Biological Forum – An International Journal **15(6): 1030-1034(2023)**

ISSN No. (Print): 0975-1130
ISSN No. (Online): 2249-3239

Regio- and Diastereoselective Synthesis of Novel Spiro/Dispiro Heterocycles

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(Received: 14 April 2023; Revised: 16 May 2023; Accepted: 24 May 2023; Published: 15 June 2023)
(Published by Research Trend)

ABSTRACT: The regio- and diastereoselective synthesis of novel spiro/dispiro heterocyclic derivatives was achieved using fluorous solvents, which facilitated enhanced selectivity and efficiency in the reaction processes. This methodology capitalizes on the unique properties of fluorous solvents to control the stereochemistry and regioselectivity of the heterocyclic rings, resulting in the formation of a range of spiro and dispiro compounds. The synthesized derivatives were rigorously characterized using various spectroscopic techniques, including NMR, IR, and mass spectrometry. In addition, the antimalarial activity of the newly synthesized compounds was evaluated against *Plasmodium falciparum* strains. The compounds 4b and 4e show the most promising antimalarial activity, which are comparable to or slightly better than the standard.

Keywords: Diastereoselective, Regioselective, Synthesis, Antimalarial.

INTRODUCTION

Regio- and diastereoselective synthesis are critical concepts in modern organic chemistry, especially in the design of complex molecules with specific spatial arrangements and functionalities (Ford *et al.*, 2015; Nakliang *et al.*, 2021). These synthetic strategies are central to producing compounds with precise biological activities, making them indispensable in fields such as natural product synthesis, medicinal chemistry, and materials science (Galloway *et al.*, 2010; Masamune *et al.*, 1985).

Regioselectivity indicates to preferential formation of one constitutional isomer over others when a reaction can lead to multiple structural arrangements (Beckwith, 1981). This selectivity arises from the controlled reactivity of functional groups or specific positions within a molecule (Afagh & Yudin 2010). For example, in electrophilic aromatic substitution reactions, the directing effects of substituents on the aromatic ring determine the regioselectivity of the products (Galabov *et al.*, 2016).

The ability to control regioselectivity is particularly important in synthesizing complex molecules, where the placement of functional groups significantly impacts their properties and reactivity (Huang & Dong 2017). Advanced strategies for achieving regioselectivity include the use of directing groups, catalysts, and tailored reaction conditions that favor specific pathways (Sambiagio *et al.*, 2018). Regioselective reactions are often quantified using the regioisomeric ratio (RR), which provides insight into the efficiency of selectivity (Adamson & Malcolmson 2019).

Diastereoselectivity focuses on the spatial arrangement of substituents around a chiral center or other stereochemical elements, leading to preferential formation of one diastereomer over others (Peluso & Chankvetadze 2022). Unlike enantioselective reactions, which deal with chiral molecules' mirror images, diastereoselective synthesis concerns stereoisomers which are not mirror images (Bentley, 2006).

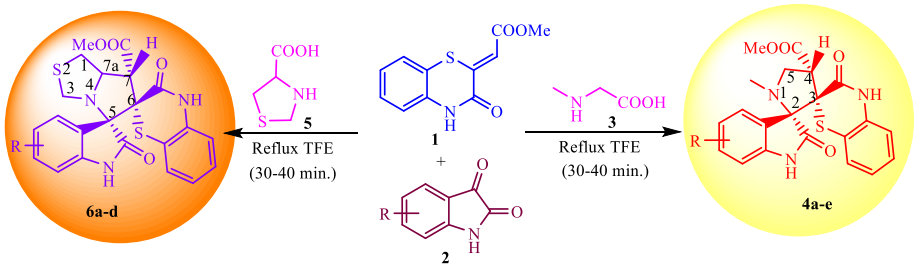
Diastereoselective synthesis is vital for creating stereochemically complex molecules, such as natural products and pharmaceuticals (Borthwick, 2012). The stereochemistry of a molecule often dictates its biological activity, so achieving the correct diastereomer is crucial (Peluso & Chankvetadze 2022). Common methods to achieve Dia stereoselectivity include using chiral auxiliaries, catalysts, and reagents, as well as exploiting steric and electronic effects in the transition state (Huang & Hayashi 2022).

The various facets of the chemistry of cyclopropane derivatives, the smallest carbocycle, are amazingly diverse and continue to fascinate theoreticians, synthetic or structural chemists having an interest in fundamental physical, medicinal chemistry, and natural product synthesis (Reissig & Zimmer 2003; Kumari *et al.*, 2021; Pathade *et al.*, 2023). The challenges generated by this intriguing cyclic arrangement of only three tetravalent carbons represent a wide area of the chemical spectrum (Georgakilas *et al.*, 2015). From fundamental aspects of bonding through the synthesis of highly strained molecules, the understanding of the mode of action in biological systems to the selective cleavage into acyclic substrates makes the chemistry of these small rings fascinating (Beyer & Clausen-Schaumann 2005). Therefore, efficient routes to prepare differently polysubstituted cyclopropanes have always

been of a primordial importance (Dian & Marek 2018). In the past decade, we and others have expanded the scope of the carbometalation reaction of cyclopropenes as a broad and general method to the formation of stereodefined cyclopropane derivatives (Cohen & Marek 2022). Although cyclopropenes, with their even higher strain energy, easily undergo addition reactions of organometallic reagents, their carbometalation reactions generate new regio-, diastereo-, and enantioselectivity issues that needed to be addressed (Gordon, 1980; Verma *et al*., 2022). These various stereochemical aspects accompanied our research from its origins to today, and we are proposing in this Account, a didactic overview of the different ways by which cyclopropenes can lead to the formation of polysubstituted cyclopropanes or open-products possessing several stereogenic centers as a single regio- and diastereomer (Eschenmoser & Arigoni 2005; Cohen & Marek 2022).

To investigate the effectiveness of the aforementioned 2,2,2-trifluoroethanol solvent, we have synthesized a novel dispiroheterocyclic hybrid utilizing TFE as the solvent (Dandia *et al.*, 2015). The study identified a highly effective green reaction medium and catalyst for the rapid construction of a diversity-oriented library of novel dispiroheterocyclic hybrids featuring benzo[1,4]thiazine, 1,3-indanedione, and pyrrolidine/thiapyrrolizidine moieties (Singh & Chowdhury 2012; Dandia *et al*., 2017). This was achieved through a facile regio- and stereoselective process via a 1,3-dipolar cycloaddition reaction involving isatin, α-amino acid (sarcosine or 1,3-thiazoles-4-carboxylic acid), and (3-oxo-3,4-dihydro-benzo[1,4]thiazin-2-ylidene)-acetic acid methyl ester (Scheme 1).

Exocyclic olefins produced from dipolarophile (3-oxo-3,4-dihydro-benzo[1,4]thiazin-2-ylidene)-acetic acid methyl esters have not been reported, as far as we are aware. So far, no one has reported the synthesis of novel heterocyclic hybrids 4/6 comprising benzo[1,4]thiazine employing a ylide formation/cycloaddition pathway (Scheme 1).



Scheme 1. Synthesis of dispiroheterocyclic hybrid.

EXPERIMENTAL WORK

Standard Protocol for the Synthesis of dispiropyrrolidine derivatives (4a-e)

An equimolar mixture of dipolarophile **1** (1 mmol), isatin **2a–e** (1 mmol) and sarcosine **3** (1 mmol) in 2,2,2-trifluoroethanol (5 ml) was refluxed for the appropriate time (30–40 min). When reaction is finished, as indicated by (TLC), the solid precipitates were filtered then washed using ethanol to furnish pure corresponding dispiropyrrolidine derivatives **4a-e** (**Scheme 1**).

1-methyl-4-(methylester)-dispiro[(indolin-2-one)-3′.2-pyrrolidine-3.2″- benzo[1,4]thiazine]-2′,3″-dione (4a)

White solid; (Yield: 92%); mp 252-254°C; IR (KBr) (ν_{max}, cm^{-1}): 3250, 1745, 1720, 1675; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.88 (s, 3H, *N*–CH_3), 3.19 (t, 1H, *J* = 8.0 Hz, CH,), 3.64 (s, 3H, *O*–CH_3), 3.87 (t, 1H, *J* = 8.8Hz, CH), 4.75 (t, 1H, *J* = 8.0 Hz, CH), 6.15-7.13 (m, 8H, Ar─H), 9.96 (s, 1H, NH), 10.59 (s, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 34.63, 45.74, 51.56, 52.75, 56.49, 77.99, 108.33, 115.02, 116.11, 120.92, 122.59, 124.43, 125.65, 127.08, 129.35, 136.27, 142.98, 165.14, 169.90, 173.99 ppm; MS ($C_{21}H_{19}N_3O_4S$): m/z 410.07 $[M+H]^+$.

1-methyl-4-(methylester)-dispiro[(5-chloroindolin-2-one)-3′.2-pyrrolidine-3.2″- benzo[1,4]thiazine]-2′,3″-dione (4b)

White solid; (Yield: 91%); mp 260-262°C; IR (KBr) (ν_{max}, cm^{-1}): 3250, 1750, 1725, 1650; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.90 (s, 3H, *N*–CH_3), 3.22 (t, 1H, *J* = 8.4 Hz, CH), 3.65 (s, 3H, *O*–CH_3), 3.83 (t, 1H, *J* = 9.2 Hz, CH), 4.72 (t, 1H, *J* = 8.0 Hz, CH), 6.19-7.44 (m, 7H, Ar–H), 10.15 (s, 1H, NH), 10.85 (s, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 34.69, 45.68, 51.63, 52.85, 56.75, 77.98, 109.81, 115.15, 116.15, 117.05, 122.79, 124.30, 125.23, 127.42, 127.72, 129.29, 136.28, 141.91, 164.95, 169.74, 173.65 ppm; MS ($C_{21}H_{18}ClN_3O_4S$): m/z 444.20 $[M+H]^+$.

1-methyl-4-(methylester)-dispiro[(5-bromoindolin-2-one)-3′.2-pyrrolidine-3.2″- benzo[1,4]thiazine]-2′,3″-dione (4c)

White solid; (Yield: 90%); mp 244-248°C; IR (KBr) (ν_{max}, cm^{-1}): 3250, 1750, 1725, 1650; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.89 (s, 3H, *N*–CH_3), 3.21 (t, 1H, *J* = 8.4 Hz, CH), 3.64 (s, 3H, *O*–CH_3), 3.81 (t, 1H, *J* = 9.2 Hz, CH), 4.70 (t, 1H, *J* = 8.0 Hz, CH), 6.15-7.43 (m, 7H, Ar–H), 10.16 (s, 1H, NH), 10.85 (s, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 34.68, 45.62, 51.71, 52.84, 56.71, 77.96, 110.34, 112.86, 115.20, 116.14, 122.83, 125.16, 126.97, 127.43, 128.05, 132.58, 136.24, 142.25, 164.96, 169.77, 173.57 ppm; MS ($C_{21}H_{18}BrN_3O_4S$): m/z 488.19 $[M+H]^+$.

1-methyl-4-(methylester)-dispiro[(5,7-dimethylindolin-2-one)-3′.2-pyrrolidine-3.2″- benzo[1,4]thiazine]-2′,3″-dione (4d)

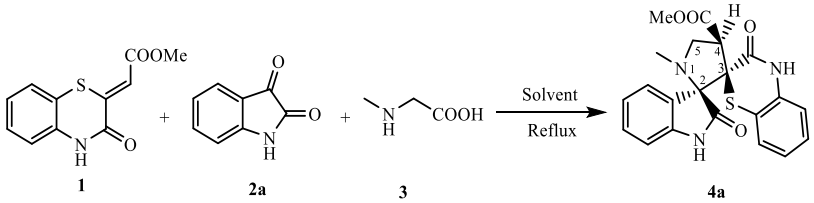
White solid; (Yield: 89%); mp 265-268°C; IR (KBr) (ν_{max}, cm^{-1}): 3250, 1745, 1710, 1675; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.68 (s, 3H, CH_3), 1.90 (s, 3H, CH_3), 2.19 (s, 3H, *N*–CH_3), 3.17 (t, 1H, *J* = 8.0 Hz,

CH), 3.64 (s, 3H, *O*–CH_3), 3.90 (t, 1H, *J* = 8.8 Hz, CH), 4.72 (t, 1H, *J* = 8.0 Hz, CH), 6.19-7.11 (m, 6H, Ar–H), 9.87 (s, 1H, NH), 10.56 (s, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 15.67, 20.65, 34.77, 45.51, 51.53, 52.81, 56.32, 78.46, 114.96, 116.10, 117.56, 122.34, 122.40, 125.37, 126.92, 127.17, 129.58, 131.05, 136.26, 139.04, 165.52, 169.98, 174.64 ppm; MS ($C_{23}H_{23}N_3O_4S$): m/z 438.27 $[M+H]^+$.

1-methyl-4-(methylester)-dispiro[(5-fluororindolin-2-one)-3′.2-pyrrolidine-3.2″- benzo[1,4]thiazine]-2′,3″-dione (4e)

White solid; (Yield: 91%); mp 278-280°C; IR (KBr) (ν_{max}, cm^{-1}): 3260, 3024, 1752, 1737, 1724; ^{1}H NMR (400 MHz, DMSO-d_6): δ1.90 (s, 3H, *N*–CH_3), 3.20 (t, 1H, *J* = 8.4 Hz), 3.73 (s, 3H, *O*–CH_3), 3.85 (t, 1H, *J* = 9.2Hz, CH), 4.73 (t, 1H, *J* = 8.0 Hz, CH), 6.15-7.15 (m, 7H, Ar-H), 10.06 (s, 1H, NH), 10.81 (s, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ34.68, 45.73, 51.63, 52.80, 56.73, 78.08, 109.18, 111.76, 112.01, 114.98, 115.96, 116.06, 125.20, 127.36, 136.22, 139.21, 156.47, 158.82, 165.03, 169.76, 173.90 ppm; MS ($C_{21}H_{18}FN_3O_4S$): m/z 428.14 $[M+H]^+$.

Table 1: Optimisation of reaction environment for production of 1-methyl-4-(methylester)-dispiro[indole-3′.2-pyrrolidine-3.2″-benzo[1,4]thiazine]-2′,3″-dione (4a)



1 2a 3 4a

Entry	Solvent	Temperature	Time	Yield[a] (%)
1	Toluene	Reflux	6h	43
2	1,4-Dioxane	Reflux	6h	56
3	Acetonitrile	Reflux	6h	62
4	Ethanol	Reflux	6h	71
5	Methanol	Reflux	6h	74
6	HFIP	Reflux	1h	50
7	TFE	Reflux	30 min	92

[a]Isolated yield

Table 2: Synthesis of dispiro oxindolyl[pyrrolidine-3.2″-benzothiazines] (4a-e).

Product	R	Time (min.)	Yield[a] (%)	Mp (°C)
4a	H	36	92	252-254
4b	5-Cl	33	91	260-262
4c	5-Br	35	90	244-248
4d	5,7-diCH_3	40	89	265-268
4e	5-F	30	91	278-280

[a]Isolated yield

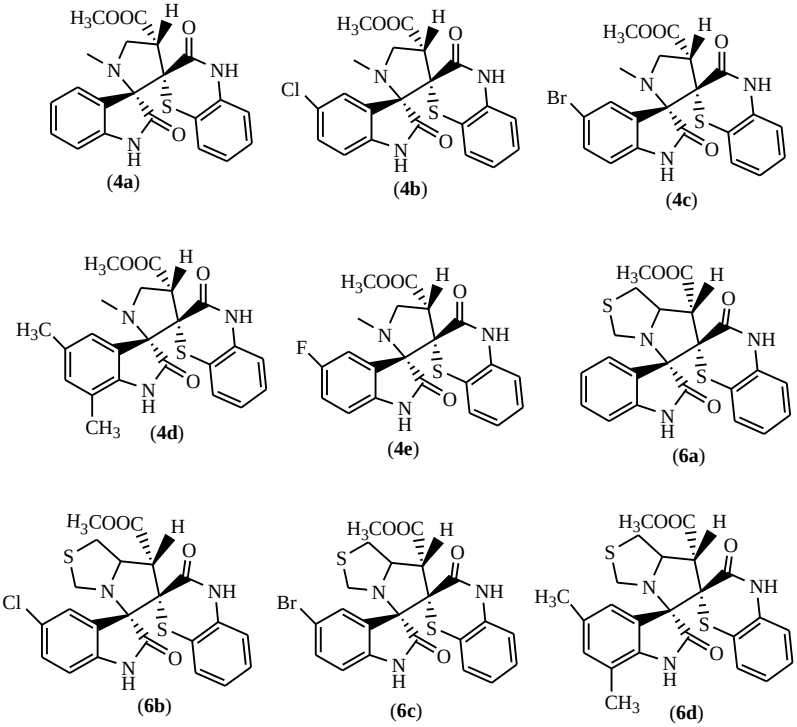


Fig. 1. Library of synthesized dispiro-oxindole pyrrolidine/thiapyrrolizidine derivatives.

RESULTS AND DISCUSSION

To identify the optimal solvent, we investigated the cycloaddition reaction of reactant in different solvents, including toluene, 1,4-dioxane, acetonitrile, ethanol, methanol, hexafluoroisopropanol (HFIP), and 2,2,2-trifluoroethanol, to yield the desired cycloadduct. 1-methyl-4-(methyl ester)-dispiro[indole-3′.2-pyrrolidine-3.2″-ben-2′,3″-dione 4a. It is clearly demonstrates that the optimal results were achieved with 2,2,2-trifluoroethanol, yielding a single regioisomer 4a in greater yield

CONCLUSIONS

All the compounds Synthesized by cycloaddition reaction of the reactant with optimal solvent, we investigated that in different solvents all the compounds show 90% yield.

FUTURE SCOPE

The future scope of regio- and diastereoselective synthesis of novel spiro/dispiro heterocycles is vast, encompassing advancements in synthetic methodologies, biological applications, and material science. One key direction is the expansion of structural diversity by developing new reaction strategies that enable the synthesis of a broader range of spiro/dispiro heterocycles with tailored functional groups. The use of green and sustainable approaches, such as biocatalysis and eco-friendly solvents, can further enhance regio- and diastereoselectivity while minimizing environmental impact.

Acknowledgement. The authors are thankful to department of chemistry, Bhupal Nobles' University, Udaipur-313001, India.
Conflict of Interest. None.

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How to cite this article: Suman Shaktawat, Arpita Matta, Akash Kalundha, Narendra Singh Chundawat and Girdhar Pal Singh (2023). Regio- and Diastereoselective Synthesis of Novel Spiro/Dispiro Heterocycles. *Biological Forum – An International Journal*, *15*(6): 1030-1034.