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Iodine-Catalyzed Microwave-Induced Multicomponent Aza-Diels Alder [4+2] Cycloaddition Reaction: A Versatile Approach Towards Bicyclo-[2,2,2]-Octanones

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Abstract

Molecular iodine-catalyzed microwave-assisted one-pot three components aza-Diels-Alder reaction has been investigated. This method has been used for an efficient synthesis of 2-azabicyclo-[2, 2, 2]-cyclooctanones.

Keywords: Aza-diels-alder; Microwave chemistry; Azabicycle; Keto-Enol tautomerization; Alkaloids

Introduction

The Aza-Diels-Alder reaction has served as one of the most promising tools for the synthesis of bicyclic nitrogen-containing heterocyclic scaffolds of naturally occurring biologically active products [1-12]. The reaction of various aromatic amines, aldehydes and enones provides a viable route for the synthesis of bicycle-[2,2,2]-octanes in the presence of specific catalyst. This ring has serve as an important precursor for natural product synthesis and has immense synthetic applications. The 2-azabicyclo-[2,2,2]-octane skeleton is found in a variety of natural products, particularly the Iboga family of alkaloids [13,14]. The imine derived in situ acts as a dienophile in this reaction. The application of various Lewis and Bronsted acids has been well documented in the literature to promote this reaction. However, many Lewis acids are not environmentally benign and are corrosive in nature. Imines are also not well tolerated in presence of these acidic conditions.

In connection with our studies on molecular iodine-catalyzed reactions, we describe herein a versatile method for the synthesis of various bicyclic nitrogen-containing heterocycles by a three component aza-Diels-Alder reaction [15-24].

Experimental Section

General

Melting points were determined in a Fisher Scientific electrochemical Mel-Temp* manual melting point apparatus (Model 1001) equipped with a 300°C thermometer. FT-IR spectra were recorded on a Bruker Alpha Modular Platinum-ATR FT-IR spectrometer with OPUS software, using the samples directly (neat) without making pallets. 1H-NMR (600 MHz) and 13C-NMR (150 MHz) spectra were obtained at room temperature with Bruker superconducting UltrashieldTM Plus 600 MHz NMR spectrometer with central field 14.09 Tesla, coil inductance 89.1 Henry and magnetic energy 1127.2 kJ using $CDCl_3$ as solvent. Iodine (reagent grade,) 98%) purchased from Sigma-Aldrich Corporation was used. All other chemicals were purchased from Sigma-Aldrich Corporation (analytical grade). Throughout the project solvents were purchased from Fisher-Scientific. Deionized water was used for the preparation of all aqueous solutions. The spectral data for the few of endo adducts are as follows:

2, 3- Diphenyl-2-azabicyclo[2.2.2]octane-5-one(4a): ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.35-7.30 (2 H, m), 7.24-7.20 (2 H, m), 7.20-7.10 (2 H, m), 6.65-6.63 (2 H, m), 6.53-6.52 (2 H, m), 4.71 (1 H, d, J=2.3 Hz), 4.48 (1 H, t, J=3.1 Hz), 2.63 (1 H, q, J=3.0 Hz), 2.34 (1 H, dd, J=1.8, 18.7 Hz), 2.19-2.18 (1 H, m), 1.84-1.83 (1 H, m), 1.65-1.49 (2 H, m); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 16.4 (CH_2), 26.0 (CH_2), 42.3 (CH_2), 48.2 (CH), 51.0 (CH), 62.4 (CH), 113.1 (CH), 117.7 (CH), 126.2 (2 CH), 127.4 (2 CH), 128.4 (2 CH), 129.3 (2 CH), 140.1 (C), 148.2 (C), 213.6 (C).

2-(4-methoxyphenyl)-3-phenyl-2-azabicyclo[2.2.2]octan-5-one (4b): ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.36-7.19 (5 H, m), 6.67-6.65 (2 H, m), 6.49-6.46 (2 H, m), 4.63 (1 H, d, J=1.7 Hz), 4.37-4.36 (1 H, m), 3.62 (3 H, s), 2.70 (1 H, qt, J=2.9 Hz), 2.30 (1 H, dd, J=1.8 Hz, 16.7 Hz), 2.23-2.10 (1 H, m), 1.84-1.78 (1 H, m), 1.78-1.53 (1 H, m); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 16.3 (CH_2), 26.3 (CH_2), 41.9 (CH_2), 48.9 (CH), 51.1 (CH), 55.6 (OCH_3), 62.7 (CH_3), 114.3 (CH), 114.8 (2 CH), 126.2 (2 CH), 127.3 (2 CH), 128.8 (2 CH), 140.4 (C), 142.7 (C), 52.2 (C), 213.9 (C).

3-(4-flurophenyl)-2-(4 methoxyphenyl)-2-azabicyclo[2.2.2]octan-5-one(4c): ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.32-7.30 (2 H, m), 7.01-6.97 (2 H, m), 6.67-6.65 (2 H,m), 6.64 (2 H, m) 4.61 (1 H, brs) 2.69 (3 H, s), 2.69-2.65 (2 H, m), 2.55-2.53 (1 H, m), 2.50 (1 H, dd, J=1.8, 18.7 Hz), 2.19-2.13 (1 H, m), 1.84-1.79 (1 H, m), 1.66-1.55 (1 H, m); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 16.3 (CH_2), 6.4 (CH_2), 41.9 (CH_2), 49.1 (CH), 51.1 (CH), 55.6 (OCH3), 62.1 (CH), 114.4 (CH), 114.9 (CH), 115.6 (CH), 115.6), 115.8 (CH), 127.8 (2 CH), 127.9 (2 CH), 142.5 (C), 152.2 (C), 161.3 (C), 163.0 (C), 214.0 (C).

2-(4-methoxyphenyl)-3-(p-tolyl)-2-azabicyclo[2.2.2]octan-5-one(4d): ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.23-7.22 (2 H, m), 7.11-7.10

(2 H, m), 6.67-6.65 (2 H, m), 6.49-6.47 (2 H, m), 4.59 (1 H, brs), 4.35 (1 H, t, J=2.3 Hz), 3.62 (3 H, s), 2.68 (1 H, t, J=3.1 Hz), 2.65 (1 H, t, J=3.1 Hz), 2.55 (1 H, q, J=2.9 Hz), 2.31 (1 H, d, J=1.7 Hz), 2.28 (3 H, s), 2.21-2.15 (1 H, m), 1.82-1.77 (1 H, m), 1.69-1.64 (1 H, m); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 16.4 (CH_2), 21.1 (CH_3), 26.3 (CH_2), 41.9 (CH_2), 48.9 (CH), 51.2 (CH), 55.7 (OCH_3), 62.5 (CH), 114.3 (2 CH), 114.8 (2 CH), 126.2 (2 CH), 129.5 (2 CH), 137.0 (C), 137.0 (C), 142.8 (C), 152.0 (C), 214.1 (C).

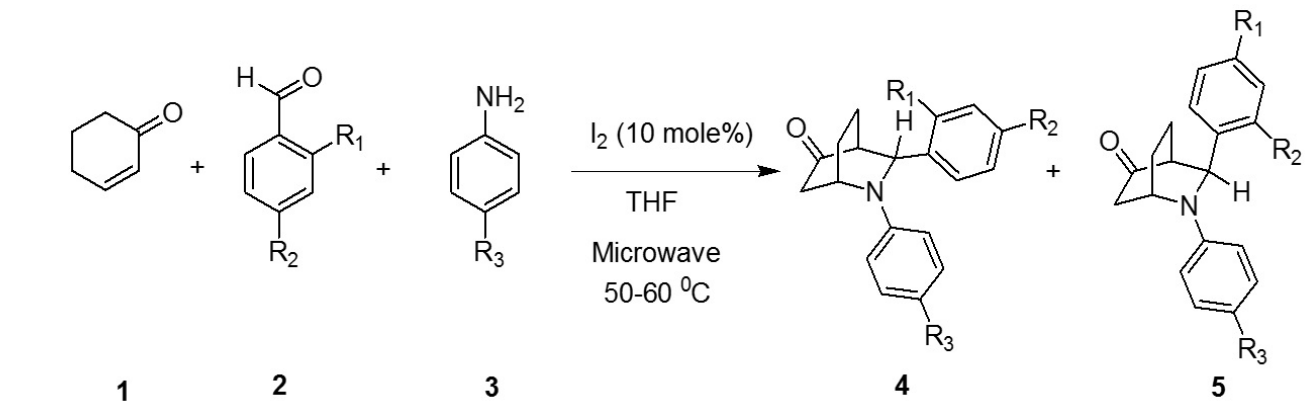
Results and Discussion

At the beginning of this investigation, we attempted to optimize the conditions for the aza-Diels-Alder reaction using aromatic aldehydes (1), amines (2) and cyclohexenone (3) in various solvents under conventional heating. The reaction of equimolar proportion of aniline (1 mmol), benzaldehyde (1 mmol) and cyclohexenone (1 mmol) was investigated in the presence of 10 mol% of molecular iodine in different solvents; e.g., THF, DCM, Ethanol, Toluene, Benzene, and DME with various rage of temperature (Scheme 1, Table 1).

Entry	Solvent (s)	Temperature (°C)	Method (s)	Yield (s)
1	Ethanol	65-70	Conventional heating	0
2	Methanol	55-65	Conventional heating	0
3	Dichloromethane	35-40	Conventional heating	0
4	Benzene	75-80	Conventional heating	Trace
5	Toluene	100-110	Dean Stark	10
6	Xylene	100-140	Dean Stark	10
7	Dimethyl Formamide	100-140	Conventional heating	20

Table 1: Solvent optimization for [4+2] Aza-Diels-Alder reaction under conventional thermal condition.

The reaction does not proceed well under these conditions. Either decomposition or charring of the starting materials was observed. Under these conditions, a very poor reaction occurred in DMF, xylene and toluene. The reaction was conducted without iodine and as usual, no desired products were formed. However, microwave-induced reaction of the same reaction mixtures in DMF and in the presence of 10 mol% of molecular iodine gave products with high stereochemical control of diastereoselectivity (endo-exo ratio) in reasonably good yield [25-32]. After the realization of successful reaction conditions, this method was extended to various aromatic aldehydes, amines, and cyclohexenone in order to synthesize 2,3-diaryl- substituted nitrogen-containing bicyclic compounds.



Scheme 1: One-pot three-component microwave-induced molecular iodine-catalyzed Aza-Diels-Alder Reaction.

The results in Table 2 indicate that the reaction with monocyclic amines affords the endo adduct as the major product. The yield of the products was mainly dependant on the groups present in the aromatic systems. The inductive effects (+I and –I effects) and the size of the groups influenced the ratio of the products. Electron-donating groups (for example, methoxy and methyl) at the para-position of the aromatic ring of aldehydes and amines favored the formation of the endo products.

Molecular iodine is an environmentally benign and very economical catalyst and possesses diverse catalytic activities in the field of organic synthesis.

Iodine has a strong ability to co-ordinate with the oxygen atoms of the cyclic enones and this process accelerates the keto-enol tautomerization. This process is obligated to shift the equilibrium toward the enol side (cyclohexadienolate) which acts as the diene component in the reaction. Aldimines works as the dienophile. The reaction between this diene and dienophile gives the product. In a representative procedure, benzaldehyde (1 mmol), aniline (1 mmol) and cyclohexenone (1 mmol) in DMF (2 mL) were taken in a microwave vial and 10 mol% of molecular iodine was added. The vial was placed in microwave reactor and irradiated at 300 W at 60°C. The reaction preceded well and produced the product in good yield. The imines were formed in the reaction mixture from the reaction of monocyclic aromatic aldehydes and primary aromatic amines. The ratio of the products was calculated from the ^{1}H NMR spectrum of the crude reaction mixture after extraction. The isomeric compounds were purified by column chromatography over silica gel. The structures of the desired products were confirmed on the basis of spectroscopic (^{1}H NMR, ^{13}C NMR, DEPT NMR, and IR) data of the pure compounds.

S.N.	Aldehyde		Amine	4/5 (endo/exo)[a]	Time (min)	Solvent	Temperature	Yield[b] (%)
	R1	R2	R3					
1	H	H	H	60/40	35	THF	50	90
2	H	H	OMe	80/20	35	THF	45	78
3	F	H	OMe	90/10	40	DCM	30	80
4	CH_3	H	OMe	70/30	40	DCM	30	80
5	OMe	OMe	OMe	70/30	50	THF	55	80
6	H	H	CH_3	75/25	25	THF	60	85
7	CH_3	CH3	2 OMe	65/35	40	THF	45	82

Table 2: I_2-Catalyzed microwave-induced synthesis of 2-Azabicyclo-[2,2,2]-octan-5-ones [a]endo/exo ratio were calculated based on ^{1}H-NMR spectra of the crude reaction mixtures. [b]isolated yield.

Conclusion

In conclusion, we have identified molecular iodine-catalyzed microwave-mediated one-pot three component aza-Diels-Alder process for the preparation of 2-azabicyclo-[2 2 2]-octa-5-ones. This reaction is simple and important products are obtained within a very short time.

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