Journal of Current Pharma Research
(An Official Publication of Human Journals)
An International Peer Reviewed Journal For Pharmacy, Medical & Biological Science
DOI: 10.25166 CODEN: JCPRD6 NLM ID: 101744065
ISSN: Print: 2230-7834 Online: 2230-7842
SJIF Impact Factor: 6.913

Human Journals
Review Article
April 2021 Vol.:11, Issue:3
© All rights are reserved by Venkata Rao B et al.

Metal- Catalyzed Cycloaddition of Oxonium Ylides: Synthesis of Spiro [Furo [2, 3-*A*] Xanthene-2, 3'-Indolin]-2'-One Scaffolds and Evaluation of Anticancer Activity

Journal of Current Pharma Research
(An Official Publication of Human Journals)
An International Peer Reviewed Journal For Pharmacy, Medical & Biological Science
DOI: 10.25166 CODEN: JCPRD6 NLM ID: 101744065

Venkata Rao B*[1], Satyavir [2], S.B.Puranik[3]

[1]*Research scholar OPJS University, Churu, Rajasthan, India*

[2]*Research Guide OPJS University, Churu, Rajasthan, India*

[3]*Drishti Institute of Distance learning, Bangalore, India*

Submitted: 01 March 2021
Revised: 21 March 2021
Accepted: 11 April 2021

HUMAN JOURNALS
www.jcpr.humanjournals.com

Keywords: Metal- Catalyzed Cycloaddition, Oxonium Ylides, Spiro [Furo [2, 3-A] Xanthene-2, 3'-Indolin]-2'-One, Anticancer Activity

ABSTRACT

An intramolecular cycloaddition of 3-diazooxindole and a bifunctional substrate i.e. 2-methyl-2-(4-methylpent-3-en-1-yl)-2*H*-chromene-3-carbaldehyde has been achieved using from 2-(trimethylsilyl) phenyl trifluoro methanesulfonate in the presence of 2.5 mol% cesium fluorideto produce a highly substituted 3,3,5a-trimethyl-3a,5,5a,11b-tetrahydro-3*H*,4*H*-spiro[furo[2,3-*a*]xanthene-2,3'-indolin]-2'-ones in good yields with high diastereo selectivity. This is the novel methodology on the synthesis of biologically relevant polycyclic frameworks from readily accessible precursors and also found some of the synthesized compounds exhibits anticancer activity against human alveolar epithelial cell line (A549) and mouse macrophage cell (B-16).

INTRODUCTION:

Spirooxindoles are frequently found in several natural products and medicinally important molecules.[1] In particular, 4,5-dihydro-3*H*-spiro[furan-2,3'-indolin]-2'-one core is an vital part of many natural products and biologically active molecules (Figure 1).[2] Among them, *N*-methylwelwitindolinone D isonitrile inhibits the growth of lung adenocarcinoma (A549) cells and hepatocellular carcinoma (HepG2) cells.[3] Gelsedine-type indole alkaloids are known to exhibit strong cytotoxic effects against the A431 human epidermoid carcinoma cells.[4] Therefore, the development of efficient methods for the synthesis of novel spiro-oxindoles and the evaluation of their bioactivities are of great importance in drug discovery.[5] On the other hand, α-diazo carbonyl compounds are versatile intermediates and susceptible to undergo various transformations such as cyclopropanation, C–H or heteroatom-H insertion, cycloaddition and ylide formation.[6,7]

In particular, the cycloaddition of carbonyl ylides with dipolarophiles provides a synthetically powerful way to make a variety of 5-membered oxacycles.[8] Furthermore, an intramolecular generation of carbonyl ylides and their subsequent cycloadditions are important for the construction of bridged oxacycles.[9]

However, the development of an operationally simple and efficient strategy in generating a novel series of polycyclic spirooxindoles is highly desirable. Because it provides rapid access to highly substituted polycyclic compounds with high structural diversity and complexity in a single step process.

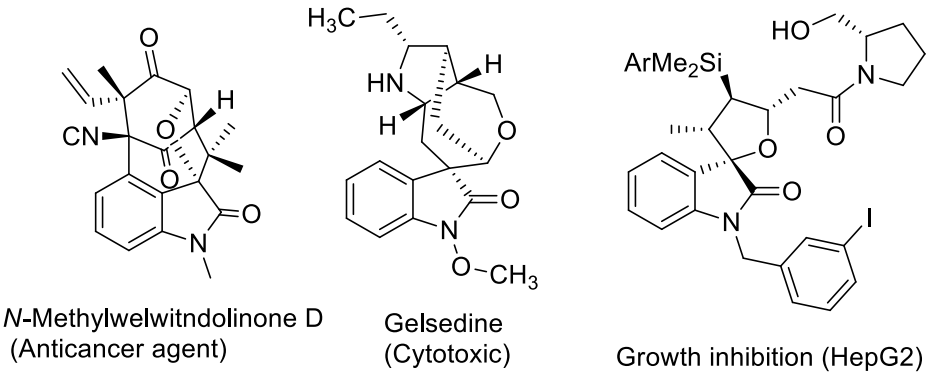
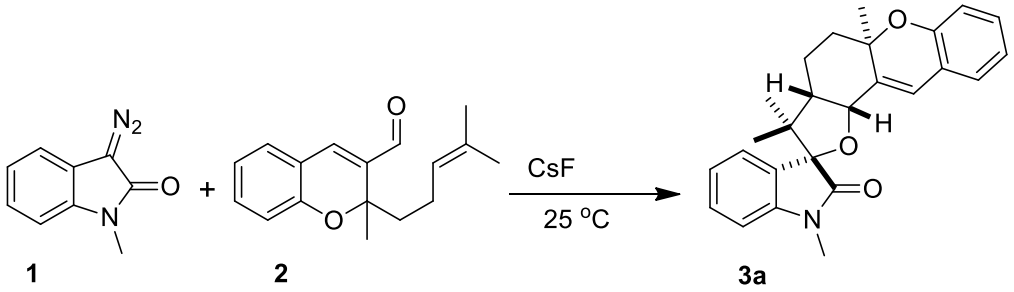


Figure No. 1: Examples of spirofurooxindole frameworks

Following our research interest on α-diazo carbonyl compounds,[10] we herein report a novel and efficient approach for the synthesis of biologically active polycyclic spiro compounds

through a CsF-catalyzed cycloaddition of carbonyl ylides generated from diazoamide and chromene-3-carboxaldehyde (Scheme 1).



Scheme No. 1: Cycloaddition of 3-diazooxindole with chromene-3-carbaldehyde

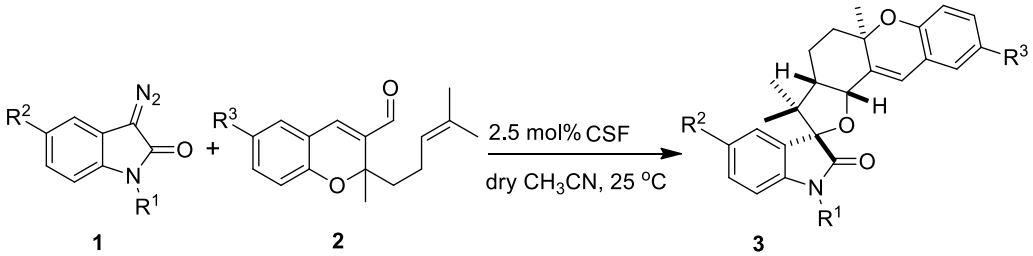
In this reaction, oxonium ylides undergo an intramolecular cycloaddition with an olefin to generate the spirocyclic frameworks. The intramolecular version is completely regio- and stereoselective affording the products in good yields. The reaction is highly chemoselective as there is no cyclopropanation between α-diazoketone and olefin. The method is operationally simple, exquisitely selective, and works with diverse substrates. As a model reaction, we investigated the cycloaddition of carbonyl ylide generated from 1 equiv of *N*-methyl 3-diazoxindole (**1**) and 1.1 equiv of alkene tethered chromene-3-carboxaldehyde (**2**) using 2-(trimethylsilyl)phenyl trifluoro methanesulfonate (2) in the presence of 2.5 mol% of CsF as a model reaction.The reaction proceeded smoothly at room temperature affording the expected spirofurooxindole **3a** in 80% yield as a single diastereomer. The structure of **3a** was confirmed by NMR, IR and HRMS analysis. To optimize the reaction conditions, we screened the reaction with different amounts of the catalyst. After several experiments, we found that 2.5 mol% of CsFis optimum (entry b, Table 1). No further improvement in conversion was observed either by increasing the amount of catalyst to 10 mol% or by decreasing it to 3 mol% (entries e and f, Table 1). The best conversion was achieved using 2.5 mol % of the catalyst. Next we examined the effect of solvents such as dichloromethane, dichloromethane, dry acetonitrile, benzene and toluene at various temperatures. Among them, dry acetonitrile appeared to give the best results in terms of yield and reaction time at room temperature (entries b,e and f, Table 1).

Table No. 1: Optimization of reaction conditions for 3a

Entry	Substrate (**1**) (equiv)	Substrate (**2**) (equiv)	Catalyst (mol%)[a]	Solvent	Time (min)	Yield of **3a** (%)[b]
a	1.0	1.1	2.5	DCM	30	73
b	1.0	1.1	2.5	dry CH_3CN	30	80
c	1.5	1.0	5	Benzene	50	65
d	1.5	1.0	5	Toluene	60	68
e	1.0	1.1	10	DCE	20	75
f	1.0	1.1	3	DCE	50	70

[a]Reaction was performed in 1 mmol scale
[b]Yield refers to pure products after chromatography

Table 2. [3+2] cycloaddition of carbonyl ylides[a]



1 2 3

Entry	R^1/R^2	R^3	Product (**3**)	Yield (%)[a,b]
a	CH_3/H	H	**3a**	81
b	CH_3/H	Cl	**3b**	80
c	CH_3/H	Br	**3c**	78
d	CH_3/Cl	H	**3d**	83
e	CH_3/Cl	Cl	**3e**	79
f	CH_3/Cl	Br	**3f**	81
g	Bn/H	H	**3g**	85
h	Bn/H	Cl	**3h**	84
i	Bn/H	Br	**3i**	84
j	Bn/Br	H	**3j**	85
k	Bn/Br	Cl	**3k**	82
l	Bn/Br	Br	**3l**	83
m	Propargyl/H	H	**3m**	88
n	Boc/H	H	**3n**	70
o	Boc/H	Cl	**3o**	60
p	Boc/H	Br	**3p**	65

[a]All the reactions were performed using CsF(2.5 mol%), diazoamide (1 equiv), chromene-3-carboxaldehyde (1.1 equiv) in dry CH_3CN at 25 °C over 30 min.
[b]Yield refers to pure product after column chromatography.

These initial findings encouraged us to study its scope with other substrates. The reaction was performed with different 3-diazooxindoles possessing substituents on the aromatic ring and *N*-protecting groups. The halo substituents such as chloro- and bromo- at 5-position of 3-diazooxindole gave the desired products in good yields (entries d-f j-l, Table 2). The protective group of nitrogen had shown some effect on conversion. The 3-diazooxindole bearing electron-releasing *N*-protective groups such as *N*-methyl, *N*-benzyl, and *N*- propargyl furnished the products in high yields (entries a-m, Table 2). Conversely, *N*-Boc protected 3-diazooxindoles gave the products in lower yields than *N*-methyl-, *N*-benzyl- and *N*-propargyl derivatives (entries n-p, Table 2). The scope of this method was further extended to substituted chromene-3-carboxaldehyde such as 5-chloro-, and 5-bromo- derivatives (entries b,c,e,f,h,i,k,l, Table 2). The results indicate that no significant electronic effect of the substituents was observed.

Finally, the structure of **3j** was confirmed unambiguously by a single crystal X-ray analysis as shown in Figure 2 (Table 2, entry j).[11]

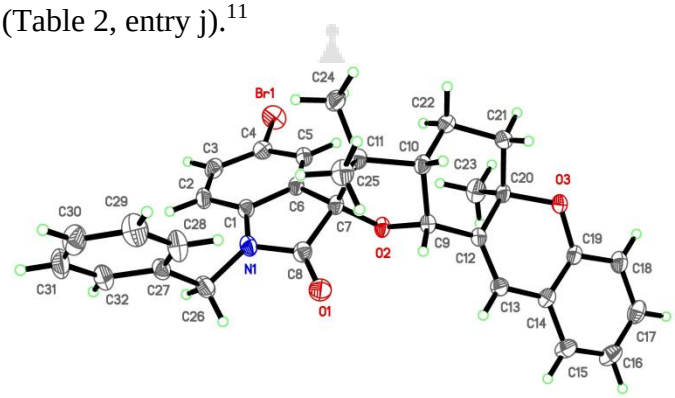
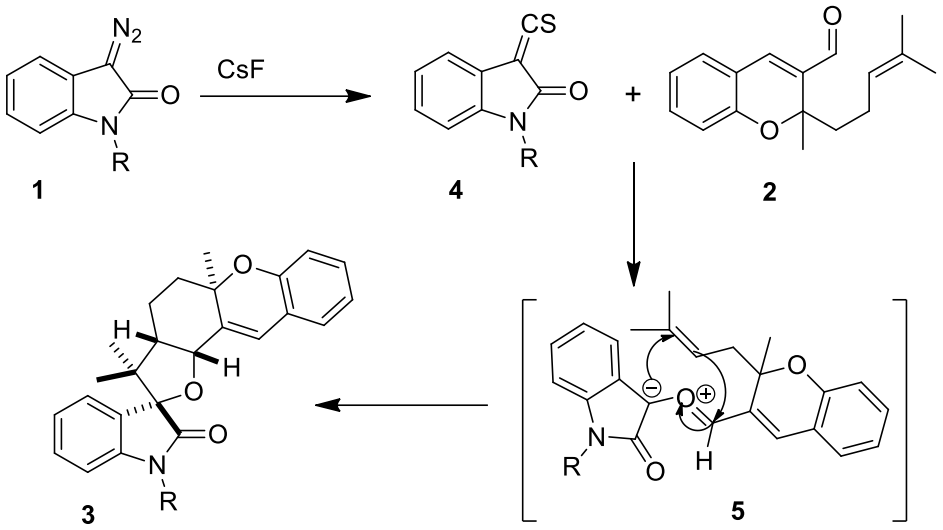


Figure 2. ORTEP diagram of **3j**

Mechanistically, the reaction is assumed to proceed through a [3+2] cycloaddition between **1** and **2**. The caesium carbenoid**4,** formed *in situ* from 3-diazooxindole (**1**) and CsFand reacts with chromene-3-carboxaldehyde (**2**) to generate the carbonyl ylide **5**. A subsequent cycloaddition of carbonyl ylide (**5**) with an internal olefin would give the desired product **3** (Scheme 2).



Scheme No. 2. [3+2]cycloadditon of carbonyl ylides[a]

Cytotoxicity:

In order to study the possible pharmacological activity, some of the selected spiro [furo [2, 3-*a*] xanthene-2, 3'-indolin]-2'-onehomologous were subjected to *insemination* cytotoxicity to human alveolar epithelial cell line (A549) and mouse macrophage cell (B-16). Cytotoxicity of test compounds in cells was determined by MTT [3-(4, 5-dimethylthaizol-2-yl)-2, 5-diphenyl tetrazolium bromide] assay.

In general, the majority of the tested compounds showed moderate to strong cytotoxicity to the above two cell lines. Among the tested compounds, **3g** showed the most potent cytotoxicity to A549 with IC50 value of 0.35 lg/mL (Table 1) and compound **3h** exhibited strongest cytotoxicity to B-16 cell line with IC50 value of 1.21g/mL (Table 1). It is noteworthy that 2H-chromene analog **3h** also showed remarkable cytotoxicity to A549cell line with IC50 value 4.31 lg/mL. It is fascinating that both the compounds **3h** and **3g** (Table 2) may be helpful to increase their cytotoxicity. Therefore, these isoxazole derivatives may become promising antitumor drug candidates for further pharmacological studies to discover efficient chemotherapeutics for the healing of human cancer diseases.

Table 3 Cytotoxicity of **spiro [furo [2, 3-a] xanthene-2, 3'-indolin]-2'-one 3**

Entry	Compound 3	Cytotoxicity to carcinoma cells $1C_{50}$ [a] (μM)	
		A549	B-16
1	3a	18.76	11.45
2	3b	22.42	12.43
3	3c	21.45	8.47
4	3d	9.58	35.7
5	3e	14.02	12.0
6	3f	23.20	21.9
7	3g	**0.35**	7.69
8	3h	**4.31**	**0.21**
9	3i	20.36	12.42
10	3j	11.26	7.32
10	Doxorubicin(control)	<0.1	<0.1

NA = no activity.

CONCLUSION:

In conclusion, we have developed an efficient strategy for the stereoselective synthesis of polycyclic frameworks through a 1,3-dipolar cycloaddition. This method is operationally simple and works under mild conditions. Due to a broad range of biological activity of spiro oxindole derivatives. Some of the compounds (3g, 3h) exhibit cytotoxicity.

REFERENCES:

1. (a) M. J. James, P. O'Brien, R. J. K. Taylor and W. P. Unsworth, *Chem. Eur. J*. 2015, **21**, 1–27; (b) G. S. Singh and Z. Y. Desta, *Chem. Rev*. 2012, **112**, 6104.
2. (a) Y. Zheng, C. M. Tice and S. B. Singh, *Bioorg. Med. Chem. Lett*. 2014, **24**, 3673; (b) E. D. Styduhar, A. D. Huters, N. A. Weires and N. K. Garg, *Angew. Chem. Int. Ed.* 2013, **52**, 12422; (c) B. M. Trost and M. K. Brennan, *Synthesis* 2009, 3003.
3. A. K. Franz, P. D. Dreyfuss and S. L. Schreiber, *J. Am. Chem. Soc.* 2007, **129**, 1020.
4. M. Kitajima, T. Nakamura, N. Kogure, M. Ogawa, Y. Mitsuno, K. Ono, S. Yano, N. Aimi and H. Takayama, *J. Nat. Prod*. 2006, **69**, 715.
5. (a) B. Yin, L. Huang, X. Wang, J. Liu and H. Jiang, *Adv. Synth. Catal*. 2013, **355**, 370; (b) B.-L. Yin, J.-Q. Lai, Z.-R. Zhang and H.-F. Jiang, *Adv. Synth. Catal.* 2011, **353**, 1961.
6. (a) Z.-Y. Cao, X. Wang, C. Tan, X.-L. Zhao, J. Zhou and K. Ding, *J. Am. Chem. Soc*., 2013, **135**, 8197; (b) B. Alcaide, P. Almendros, C. Aragoncillo, R. Callejo, M. P. Ruiz and M. R. Torres, *Eur. J. Org. Chem*., 2012, 2359; (c) M. Li, L. Zan, D. Prajapati and W.-H. Hu, *Org. Biomol. Chem*., 2012, **10**, 8808;(d) Z.-Y. Cao, F. Zhou, Y.-H. Yu and J. Zhou, *Org. Lett*., 2012, **15**, 42.

7. (a) S.-F. Zhu, Y. Cai, H.-X. Mao, J.-H. Xie and Q.-L. Zhou, *Nat. Chem*., 2010, *2*, 546; (b) S.-F. Zhu, X. Xu, J. A. Perman and X. P. Zhang, *J. Am. Chem. Soc*., 2010, **132**, 12796; (c) Y.-J. Lian and H. M. L. Davies, *J. Am. Chem. Soc*., 2010, **132**, 440; (d) C. Marti and E. M. Carreira, *J. Am. Chem. Soc*., 2005, **127**, 11505; (e) M. P. Doyle, M. A. McKervey and T. Ye, *Chem. Commun*., 1997, 983; (f) T. Ye and M. A. McKervey, *Chem. Rev*., 1994, **94**, 1091; (g) A. Padwa and D. J. Austin,*Angew. Chem., Int. Ed*., 1994, **33**, 1797; (h) D. J. Miller and C. J. Moody, *Tetrahedron*, 1995, **51**, 10811; (i) A. Padwa, and S. A. Hornbuckle, *Chem. Rev*., 1991, **91**, 263.

8. (a) A. Ford, H. Miel, A. Ring, C. N. Slattery, A. R. Maguire and M. A. McKervey, *Chem. Rev.*, 2015, **115,** 9981 and references cited therein. (b) D. M. Hodgson, A. H. Labande, F. Y. T. M. Pierard,*Synlett*2003, 59; (c) D. M. Hodgson, F. Y. T. M. Pierard, P. A. Stupple, *Chem. Soc. Rev.* 2001, **30**, 50; (d) A. Padwa, M. D. Weingarten, *Chem. Rev*. 1996, **96**, 223; (e) D. M. Hodgson, P. A. Stupple, F. Y. T. M. Pierard, A. H. Labande, C. Johnstone, *Chem. Eur. J*. 2001, **7**, 4465.

9. (a) C. H. Kim, K. P. Jang, S. Y. Choi, Y. K. Chung, E. Lee, *Angew. Chem., Int. Ed.* **2008**, *47*, 4009; (b) D. M. Hodgson, P. A. Stupple and C. Johnstone, *Tetrahedron Lett.*, 1997, **38**, 6471; (c) J. E. Baldwin, A. V. W. Mayweg, K. Neumann, G. J. Pritchard, *Org. Lett.*, **1999**, *1*, 1933; (d) Padwa, A.; Curtis, E. A.; Sandanayaka, V. P. *J. Org. Chem.*, **1996**, *61*, 73; (e) A. Padwa, D. J. Austin, A. T. Price, M. D. Weingarten, *Tetrahedron*, 1996, **52**, 3247;

10. (a) B. V. S. Reddy, M. R. Reddy, Y. G. Rao, J. S. Yadav and B. Sridhar, *Org. Lett.*, 2013, **15**, 464; (b) T. Rajasekaran, G. Karthik, B. Sridhar and B. V. S.Reddy, *Org. Lett*., 2013, **15**, 1512; (c) B. V. S. Reddy, T. Rajasekaran, G. Karthik and T. P. Rao, *Tetrahedron Lett.*, 2012, **53**, 3416.

11. CCDC893601contains supplementary crystallographic data of **3j**.