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A facile microwave assisted synthesis of spiro-1,3-oxazines from *N*-(2-(cyclohex-1-en-1-yl)ethyl)amides

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Abstract: A mild and efficient methodology has been developed for the synthesis of spiro-1,3-oxazine derivatives by the microwave assisted cyclization of *N*-2-(1'-cyclohexenyl)ethyl-acetamides/benzamides. The reaction was catalyzed by *in situ* generated trimethylsilyl iodide and featured by its very short reaction time. The starting materials were easily obtained by the condensation of substituted acetic/benzoic acids with 2-(1'-cyclohexenyl)ethyl amine.

1,3-Oxazine nucleus is one of the privileged heterocyclic motifs of remarkable pharmacological importance.[1] Both natural and synthetic compounds containing 1,3-oxazine show a wide range of biological activities like analgesics,[2] antibacterial,[3,4] antifungal,[3] anti-malarial,[5] anti-anginal,[6] antihypertensive,[7] acetylcholine esterase inhibition,[8] anti-arthritis,[9] anti-tubercular,[10,11] antitumor,[12] antiviral[13] etc. Efavirenz (**1**),[14] the anti-HIV drug and PA-824 (**2**),[15] an experimental anti-tuberculosis drug contains substituted 1,3-oxazine framework in their backbone. Recently, 1,3-oxazine derivatives were used in molecular switches,[16] cyanide detectors,[17] stimulus responsive quantum dots[18] etc. Besides, those compounds are also used as intermediates in the synthesis of a broad range of heretocyclic compounds[19] and polymers.[20] On the other hand, spirocyclic frameworks are found in a number of different biological as well as industrially important compounds.[21] Spiro-1,3-oxazines are also well known for their photochromic properties.[22]

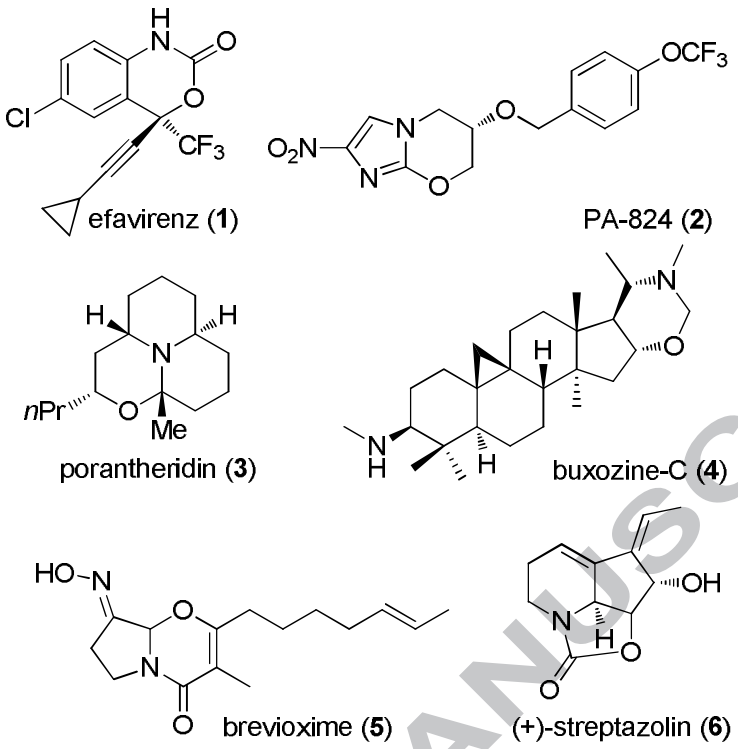
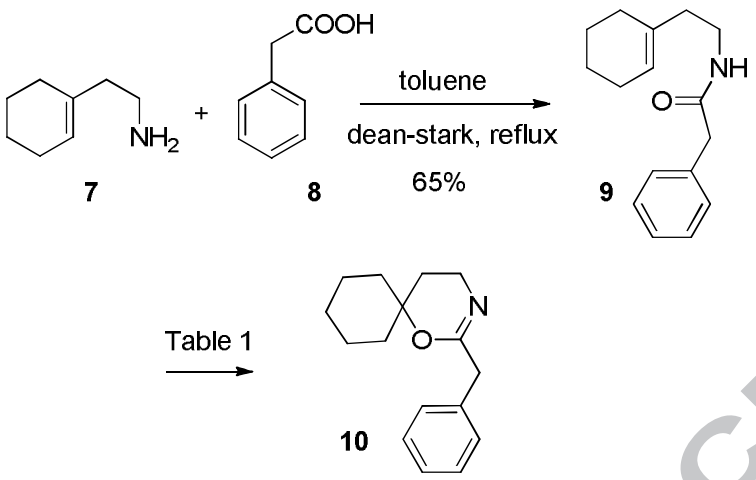


Figure 1: Representative example of 1,3-oxazine containing bioactive compounds.

A number of different methodologies have been developed for the synthesis of 1,3-oxazines.[23,24] While classical methods of condensation of 3-aminopropanol with aldehydes or ketones are widely used,[23b-e] several others like acid or base catalyzed cyclization of *N*-(3-oxopropyl)amides or *N*-(3-hydroxypropyl)amides,[23f-j] insertion of carbon monoxide into N-O bond of isoxazolidines,[23k] reaction of active methylenes with chloroalkyl isocyanates,[23l] cycloaddition of heterocumulenes with vinyl oxetanes,[23m] amidoalkylation of the terminal olefins,[23n] Pd(0)-catalyzed cyclization of γ-allylbenzamides[24] etc. are also known. Although there are many methods for the synthesis of 1,3-oxazines, only a few examples of preparation of spiroxazines are reported.[25] So, development of a versatile, mild and efficient method of the synthesis of 1,3-oxazines, especially spiro-1,3-oxazines, is still important. In this context, we report herein the synthesis of spiro-1,3-oxazines by cyclization of *N*-2-(1'-cyclohexenyl)ethyl-acetamides in the presence of *in situ* generated TMSI under microwave irradiation. Trimethylsilyl iodide (TMSI) is well known for its potential as an effective reagent in various organic reactions.[26]

In continuation of our research work in the synthesis of isoquinoline alkaloids,[27] we were interested to prepare 1-benzylisoquinoline by cyclization of *N*-(2-(cyclohex-1-en-1-yl)ethyl)-2-phenylacetamide (**9**). For this purpose, compound **9** was prepared by the condensation of 2-cyclohexynylethyl amine (**7**) with phenylacetic acid (**8**) (Scheme 1). Generally the formation of amide from acid and amine requires drastic conditions or presence of a catalyst. But in this example the compound **9** could easily be prepared by refluxing a mixture of **7** and **8** in toluene while using a Dean-Stark apparatus to remove the water formed during the reaction. Now, it was known that a phosphorous oxychloride ($POCl_3$)-mediated Bischler–Napieralski type cyclization of **9** provided 3,4,5,6,7,8-hexahydro-1-benzylisoquinoline. For a milder alternative trimethylsilyl chloride (TMSCl) was selected as a catalyst. When a mixture of **9** and TMSCl was refluxed in CH_3CN for 6 h (Entry 1, Table 1), the reaction produced a colourless solid compound after purification. A detailed spectroscopic analysis of the compound showed that spiro-1,3-oxazine **10** was produced instead of isoquinoline. The structure of the compound was confirmed by ^{1}H and ^{13}C NMR analysis. In the ^{13}C spectra there was a quaternary carbon peak at 74.7 ppm which suggested the existence of an oxygenated carbon centre of spiro-oxa skeleton. The mass spectral data also corroborated the deduced structure. To improve the yield the reaction was carried out using TMSBr and TMSI, prepared *in situ* from TMSCl by the addition of KBr and KI, respectively (Entries 2-3, Table 1). It was observed that the best yield of the product (62%) was obtained when TMSI was used. The best solvent was found to be acetonitrile[26a] and other solvents like chloroform, dichloromethane, toluene, or water gave very low yield of the product (Entry 4-7, Table 1). In the absence of TMSCl the reaction failed to produce any products. For further improvement the reaction was carried out under microwave heating condition (Entries 8-9, Table 1). In this context, it is to be noted that the microwave irradiation often leads to the dramatic acceleration of the rate of the reaction along with the increased products yields due to the direct absorption of microwave energy by the reactive species.[28] In the studied example, the reaction was complete within 1 minute with very good yield (83%) under microwave irradiation (Entry 9, Table 1).



Scheme 1. Synthesis of *N*-2-(1'-cyclohexenyl)ethyl-2-phenylacetamide (**9**) and it's cyclization

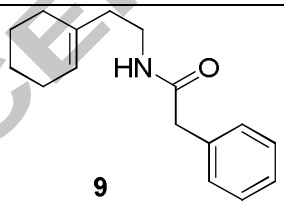
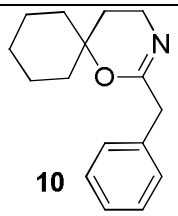
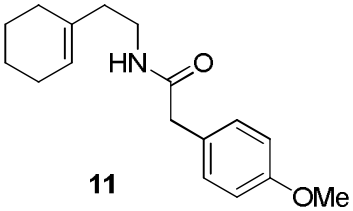
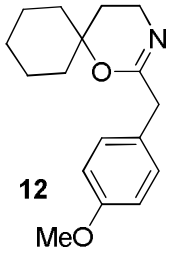
Table 1. Optimization of the spirocyclization reaction condition.

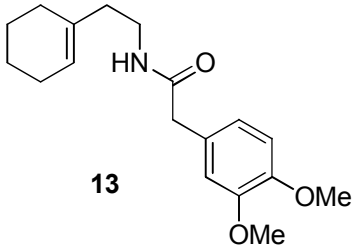
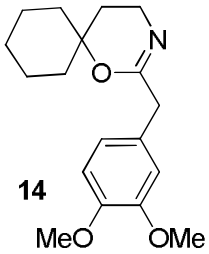
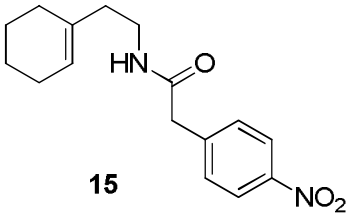
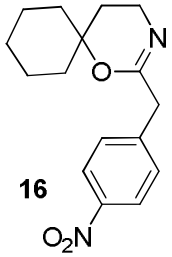
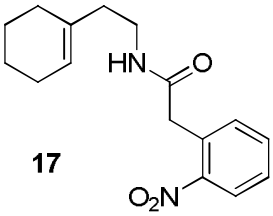
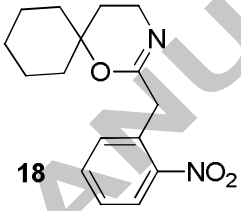
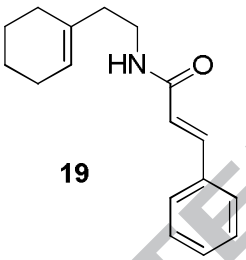
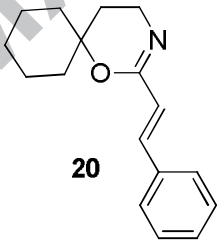
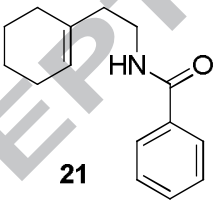
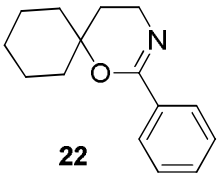
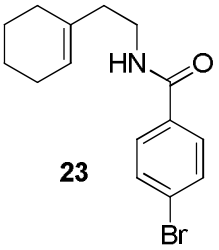
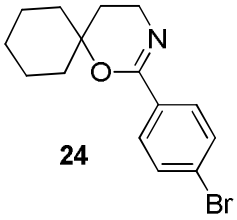
Entry	Reagents[a]	Solvents	Conditions	Time	Yield (%)[b]
1	TMSCl	CH_3CN	100 °C	6 h	40
2	TMSCl-KBr	CH_3CN	100 °C	12 h	43
3	TMSCl-KI	CH_3CN	100 °C	6 h	62
4	TMSCl-KI	$CHCl_3$	100 °C	6 h	35
5	TMSCl-KI	CH_2Cl_2	100 °C	8 h	30
6	TMSCl-KI	Toluene	100 °C	8 h	33
7	TMSCl-KI	H_2O	100 °C	8 h	30
8	TMSCl-KI	CH_3CN	μW, 100 °C	10 min	83
9	**TMSCl-KI**	**CH_3CN**	**μW, 80 °C**	**1 min**	**83**

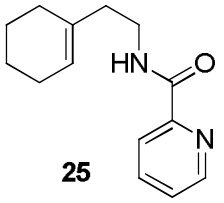
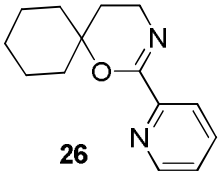
[a]1.5 equivalents of each of the TMSCl and potassium salts were used.
[b]Yields refer to isolated yield of the products.

After optimization of the conditions,[29] the applicability of the reaction towards different substrates was studied. *N*-2-(1'-cyclohexenyl)ethyl-2-(4-methoxyphenyl) acetamide (**11**) was prepared by the condensation of **7** and 4-methoxyphenylacetic acid. A cyclization of **11** under microwave heating condition produced the corresponding spiroxazine derivative **12** in 86% yield. It has to be noted that the reaction was selective and no demethylation product was observed. Similarly, dimethoxy benzyl derivative **13** produced the corresponding spiroxazine **14**. In order to evaluate the effect of an electron withdrawing group in the substrate, two nitro containing amides **15** and **17** were subjected to cyclization reaction. In both the cases spirocyclic compounds **16** and **18** were formed in 80% and 78% yield, respectively. The styrene substituted spiroxazine **20** was prepared using a similar cyclization of cinnamyl amide **19**. To widen the scope of the reaction, the benzamide derivatives **21**, **23**, and **25** was prepared by the condensation of corresponding acid chlorides with amine **7**. In these examples the benzamides could not be prepared by the direct dehydrative condensation of acid and amine. The spirocyclization of benzamides produced benzene, p-bromobenzene, and pyridine substituted spiroxazines **22**, **24**, and **26**, respectively. All compounds were well characterized by their ^{1}H, ^{13}C NMR as well as mass spectroscopic data.

Table 2. Synthesis of spiro-1,3-oxazine derivatives

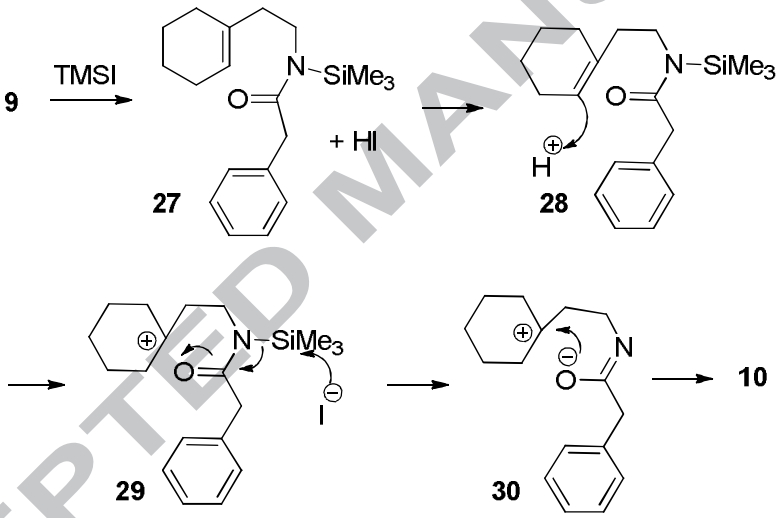
Entry	Substrates	Products	Time (min)	Yield (%)[a]
1	 **9**	 **10**	1	83
2	 **11**	 **12**	1	86

3	 **13**	 **14**	1	89
4	 **15**	 **16**	5	80
5	 **17**	 **18**	5	78
6	 **19**	 **20**	2	75
7	 **21**	 **22**	2	85
8	 **23**	 **24**	2	83

9	 **25**	 **26**	5	70

[a]Yields refer to isolated yield of the products.

Regarding the mechanism of the reaction, TMSI is proposed to react with amide to form HI which protonates the double bond of cyclohexene. The iodide promoted *N*-desilylation leads to the spirocyclization via carboxymidic acid tautomer of amide **30** (Scheme 2).



Scheme 2. Plausible mechanism of spirocyclization

In conclusion, a mild and efficient methodology has been developed for the synthesis of spiro-1,3-oxazine derivatives using a TMSI mediated cyclization of *N*-2-(1'-cyclohexenyl)ethyl-acetamides/benzamides. While TMSI is known to cleave the C-O bond of ethers and esters to the corresponding alcohols or halides, in this report it is used in C-O bond forming reaction. A very short reaction time, clean reaction profile, and mild conditions constitute the significant features of the synthesis. Application of the methodology in the synthesis of different biologically and industrially important compounds is underway.

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Supplementary data

Supplementary information containing the detailed experimental procedure and the characterization data of all the synthesized compounds can be found in the online version.

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29. **General Procedure for the preparation of 3,4,5,6,7,8-hexahydroisoquinolines :** TMSCl (1.5 mmol) and KI (1.5 mmol) was dissolved in CH_3CN (3 mL) in a 10 mL microwave reaction vial. The mixture was allowed to stir for 15 min when a deep yellow color generated. The amide (1 mmol) dissolved in CH_3CN (3 mL) was added. Sealed with a Teflon septum, the mixture was

heated under microwave at 80 °C for 1 minute. After cooling, excess ammonia was added to neutralize the solution and the CH_3CN was removed in vacuum. The mixture was extracted with ethyl acetate (2 × 20 mL) and the combined organic layer was washed with water, sodium thiosulphate, sodium bicarbonate, and brine. Drying over Na_2SO_4 and removal of the solvent under reduced pressure, produced the crude mixture which was purified by column chromatography.

Graphical Abstract

A facile microwave assisted synthesis of spiro-1,3-oxazines from N-(2-(cyclohex-1-en-1-yl)ethyl)amides

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