isolated in high yield with good diastereoselectivities (Table 1, entries d-f), suggesting that the methyl substituent on the furan ring did not have any major influence on the cycloaddition.

Scheme 1

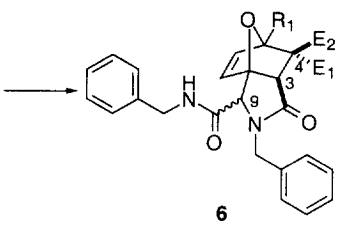


1
a. R_1 = H
b. R_1 = Me

2 **3**

4
a. E_1 = CO_2Et E_2 = H
b. E_1 = H E_2 = CO_2Et
c. E_1 = H E_2 = CONH-Bn

5



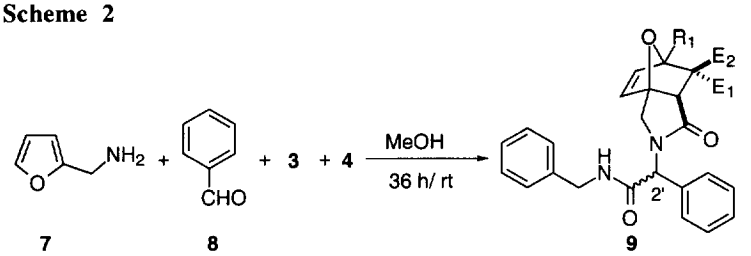
6

Table 1

Entry	R_1	E_1	E_2	Yield %	Isomer Ratio
a	H	CO_2Et	H	89	92:8
b	H	H	CO_2Et	70	92:8
c	H	H	CONH-Bn	85	86:14
d	Me	CO_2Et	H	78	92:8
e	Me	H	CO_2Et	72	93:7
f	Me	H	CONH-Bn	81	83:17

In an alternative approach, instead of **1** and **2**, furyl amine **7** and benzaldehyde **8** were condensed with **3** and **4** under previous conditions to yield, after chromatographic purification, a new tricyclic lactam scaffold **9** as a mixture of isomers (Scheme 2). In contrast to the previous approach (Scheme 1, Table 1), this approach showed poor diastereoselectivity (56:44 -64:36). Since the C-2' stereocenter is away from the tricyclic core, the rigid tricyclic structure may have little or no effect on the control of the stereochemistry at C-2'. Fumaric acid derivative **4a** gave the trans product **9a** as a 64:36 mixture of isomers in 89% combined yield whereas both maleic and maleamic acid derivatives **4b** and **4c** provided the cis products **9b** and **9c** as a 60:40 and 56:44 mixture of isomers in 75% and 88% combined yields, respectively.

Scheme 2

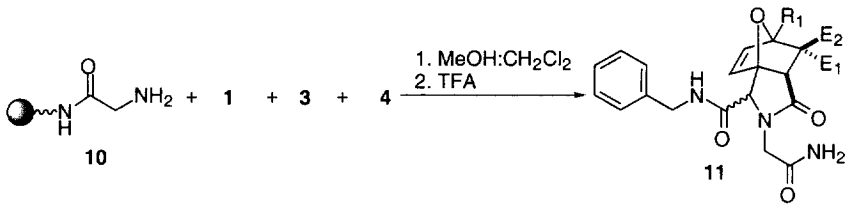


7 8 9

9	Yield	isomer
9a	89%	64:36
9b	75%	60:40
9c	88%	56:44

Adaptability of this reaction to solid phase synthesis was then investigated. Our solid phase synthesis was carried out on an acid labile ArgoGel-Rink resin. Condensation of the resin-bound amine **10**, prepared in two steps from readily available resin, with 10 fold excess of **1**, **3**, and **4** in MeOH:CH_2Cl_2 (2:1) for 36 h afforded, after cleavage with 95% TFA, the cycloaddition product **11** (Scheme 3, Table 2) as a mixture of isomers in high yield. Condensation of furaldehyde **1a** provided the products **11a-c** in high yields and good selectivities, whereas moderate selectivity was observed with 5-methylfuraldehyde **1b**. Commercial availability of a wide range of primary amines, aldehydes and furaldehydes makes this a valuable approach for the preparation of highly diversified combinatorial libraries of tricyclic lactams.

Scheme 3



10 11

Table 2

Entry	R_1	E_1	E_2	Yield %[a]	Isomer Ratio
a	H	CO_2Et	H	95	91:9
b	H	H	CO_2Et	92	89:11
c	H	H	CONH-Bn	88	88:12
d	Me	CO_2Et	H	95	78:22
e	Me	H	CO_2Et	88	77:23
f	Me	H	CONH-Bn	92	88:12

a. The yields are based on the initial loading of the resin and the weight of the isolated product. In some cases final product was purified by flash column chromatography.

In summary, we have described our initial results on the preparation of highly functionalized rigid tricyclic lactams via a tandem 4CC/ IMDA reaction under mild conditions. Extension of this approach to acyclic dienealdehydes and pyrrole aldehydes is underway and the results will be reported in due course.

References and Notes

1. Presented at the 213th ACS National Meeting, San Francisco, CA; April 1997, ORGN 575.

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4. *Solid Phase Synthesis Reviews*: (a) Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. C. *Tetrahedron*, **1997**, *53*, 5643. (b) Combinatorial Chemistry: Synthesis and Application, Wilson, S. R. and Czarnik, A. W., Ed.; Wiley & Sons, Inc. 1997. (c) Balkenhohl, F.; Hunnefeld, C. V. D.; Lansky, A.; Zechel, C. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2288.

General Procedure: **Solution Phase**. Amine (0.25 mmol), isocyanide (0.25 mmol), aldehyde (0.25 mmol), and acid (0.25 mmol), were taken in MeOH (10 mL), and the reaction mixture was stirred at rt for 36 h. Solvent was evaporated and the crude was purified by column chromatography to provide the pure compound.
Solid Phase: Resin-bound amine (0.5g, 0.165 mmole), furaldehyde (1.65 mmol), benzylisocyanide (1.65 mmol) and acid (1.65 mmol) were taken in MeOH:CH_2Cl_2 (2:1, 9 mL) and the reaction mixture was agitated for 36 h. Excess reagents were drained and the resin was washed with MeOH (2x), DMF (2x), MeOH (3x), and CH_2Cl_2 (2x). Treatement of the resin with 95% TFA and removal of the volatile provided the desired compound.

NMR Data for Selected Compounds: Compound **6a**: ^{1}H NMR ($CDCl_3$):1.25 (t, J = 7.2 Hz, 3H), 3.10 (d, J = 3.7 Hz, 1H), 3.45 (dd, J = 4.8, 3.7 Hz, 1H), 4.06 (d, J = 15.0 Hz, 1H), 4.12 (q, J = 7.2 Hz, 2H), 4.13 (s, 1H), 4.41 (d, J = 5.5 Hz, 2H), 4.96 (d, J = 15.0 Hz, 1H), 5.24 (dd, J = 4.8, 1.8 Hz, 1H), 6.29 (dd, J = 5.9, 1.8 Hz, 1H), 6.4 (d, J = 5.9 Hz, 1H), 6.57 (t, J = 5.5 Hz, 1H), 7.14-7.36 (m, 10H). ^{13}C NMR ($CDCl_3$):14.5, 43.9, 46.1, 47.2, 50.7, 61.3, 63.3, 80.2, 91.9, 127,5, 127.8, 127.9, 128.6, 128.8, 134.2, 134.8, 134.9, 137.8, 166.6, 169.9, 174.0. Compound **6b**. ^{1}H NMR ($CDCl_3$):1.26 (t, J=7.2 Hz, 3H), 2.63 (d, J = 9.2 Hz, 1H), 2.94 (d, J = 9.2 Hz, 1H), 3.91 (d, J = 15.4 Hz, 1H), 4.08 (q, 7.2 Hz, 2H), 4.19 (s, 1H), 4.36 (d, J = 5.1 Hz, 1H), 4.87 (d, J = 15.4 Hz, 1H), 5.03 (d, J = 1.8 Hz, 1H), 6.22 (d, J = 5.9 Hz, 1H), 6.30 (dd, J = 5.9, 1.8 Hz, 1H), 7.12-7.32 (m, 10H). ^{13}C NMR ($CDCl_3$):14.2, 43.4, 45.1, 45.5, 49.9, 61.0, 62.1, 81.2, 90.1, 127.27, 127.3, 127.4, 127.5, 128.38, 128.4, 134.0, 135.0, 136.2, 137.7, 166.8, 171.4, 171.7. Compound **6d** (major) ^{1}H NMR ($CDCl_3$):1.25 (t, J = 7.0 Hz, 3H), 1.76 (s, 3H), 3.07 (d, J = 3.7 Hz, 1H), 3.2 (d, J = 3.7 Hz, 1H), 4.09-4.16 (m, 4H), 4.36 (d, J = 5.9 Hz, 1H), 4.85 (d, J = 15.0 Hz, 1H), 6.12 (d, J = 5.9 Hz, 1H), 6.35 (d, J = 5.9 Hz, 1H), 6.62 (t, J = 5.9 Hz, 1H), 7.14-7.34 (m, 10H). ^{13}C NMR ($CDCl_3$):14.5, 18.7, 43.9, 46.3, 52.1, 53.8, 61.3, 63.7, 89.2, 90.7, 127.6, 127.8, 127.9, 128.0, 128.6, 128.7, 134.2, 135.0, 137.7, 138.0, 166.6, 170.2, 174.1. Compound **6d** (minor): ^{1}H NMR ($CDCl_3$):1.26 (t, J = 7.0 Hz, 3H), 1.74 (s, 3H), 3.00 (d, J = 3.7 Hz, 1H), 3.14 (d, J = 3.7 Hz, 1H), 3.99 (d, J = 14.7 Hz, 1H), 4.12 (m, 2H), 4.34 (dd, J = 14.7, 6.2 Hz, 1H), 4.43 (s, 1H), 4.55 (dd, J = 14.7, 6.2 Hz, 1H), 5.10 (d, J = 14.7 Hz, 1H), 6.15 (d, J = 5.8 Hz, 1H), 6.34 (b, 1H), 6.51 (d, J = 5.8 Hz, 1H), 6.7 (b, 1H), 7.15-7.34 (m, 10H). ^{13}C NMR ($CDCl_3$):14.5, 18.7, 43.7, 46.14, 51.9, 54.8, 61.5, 62.3, 89.6, 89.7, 127.5, 127.7, 127.9, 128.5, 128.7. 128.9, 134.4, 135.4, 137.5, 138.5, 165.5, 170.1, 173.8. Compound **9a** (major) ^{1}H NMR ($CDCl_3$): 1.24 (t, J = 7.0 Hz, 3H), 3.00 (d, J = 3.7 Hz, 1H), 3.39 (d, J = 3.7 Hz, 1H), 3.43 (d, J = 12.1 Hz, 1H), 4.12 (q, J = 7.0 Hz, 2H), 4.35 (d, J = 12.1 Hz. 1H), 4.49 (m, 2H), 5.18 (dd, J = 4.8, 1.5 Hz, 1H), 5.96 (s, 1H), 6.28 (dd, J = 5.9, 1.5 Hz, 1H), 6.50 (d, J = 5.9 Hz, 1H), 6.60 (b, 1H), 7.24 - 7.40 (m, 10 H). ^{13}C NMR ($CDCl_3$): 14.3, 43.5, 46.8, 47.3, 51.6, 58.2, 61.1, 80.1, 90.5, 127.2. 127.5, 128.2, 128.4, 128.7, 129.1, 134.3, 134.6, 135.1, 137.9, 169.1, 170.1, 173.0. Compound **9a** (minor) ^{1}H NMR ($CDCl_3$):1.24 (t, J = 7.0 Hz, 3H), 2.93 (d, J = 3.7 Hz, 1H), 3.40 (d, J = 3.7 Hz, 1H), 3.53 (d, J = 11.7 Hz, 1H), 3.83 (d, J = 11.7 Hz, 1H), 4.12 (q, J = 7.0 Hz, 2H), 4.43 (dd, J = 15.0, 5.9 Hz, 1H), 4.56 (dd, J = 15.0, 5.9 Hz, 1H), 5.09 (dd, J = 4.8, 1.5 Hz, 1H), 5.94 (s, 1H), 6.29 (dd, J = 5.9, 1.5 Hz, 1H), 6.41 (d, J = 5.9 Hz, 1H), 7.24 - 7.40 (m, 10 H). ^{13}C NMR ($CDCl_3$):14.3, 43.6, 47.1, 47.5, 51.1, 58.8, 61.2, 80.2, 90.4, 127.2, 127.6. 128.2, 128.4, 128.8, 134.2, 134.3, 134.6, 135.0, 137.7, 168.3, 170.0, 172.7.