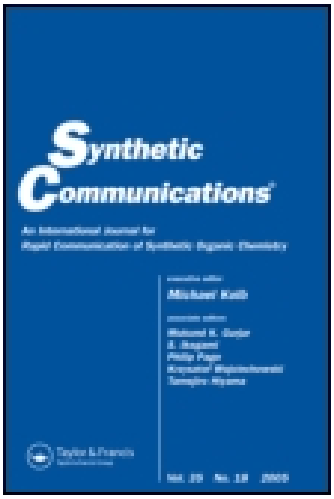

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Domino Reaction for the Synthesis of Highly Functionalized Triazatricyclo[6.2.2.$0^{1,6}$]dodecane

Gunasekar Ramachandran[a] & Kulathu Iyer Sathiyanarayanan[a]
[a] Chemistry Division, School of Advanced Sciences, VIT University, Vellore, India

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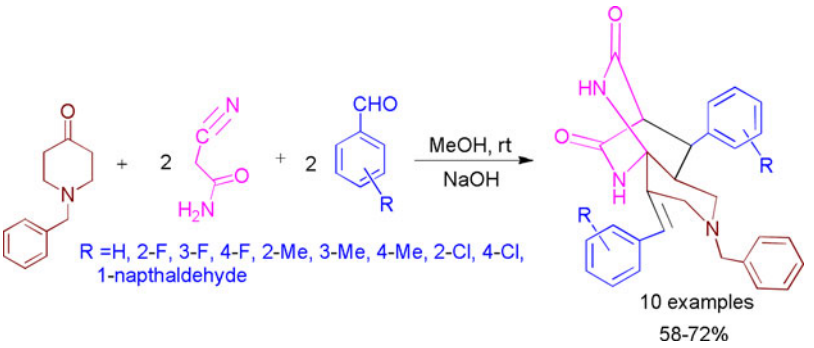
DOMINO REACTION FOR THE SYNTHESIS OF HIGHLY FUNCTIONALIZED TRIAZATRICYCLO[6.2.2.0^{1,6}] DODECANE

Gunasekar Ramachandran and Kulathu Iyer Sathiyanarayanan
Chemistry Division, School of Advanced Sciences, VIT University, Vellore, India

GRAPHICAL ABSTRACT



Abstract *A simple and highly efficient protocol has been developed for the synthesis of triazatricyclo[6.2.2.0^{1,6}]dodecane-9,12-dione (TATCD) derivatives. Use of metal hydroxide catalyst in the presence of protic solvent plays a key role in these reaction transformations. Mechanistic studies specify that the proposed mechanism proceeds only via aldol reaction, condensation, cyclization, and dehydration to form the desired product. This current protocol provides several advantages such as use of a readily available precursor, consumption of less energy, short reaction time, moderate to good yields, and convenient workup.*

Keywords Aldol condensation; cyclization; Domino reaction; triazatricyclo[6.2.2.0^{1,6}] dodecane-9,12-dione

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Address correspondence to Kulathu Iyer Sathiyanarayanan, Chemistry Division, School of Advanced Sciences, VIT University, Vellore 632 014, India. E-mail: sathiya_kuna@hotmail.com

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INTRODUCTION

It is well known that six-membered nitrogen-containing heterocycles are of great pharmacological and biological interest. In particular, lactam motifs possess numerous bioactive molecules implanted in several biological compounds as subunit structures.[1,2] Our long-term goal is to develop cost-effective and environmentally benign synthetic routes to pharmaceutically and industrially useful heterocyclic scaffolds. We have successfully synthesized many such scaffolds using domino reactions.[3] Numerous research groups have exploited the uniqueness of the domino reaction as a powerful tool to explore various therapeutic scaffolds, and this is the most challenging objective in synthetic chemistry.[4,5] The domino reaction has emerged as an effective and a significant method for environmentally benign synthesis.[6] This is because of its good yields, convergence, facile execution, and ability to generate diverse sets of compounds using commercially available starting materials in a single process.[7] In the past few decades, combinatorial synthesis has gained significant attention and it has produced substantial interest in the domino reaction, in which several reactions offer promise in the generation of C=C and C=X bonds in organic chemistry. They serve as useful tools in building fascinating and novel drug-like scaffolds.[8] Synthesis of fused cyclic amide rings has been the most challenging objective in synthetic organic chemistry for the past few decades because such derivatives are considerably important scaffolds for synthesis and drug design as they can directly serve in pharmaceutical research.[9]

RESULTS AND DISCUSSION

We report the synthesis of highly functionalized triazatricyclo[6.2.2.0^{1,6}] dodecane-9,12-dione (TATCD) starting from N-benzylpiperidone (NBP), cyanoacetamide, and aryl aldehydes using sodium hydroxide as catalyst in methanol via a domino reaction (aldol reaction/condensation/cyclization and dehydration). This reaction offers several advantages such as use of low-cost simple precursors, reduced reaction time, less energy, good yield, and easy workup. Initially, we carried out this reaction using similar conditions, as previously reported, to obtain TATCD fluorophore,[10] but unexpectedly, we got a nonfluorescent compound of highly functionalized lactam derivatives. To investigate further, we focused on the mechanism to study the path in which the reaction proceeded and observed that the mechanism followed aldol reaction/condensation/cyclization followed by dehydration to give the desired product. This reaction was more fascinating because it provided access to TATCD possessing two quaternary amino functionalities among four stereogenic centers (Fig. 1). Such an observation is rare, interesting, and quite exciting in organic chemistry.[10,11] Finally, we carried out two reactions, one between **int1** and **int2** (Scheme 1), and the other between **int3** and **int4** (Scheme 2).

In our initial study, we investigated the optimal condition to evaluate the efficiency of the catalyst for this reaction under various conditions. To optimize the reaction conditions, several metal hydroxides were screened in this reaction. When the reaction was performed in the absence of base catalyst, the reaction did not proceed further, but when the reaction was performed using any of the

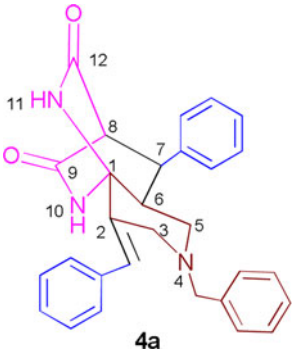
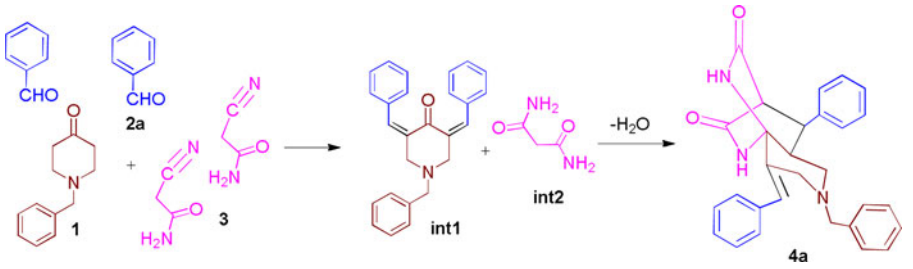
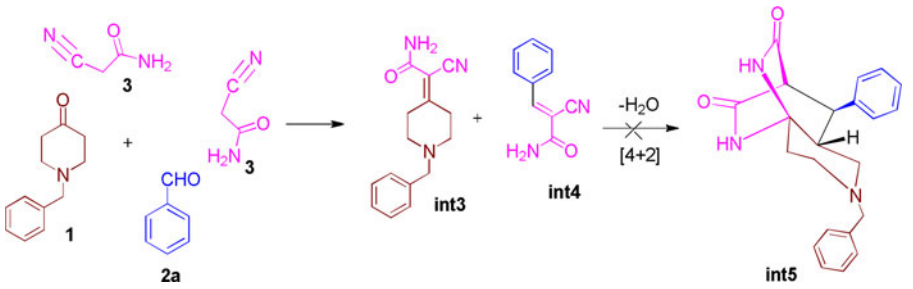


Figure 1. Structure of 2-benzylidene-4-benzyl-7-phenyl-4,10,11-triazatricyclo[6.2.2.0^{1,6}]dodecane-9,12-dione.



Scheme 1. Synthesis of tricyclic dilactam (**4a**) via int1 and int2.

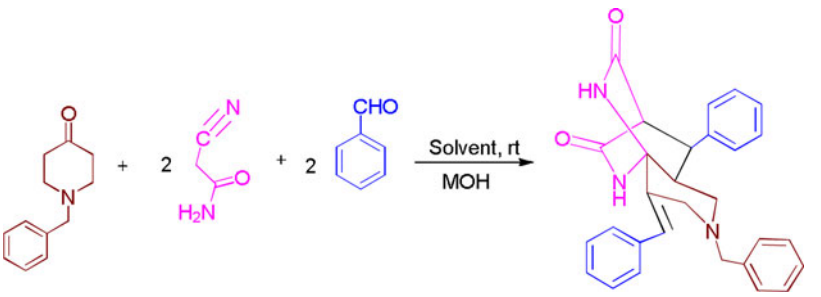


Scheme 2. Synthesis of tricyclic dilactam (**4a**) via int3, int4, and int5.

metal hydroxides, the reaction proceeded to form highly functionalized TATCD. When sodium hydroxide was used as catalyst, we noted that the reaction provided remarkable yield. We carried out the reaction with 0.25 mol% and increased this up to 2 mol% of catalyst to examine further the catalyst efficiency and the required molar percentage of the catalyst to generate excellent yield. When 0.5 mol% of NaOH was used as catalyst, a good yield was observed, whereas it did not further improve the yield significantly when the quantities of catalyst were increased, and thus we used 0.5 mol% of NaOH as catalyst in this reaction.

The solvent was the major factor that influenced the formation of the product and also affected the product yield. Hence, we carried out this reaction with a variety of solvents such as polar protic, aprotic, and nonpolar solvents using 0.5 mol% of NaOH as the catalyst (Table 1, entries 8 and 10–16) to investigate the best solvent suitable for this reaction. We obtained good yields with polar protic solvents such as ethanol, methanol, and isopropyl alcohol (IPA) but the product was not obtained in the absence of solvent, with polar aprotic solvents such as acetonitrile and dichloromethane (DCM), and with nonpolar solvents such as hexane and benzene. Thus, the optimal solvent for these reaction transformations was methanol. The appropriate optimal condition for these reaction transformations was 0.5 mol% of sodium hydroxide as catalyst and methanol as solvent. We also investigated the scope and the limitation of these reactions. To evaluate the generality of this reaction in other systems, the reaction was carried out using a diverse range of aromatic aldehydes under the same conditions. Thus we used both electron-donating group (EDG) and electron-withdrawing group (EWG) of aryl aldehyde substrate for the formation of diverse TATCD derivatives. We obtained TATCD molecule in moderate to good

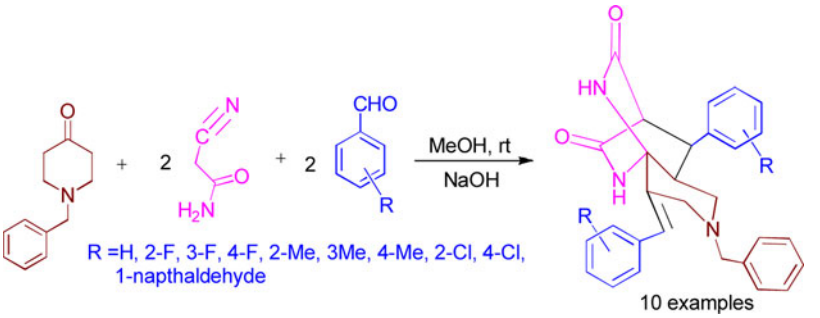
Table 1. Screening of catalyst and solvent effect for the synthesis of TATCD[a]



Entry	Catalyst (mol%)	Solvent (mL)	Yield (%)[b]
1	None	Methanol	—
2	LiOH (1)	Methanol	21
3	LiOH (0.5)	Methanol	—
4	KOH (1)	Methanol	39
5	KOH (0.5)	Methanol	28
6	NaOH (2)	Methanol	71
7	NaOH (1)	Methanol	70
8	NaOH (0.5)	Methanol	70
9	NaOH (0.25)	Methanol	58
10	NaOH (0.5)	None	51
11	NaOH (0.5)	CH_3CN	—
12	NaOH (0.5)	DCM	—
13	NaOH (0.5)	Ethanol	53
14	NaOH (0.5)	IPA	48
15	NaOH (0.5)	Benzene	—
16	NaOH (0.5)	Hexane	—

[a]Reaction conditions: N-benzyl-4-piperidone (10 mmol), benzaldehyde (20 mmol), and cyanoacetamide (20 mmol) at room temperature (30 °C).
[b]Isolated yield.

Table 2. Domino reactions for the synthesis of synthesis of TATCD[a]



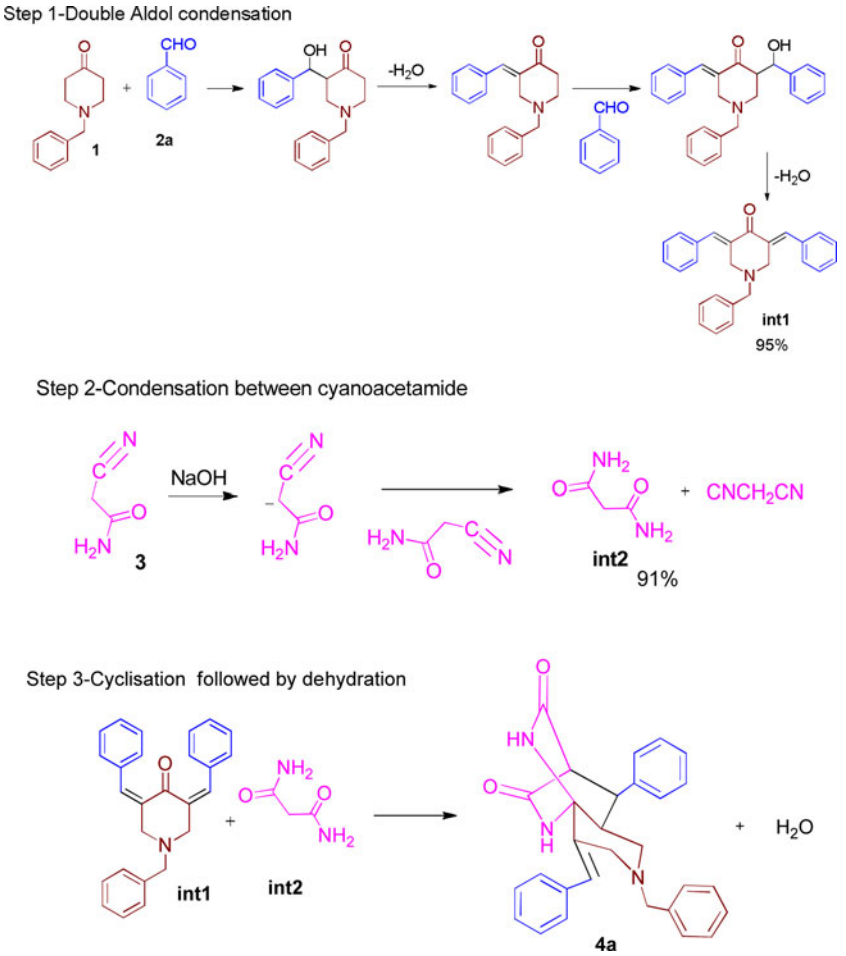
Entry	ArCHO	Product	Yield (%)[b]
1	H	**4a**	70
2	2-F	**4b**	72
3	3-F	**4c**	60
4	4-F	**4d**	68
5	2-Me	**4e**	66
6	3-Me	**4f**	58
7	4-Me	**4 g**	62
8	2-Cl	**4 h**	71
9	4-Cl	**4i**	70
10	1-Napthaldehyde	**4j**	61

[a]Reaction conditions: N-benzyl-4-piperidone (10 mmol), benzaldehydes (20 mmol), and cyanoacetamide (20 mmol) at room temperature (30 °C).
[b]Isolated yield.

yield using either EWG or EDG of aryl aldehyde substrate. The results obtained are summarized in Table 2. Initially, we tried this reaction with other cyclic ketone to synthesize various TATCD moities. Unexpectedly, we obtained dimeric tetracyclic dilactam fluorophores (DTDF).[10] Extensive studies of those DTDF were discussed in our previous report.[10] Initially, we expected that the synthesized TATCD would be a fluorophore motif, but it did not show any fluorescence properties. Hence, we focused on the mechanism of the path in which the reaction proceeded to form TATCD. There are two mechanisms possible for the formation of TATCD (**4**). One possible mechanism is the formation of aldol product in the first step, the second step is the formation of malonamide from the condensation of cyanoacetamide, and the final step is the cyclization of these two intermediates to give the desired product. Another possible mechanism is the formation of two different intermediates of Knoevenagel condensation, which in turn rearrange C=C bond followed by [4 + 2] cycloaddition, subsequently undergoing intramolecular Michael-type addition followed by the attack of aryl aldehyde via aldol condensation to give the desired product.

Thus, to investigate the exact mechanism, we carried out several reactions under optimal conditions. Initially we carried out a few reactions to synthesize aldol product between **1** and **2a** (**int1**) and condensation between two molecules of **3** (**int2**). Similarly, we formed two different Knoevenagel products between **1** and **3** (**int3**) and **2a** and **3** (**int4**) under the same conditions.

Finally, we carried out two reactions, one between **int1** and **int2**; the other between **int3** and **int4**. In the first reaction, we successfully got the expected product (**4a**), whereas in the second reaction we did not get the expected intermediate (**int5**), which could further react with benzaldehyde to give the product **4a**. Thus, from these mechanistic studies, we infer that the mechanism proceeds only via aldol reaction, condensation, followed by cyclization and dehydration to form the desired product (Scheme 3). However, the mechanism for the formation of tetracyclic dilactam fluorophore discussed in the previous report[10] proceeded in another way. Thus, from Scheme 3, it is very clear that the first step involves double aldol reaction between **1** and 2 equivalents of **2a.** The second step is the condensation between two molecules of cyanoacetamide, and finally this condensed intermediate reacts with aldol product obtained in the first step, leading to cyclization and dehydration to yield the final product.



Scheme 3. Most feasible mechanism for the formation of product **(4)**.

CONCLUSION

Herein, for the first time, we report the synthesis of a new series of multifunctionalized TATCD derivatives via a domino reaction using NaOH as catalyst. A wide range of easily available chemicals, namely N-benzyl-4-piperidone, aryl aldehyde, and cyanoacetamide, were employed as substrates. The synthesized TATCD derivatives afford enormous flexibility for additional structural alterations and the synthesized TATCD derivatives are indeed lactam analogs, which are directly useful in medicinal and pharmaceutical chemistry.

EXPERIMENTAL

A dry 100-mL Erlenmeyer flask was charged with N-benzyl-4-piperidone (10 mmol), aromatic aldehydes (20 mmol), cyanoacetamide (20 mmol), sodium hydroxide (0.5 mol%), and methanol (15 mL). The reaction mixture was stirred at room temperature for 30–60 min. The reaction was monitored by thin-layer chromatography (TLC), and after the completion of reaction, the mixture was neutralized using 0.1 N HCl and extracted with DCM (3×20 mL). The crude reaction mixture was purified by column chromatography on silica gel using ethyl acetate/hexane as the eluents. Light creamy powder; yield 70%; mp > 300 °C; R_f 0.67 (60% ethyl acetate/hexane); FTIR (KBr) ν: 3541, 3309, 3045, 2870, 1687 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): 1.63 (s, CH_2, 2H), 1.92 (s, CH, 1H), 1.99 (s, CH, 1H), 2.41 (t, CH_2, 1H), 2.76 (q, CH_2, 1H), 3.94 (s, CH, 1H), 4.04 (s, CH_2, 2H), 6.05 (s, vinylic-H, 1H), 6.98–7.49 (ArH, 15H), 9.43 (s, amide NH, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): 26.36, 28.90, 49.68, 58.39, 70.91, 126.48, 127.68, 128.04, 128.95, 129.08, 129.66, 131.50, 133.35, 137.32 169.60, 169.73 ppm. HRMS: calculated for $C_{29}H_{27}N_3O_2$ ($[M]^+$) 449.2103; found 449.2102.

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SUPPORTING INFORMATION

Supplemental data for this article can be accessed on the publisher's website.

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