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Four-component Domino Reaction Providing an Easy Access to Multifunctionalized Tricyclo[6.2.2.0^{1,6}]dodecane Derivatives

Bo Jiang[a,b], **Chao Li**[a], **Feng Shi**[a], **Shu-Jiang Tu**[*,a,b], **Parminder Kaur**[c], **Walter Wever**[c], and **Guigen Li**[*,c]

[a]School of Chemistry and Chemical Engineering, Xuzhou Normal University, Xuzhou, 221116, Jiangsu, P. R. China

[b]College of Chemistry, Chemical Engineering and Materials, Science, Suzhou University, Suzhou, 215123, Jiangsu, P. R. China

[c]Department of Chemistry and Biochemistry, Texas Tech University, Lubbock, TX 79409-1061. USA

Abstract

A novel four-component domino reaction has been discovered. The reaction is easy to perform simply by mixing four common reactants and Cs_2CO_3 in ethylene glycol under microwave heating. The reaction proceeds at fast rates and can be finished within 15–24 min, which makes work-up convenient. Four stereogenic centers with one quaternary carbon-amino function have been controlled completely. The stereochemistry has been unequivocally determined by X-ray structural analysis. The resulting tricyclo[6.2.2.0^{1,6}]dodecane derivatives are of importance for organic and medicinal research.

Keywords

microwave (MW)-irradiated reaction; multi-component domino reaction; stereochemistry; tricyclo[6.2.2.0^{1,6}]dodecanes; tricyclo[5.2.2.0^{1,5}]undecane

Introduction

Efficient and elegant assembly of complex structures with multiple stereocenters has become an important topic in chemical sciences.[1–4] Multi-component domino reaction has thus emerged as a powerful tool for this purpose in which a series of chemical processes can be controlled in a one-pot operation; it can avoid time-consuming and costly syntheses, tedious work-up and purifications of precursors as well as protection/deprotection of functional groups.[5–6]

In the past several years, we have been engaging in the development of multi-component domino reactions that can provide easy accesses to useful core structures of chemical and pharmaceutical interests.[7–8] Very recently, we discovered a new four-component domino reaction for the synthesis of multifunctionalized quinazoline derivatives.[7a] The reaction is easy to perform simply by mixing readily available starting materials, aromatic aldehyde, cyclopentanone and cyanoacetamide with K_2CO_3 in ethylene glycol under microwave (MW)

*CORRESPONDING AUTHOR: FAX: 86-516-83500065; 806-742-1289.

Supporting Information Available. X-ray structures, experimental details, analytical data and ^{1}H and ^{13}C NMR spectra of all pure products (31 pages) are available free of charge via the Internet at http://pubs.acs.org.

irradiation. This reaction is believed to undergo the tandem formations of two different Knoevenagel intermediates followed by C=C bond rearrangement, [4+2] cycloaddition, intramolecular Michael-type addition and carbonyl addition/elimination reactions.

During continuing this project, we found that when aromatic aldehydes employed in our previous system were replaced by their aliphatic counterparts, the quinazoline derivatives were not generated. Instead, the reaction occurred to another direction to form multi-functionalized tricyclo[6.2.2.0^{1,6}]dodecanes that belong to another family of important scaffolds for organic synthesis and drug design in pharmaceutical sciences.[9] In this communication, we would like to disclose the discovery of this novel four-component domino reaction (Scheme 1).

Results and Discussion

We started this study by subjecting *iso*-butyraldehyde and cycloketones **2a** to the reactions with cyanoacetamide **3** in the presence of K_2CO_3 under microwave (MW) irradiation (Scheme 2).[7a] As described in our previous communication, the original reaction worked best in ethylene glycol at 120 °C. However, in the current aliphatic aldehyde-based system, the product **4a** was only obtained in a yield of 42%. We then decreased the temperature to 80 °C and found the yield can be enhanced to 51% (a similar yield was obtained at 100 °C). Pleasingly, when we utilized one equiv. of Cs_2CO_3 to replace K_2CO_3 as the base additive at this temperature, the yield can be further increased to 73% (Table 1, entry 3).

Under the above optimized conditions, the substrate scope of this reaction was examined by using readily available starting materials. As revealed in Table 1, a range of aliphatic aldehydes are suitable for reacting with various cyclic cycloketones **2** and cyanoacetamide **3** under microwave heating. In addition, the scope of cycloketones **2** was also proven to be remarkable, which include normal cycloketones (**2a** and **2b**) and heteroatom (O, S, and N)-attached cycloketones, such as tetrahydropyran-4-one **2c**, tetrahydrothiopyran-4-one **2d**, *N*-*t*-Boc and *N*-Bn-piperidin-4-one **2e**–**f**. Particularly, the *N*-*t*-Boc-amino cycloketone substrate (**2d**) led to cycloamino products **4l–4o** in which *N*-*t*-Boc functionality was found to be stable under microwave irradiation at 80 °C.

Most functionalities of resulting tricyclo[5.2.2.0^{1,5}]undecane products offer a great flexibility for further structural modifications. These products are indeed lactam analogs that are directly useful for drug design; their rings can be opened for peptide/protein mimetic studies. In fact, after careful hydrolysis of cyano group, a series of special dehydro β-amino acids can be obtained.[10]

Similar to our previous four-component domino process,[7a] the present reaction also showed *the following attractive characteristics*: (1) fast reaction rates which enable the reaction to be completed within 15–24 min, which can save energy and manpower for future industrial production; (2) the environmentally friendly process in which water is the major by-product; (3) the convenient work-up which only needs simple filtration since the products directly precipitate out after the reaction is finished and when its mixtures are diluted with cold water; (4) readily available starting materials of aldehydes, cycloketones and cyanoacetamide. Moreover, all stereogenetic centers and geometry have been completely controlled including a quaternary amino center attached on the lactam ring. *The present reaction is among a very few cases in organic chemistry in which multiple-rings, four stereocenters and geometry can be controlled in a one-pot intermolecular manner*.

X-ray diffraction of single crystals of tricyclo[5.2.2.0^{1,5}]undecanes **4a** has been unambiguously determined.[11] The structural elucidation and attribution of relative stereochemistry of all products have been fully characterized by ^{1}H- and ^{13}C-NMR and other analyses.

The mechanism of this domino reaction is proposed as shown in Scheme 3. Similar to the aromatic aldehyde-based reaction, the initial steps involve Knoevenagel condensations to generate two individual Knoevenagel intermediates **A** and **B**. However, these two intermediates do not occur through [4+2] cyclic addition. Instead, they undergo α,β-unsaturated addition in which **A** is added onto **B** to give intermediate **C**; this would be attributed to the fact that β-alkyl intermediates **B** are less stable (more partially separated charges exist) than its β-aryl counterparts, which favors Michael-type addition by enolate anion under the basic condition. The next step involves an intramolecular tandem process of another Michael-type addition and carbonyl addition to form intermediate **D** to form the key tricyclic skeleton. The subsequent amide hydrolysis and decarboxylation result in the final product **4**. It seems that Cs_2CO_3 is more effective than K_2CO_3 by acting as the base for dehydration and decarboxylation during this domino process to drive the reaction toward the formation of tricyclo[5.2.2.$0^{1,5}$]undecane product.

In conclusion, a novel four-component domino reaction and the unprecedented challenging mechanism have been discovered and proposed, respectively. This reaction is very simple and easy to perform simply by mixing four common reactants and Cs_2CO_3 in ethylene glycol under microwave irradiation. A wide range of readily available commercial chemicals of aliphatic aldehydes, cycloketones and cyanoacetamide can be employed as substrates. This domino method provides a rapid access to highly functionalized tricyclo[5.2.2.$0^{1,5}$]undecanes (tricyclic lactams) with the complete control of stereo and regiochemistry in which four stereogenic centers with one quaternary carbon-amino attachment. The stereochemistry has been unequivocally determined by X-ray structural analysis. The asymmetric versions of the present and previous new domino reactions are being studied in our laboratories.

Experimental Section

General

Microwave irradiation was carried out with microwave oven Emrys Creator from Personal Chemistry, Uppsala, Sweden.

Example for the synthesis of **4a**: **11-Amino-6-isopropyl-8-oxo-9-azatricyclo[5.2.2.$0^{1,5}$] undec-10-ene-10-carbonitrile** (**4a**)

Microwave Heating—*i*-Butyraldehyde (**1a**, 2.2 mmol, 0.16 g, 1.1 equiv.) was introduced in a 10-mL Emrys™ reaction vial, cyclopentanone (**2a**, 2.0 mmol, 0.17 g, 1.0 equiv.) and cyanoacetamide (**3**, 4.0 mmol, 0.34g, 2.0 equiv.) were then successively added, followed by the catalyst Cs_2CO_3 (2 mmol, 0.65g, 2 equiv.) and ethylene glycol (1.5 mL). Subsequently, the reaction vial was capped and then pre-stiring for 20 second. The mixture was irradiated (initial power 50 W and maximum power 100 W) at 80 °C until TLC (petroleum ether: acetone 3:1) revealed that conversion of the starting material **1a** was complete (15 min). The reaction mixture was then cooled to room temperature and then diluted with cold water (40 ml). The solid product was collected by Büchner filtration and was purified by flash column chromatography (silica gel, mixtures of petroleum ether / acetone, 10:1, v/v) to afford the desired pure products **4a** as white solid (Mp: > 300 °C).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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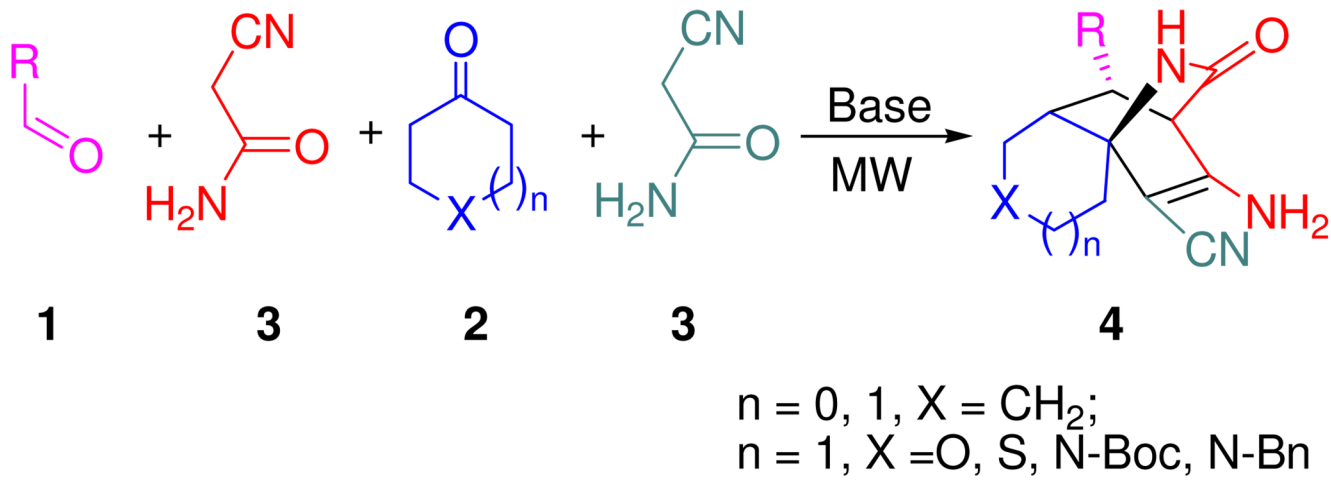
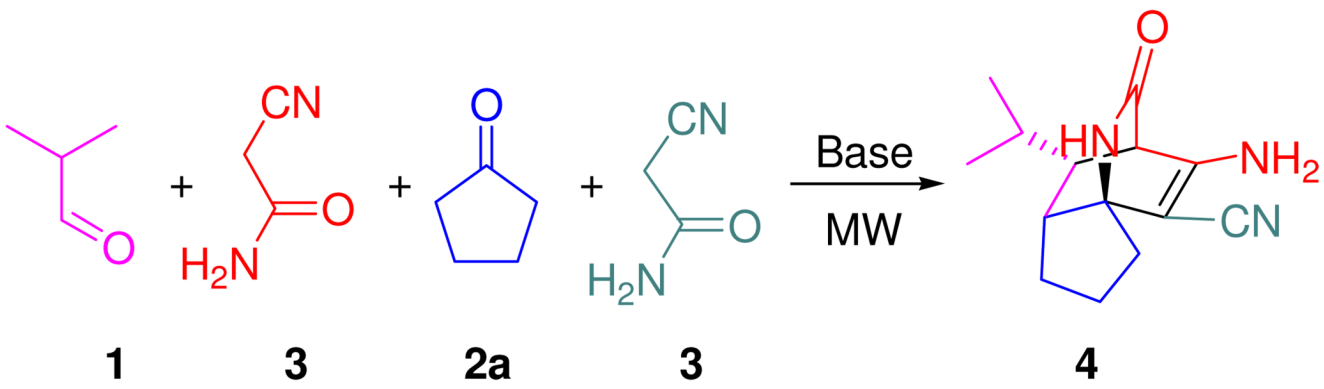
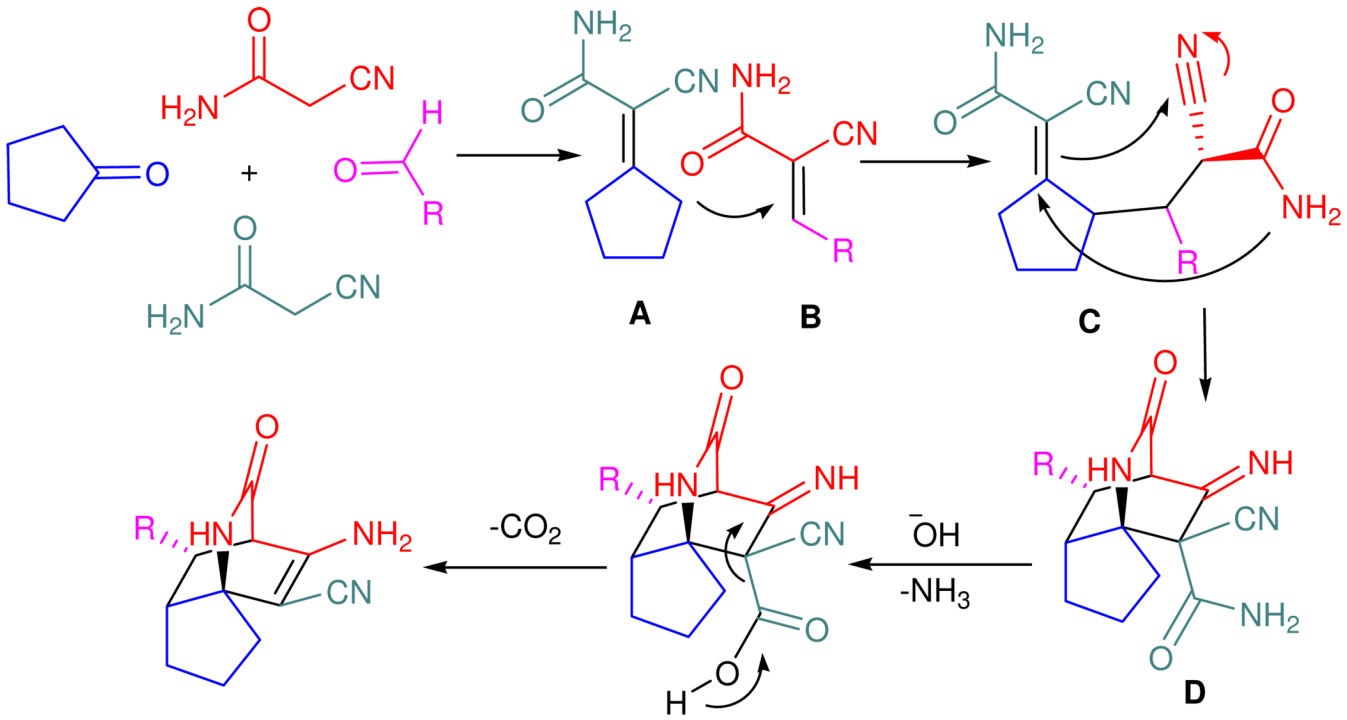
10. (a) Trost BM, Dake GR. J. Am. Chem. Soc 1997;119:7595–7596. (b) Chen D, Guo L, Kirtane S, Cannon JF, Li G. Org. Lett 2005;7:921–924. [PubMed: 15727475]
11. Single crystals of product **4a** were obtained *via* careful evaporation of co-solvent of DMF and ethanol solvent. For crystal data, see Supporting Information.



Scheme 1.
The four-component domino reaction



Scheme 2.
The four-component domino reaction of **1** with **2a** and **3**



Scheme 3.
The reasonable mechanism of formation of tricyclo[5.2.2.0^{1,5}]undecanes

Table 1

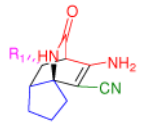
Optimization of reaction conditions

Entry	Base	T / °C	Time / min	Yield /%[a]
1	K_2CO_3	120	20	47
2	K_2CO_3	80	16	51
3	Cs_2CO_3	80	15	73

[a]Isolated yield

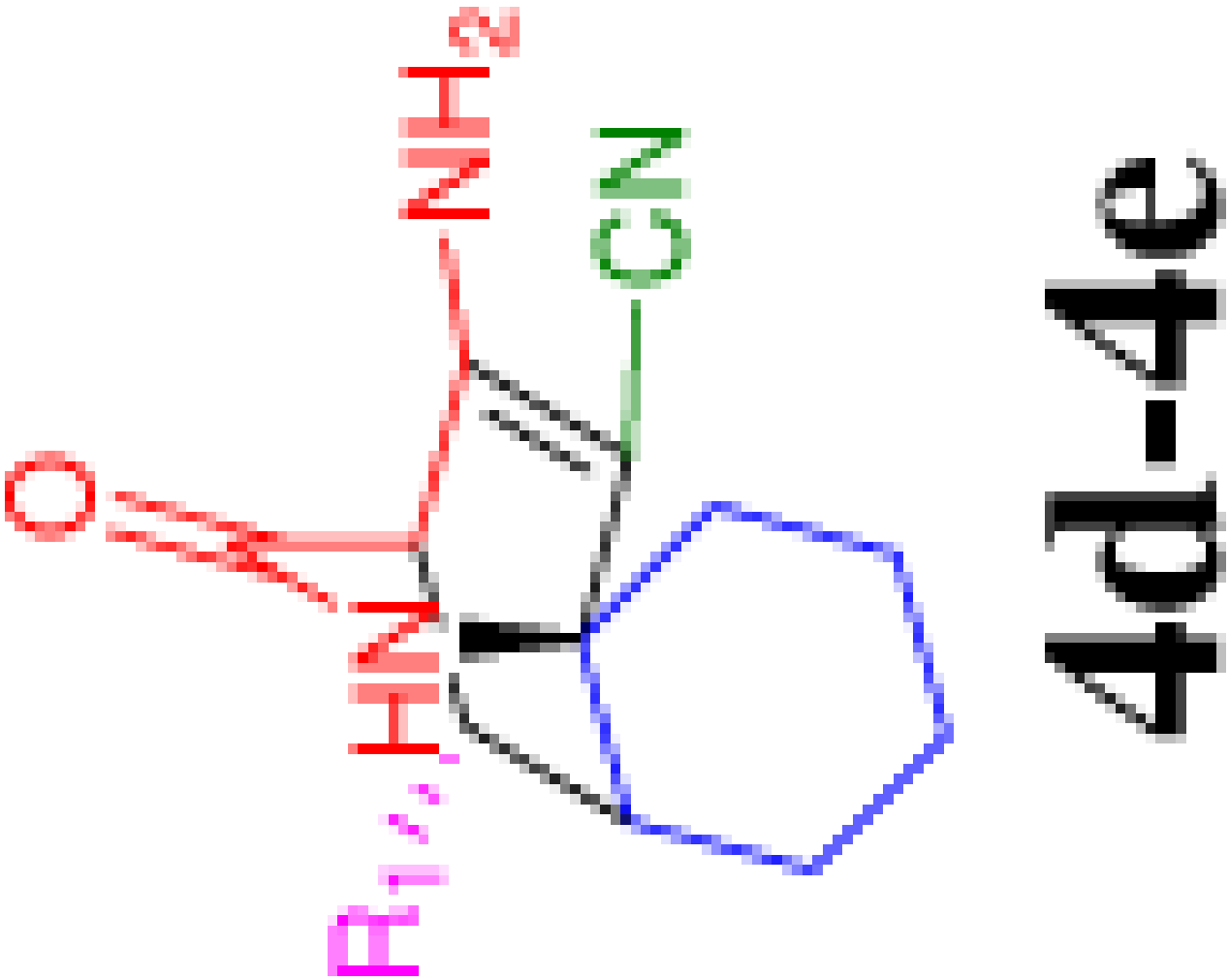
Table 2

ne Derivatives **4**[a]

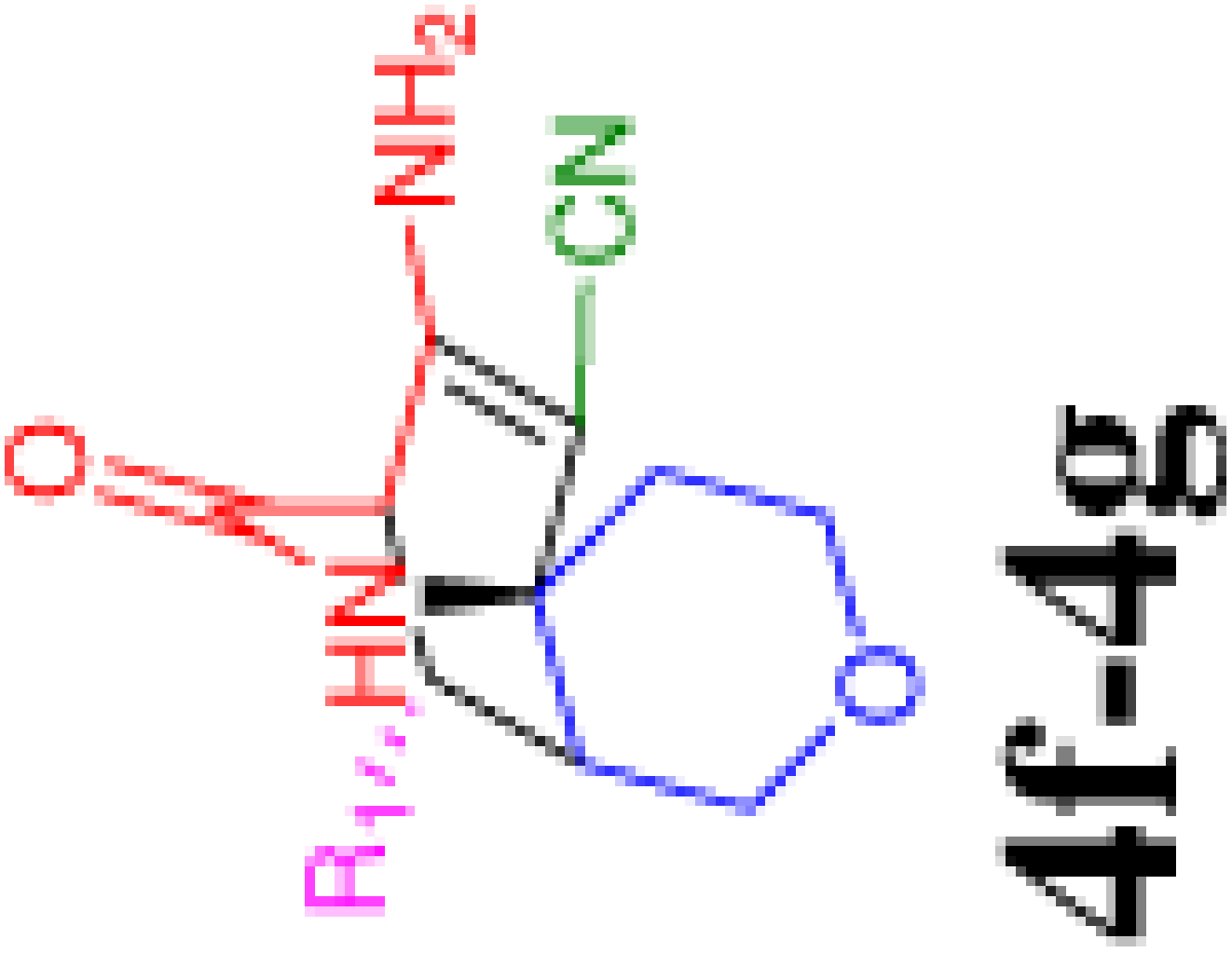
	Product 4[b]	R =	Time / min	Yield[b] /%
2a		**4a**, *i*-Propyl	15	73
2a		**4b**, *sec*-Butyl	16	65
2a		**4c**, *i*-Butyl	22	61

4a-4c

Product 4[b]	R =	Time / min	Yield[b] /%
2b	**4d**, *i*-Propyl	16	67
2b	**4e**, Cyclohexyl	24	49

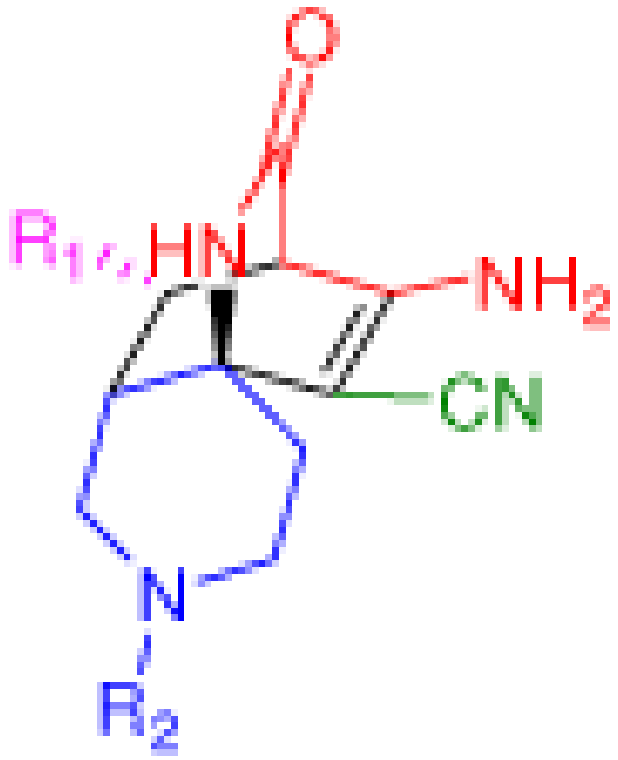


Product 4[b]	R =	Time / min	Yield[b] /%
2c	**4f**, *i*-Propyl	20	74
2c	**4g**, *i*-Butyl	22	58



	Product 4[b]	R =	Time / min	Yield[b] /%
2d		**4h**, *i*-Propyl	18	70
2d		**4i**, sec-Butyl	18	65
2d		**4j**, *n*-Propyl	22	50
2d		**4k**, Cyclohexyl	24	52

4h-4k

	Product 4[b]	R =	Time / min	Yield[b] /%
2e		**4l**, *i*-Propyl	18	67
2e		**4m**, *sec*-Butyl	20	63
2e		**4n**, *i*-Butyl	20	60
2e		**4o**, *i*-Pentyl	24	54
2f		**4p**, *i*-Propyl	18	66

4l-4p

2e, R_2 = Boc

2f, R_2 = Bn

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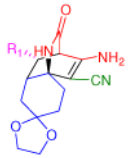
	Product 4[b]	R =	Time / min	Yield[b] /%
2g		**4q**, *i*-Propyl	18	70
2g		**4r**, *sec*-Butyl	20	63
2g		**4s**, *i*-Pentyl	22	58

4q-4s

glycol, microwave heating.