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DBU-Promoted [3+2] Cycloaddition for the Synthesis of Trispiro Heterocycles from Acetylpyrazolyl-Substituted Oxindoles and Substituted Isatins

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Abstract

Stable and highly reactive 3-pyrazolyl oxindole derivatives have been developed as a novel three-carbon synthon, which undergo a formal [3+2] annulation with isatin promoted by non-nucleophilic base. This protocol provides a direct route for the rapid construction of a novel class of 3,3'-polyspiro oxindole-γ-butyrolactone scaffolds. These polyspiro frameworks are recognized as privileged scaffolds for a wide range of bioactive compounds. The developed protocol features mild reaction conditions, a broad substrate scope, and scalability.

Keywords

3-Pyrazolyl oxindole; base-promoted; [3+2] annulation; polyspiro oxindole

Introduction

In recent years, spirocyclic architectures have garnered significant attention in drug discovery, leading to remarkable progress in their synthetic chemistry. Spirocycles are inherently three-dimensional (3D) structures, where the shared tetrahedral sp^3-carbon atom forces the two rings into an orthogonal arrangement, creating a substantial 3D spatial profile[1]. While this rigidity introduces torsional strain,

spirooxindoles possess novel frameworks compared to their monocyclic counterparts, and serve as bioisosteres for groups such as piperazines[2], cyanopyrrolidines[3], and carbamoylpiperidines[4]. This substitution can effectively improve key physicochemical properties, including optimizing lipophilicity and aqueous solubility, reducing cytotoxicity, and enhancing metabolic stability. These five-membered spirooxindoles, accessible via total synthesis or isolated from natural sources, exhibit significant biological activities, acting as core scaffolds for anticancer agents, antiviral agents, and molecular probes for neurotransmitter receptors[5]. Consequently, these compounds have emerged as a crucial class of building blocks in modern organic synthesis[6], drug discovery[7], and natural product chemistry[8].

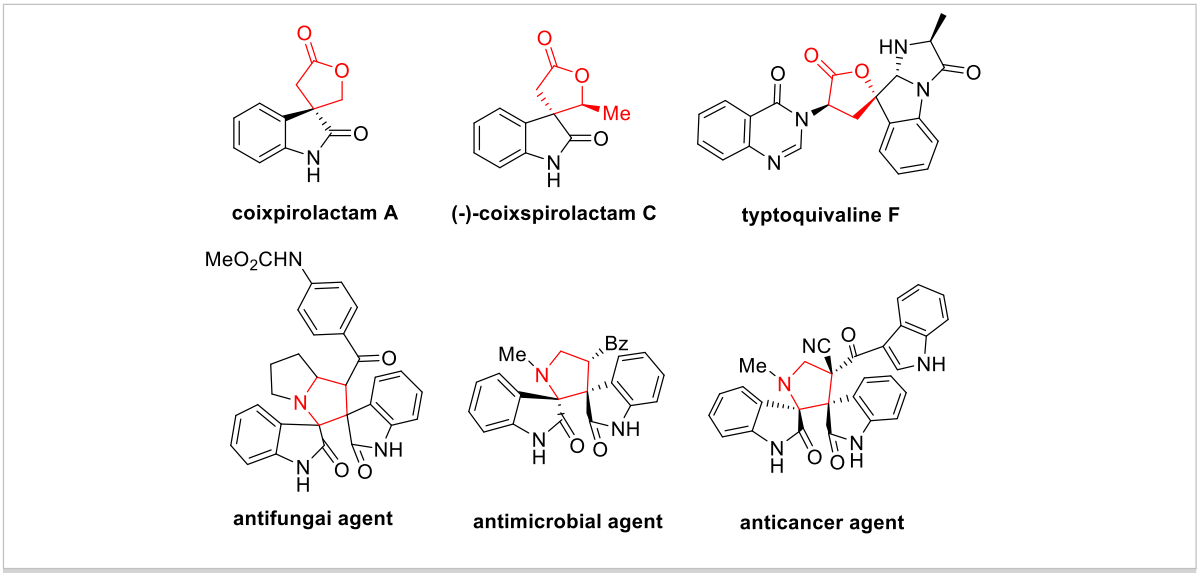
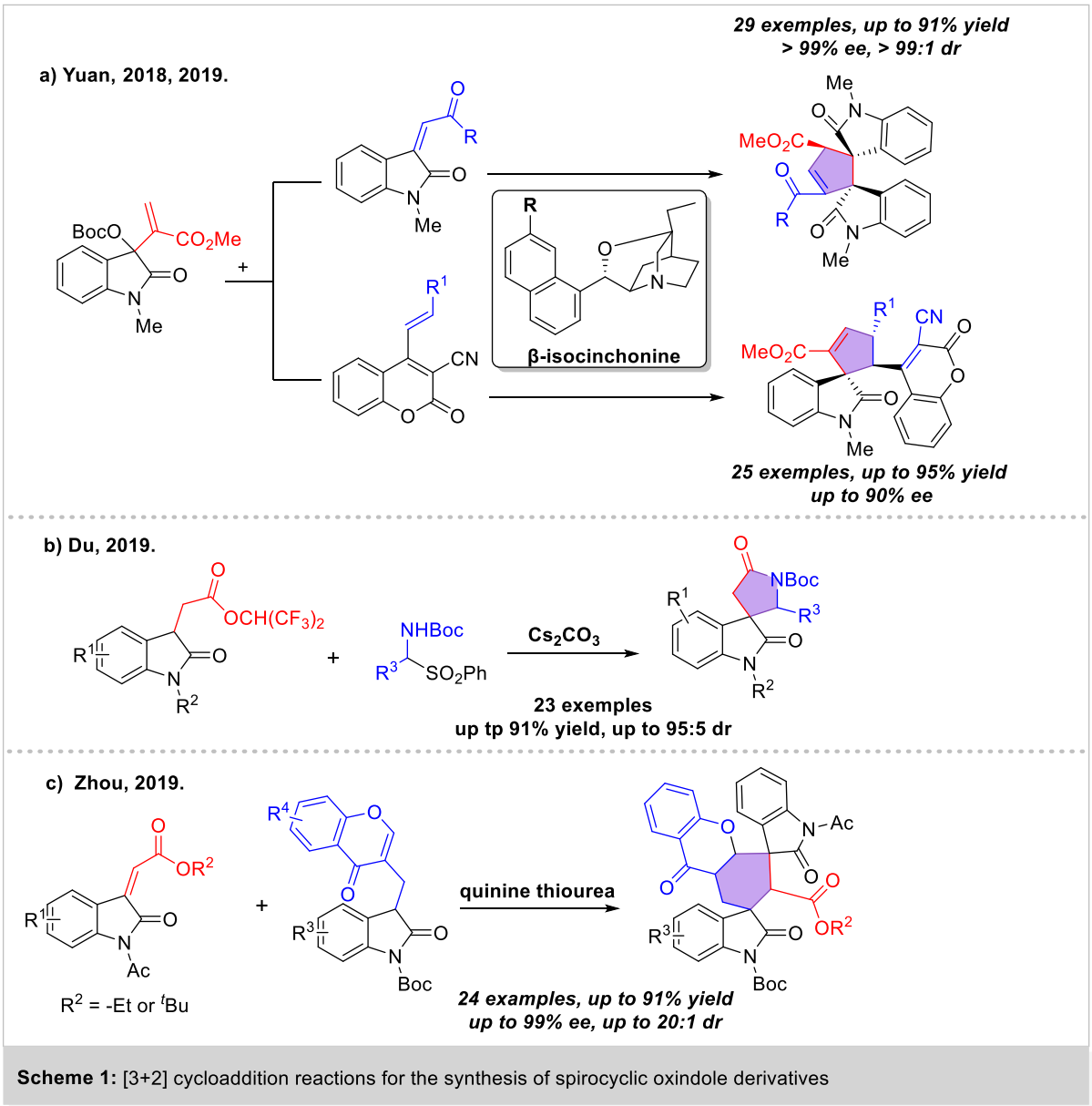


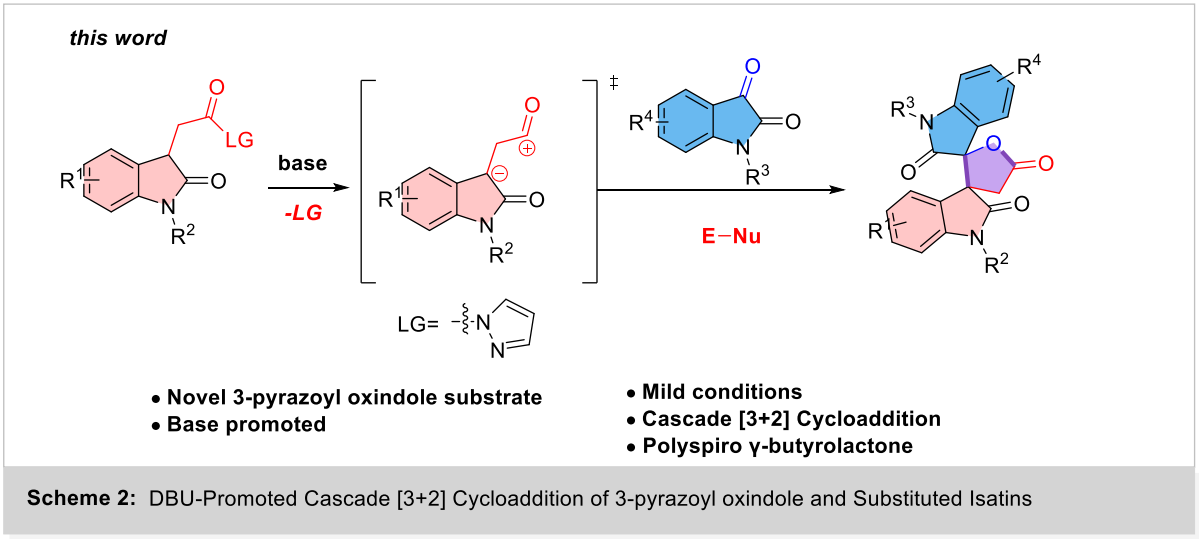
figure 1: Selected examples of bioactive spirotetrahydrofuran oxindoles

Significant progress has been made in the synthesis of these important spirocyclic frameworks. A variety of synthetic strategies, including natural product synthesis[9], cycloaddition[10], C–H activation/cross-coupling[11], ring expansion[12], and discrete coupling strategies[13] have been successfully employed to construct diverse five-membered spirooxindoles. Among these, the [3+2] cycloaddition has emerged as one of the most pivotal synthetic approaches. This methodology enables the highly efficient and selective synthesis of various products, such as dispirooxindoles and spiro-pyrrolidinones, by utilizing common synthons like Morita-Baylis-Hillman (MBH) carbonates, 3-amino oxindoles, and isatin derivatives, typically under organocatalysis. For instance, Yuan Weicheng's group reported the synthesis of 3,3'-cyclopentenylspirooxindoles via [3+2] cycloaddition with 3-methyleneoxindoles[10b] and 1,6-addition with 3-cyano-4-alkenyl-2H-chromen-2-ones[14]. These reactions employed isatin-derived MBH esters catalyzed by β-isocinchonine-type chiral catalysts. In addition to MBH esters, isatin-derived saturated esters have also been demonstrated to undergo [3+2][10e] and [3+3] [15] annulations with various partners under base promotion to afford spirooxindole skeletons. Notably, the catalytic enantioselective synthesis of a spiro quaternary stereocenter remains a long-standing challenge in synthetic chemistry.



Scheme 1: [3+2] cycloaddition reactions for the synthesis of spirocyclic oxindole derivatives

Despite these considerable advances, the synthesis of 3,3'-spirooxindole-γ-butyrolactams has not yet been reported. Given the significance of the spirooxindole scaffold, it is therefore highly desirable to develop direct and versatile new synthetic methods to access a broader library of structurally diverse 3,3'-spirooxindole-γ-butyrolactam compounds. Herein, we have developed a novel, metal-free [3+2] cycloaddition method promoted by an organic base. This protocol utilizes 3-pyrazolyl oxindole derivatives 1, which we synthesized for the first time, as a new type of C3 synthon. These react efficiently with isatin 2 to provide a series of polyspiro oxindole-γ-butyrolactones 3. Under basic conditions, these novel substrates generate a highly reactive amphiphilic intermediate in situ through the departure of the pyrazolyl group, demonstrating excellent reactivity.

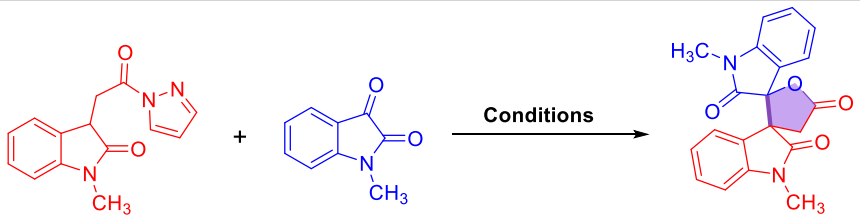


Scheme 2: DBU-Promoted Cascade [3+2] Cycloaddition of 3-pyrazoyl oxindole and Substituted Isatins

Results and Discussion

Our investigation started with the [3+2] cycloadditon between 1-methyl-3-(2-oxo-2-(1H-pyrazol-1-yl)ethyl)indolin-2-one (1a) and 1-methylindoline-2,3-dione (2a) as the model substrates. The optimization results are presented in Table 1. To simultaneously optimize reaction yield and diastereoselectivity, a systematic screening of bases, solvents, and reaction parameters was conducted (for details, see the SI). Among inorganic bases, K_2CO_3 afforded the product in a moderate yield (83 %, Entry 1), whereas Na_2CO_3 failed to promote the reaction (Entry 2). Subsequently, a series of organic bases were evaluated. DBU proved to be the most effective, delivering the target product in a high yield (81 %, Entry 7), albeit without a significant improvement in diastereomeric ratio (dr). In contrast, DABCO and DMAP provided better diastereoselectivity, but with significantly lower yields (35-47 %, Entries 3-6). Prioritizing reaction yield as the primary metric, DBU was selected as the optimal base. A subsequent solvent screening revealed that the choice of solvent was critical for the DBU-promoted system. Acetonitrile (CH_3CN) was identified as the optimal solvent, enhancing the isolated yield to 94 %, although the dr value remained largely unchanged (Entry 10).

Table 1: Optimization of the reaction conditions[a].



1a 2a 3a

Entry	Base	Solvent	Time/h	Yield/%[b]	dr[c]
1	K_2CO_3	DCM	4	83	1.4:1
2	Na_2CO_3	DCM	16	n.d.	-
3	DABCO	DCM	6	40	17.0:1
4	DMAP	DCM	6	47	19.1:1
5	Et_3N	DCM	6	45	5.5:1
6	TMG	DCM	2	35	2.1:1
7	DBU	DCM	3	81	1.1:1
8	DBU	DCE	5	76	2.5:1
9	DBU	THF	5	54	1.3:1
10	DBU	CH_3CN	3	94	1.2:1
11[d]	DBU	CH_3CN	3	96	2.7:1
12[e]	DBU	CH_3CN	6	79	1.7:1
13[f]	DBU	CH_3CN	3	74	1.2:1
14[g]	DBU	CH_3CN	3	92	1.2:1
15[h]	DBU	CH_3CN	10	90	1.4:1

[a]Unless noted, the reactions were carried out with 1a (0.1 mmol), 2a (0.11 mmol) and 1.0 eq. base in 1.0 mL of solvent at room temperature. [b]Isolated yields. [c]The diastereomeric ratio (dr) was determined from the isolated yields of the diastereomers. [d]DBU (0.15 mmol, 1.5 eq.). [e]DBU (0.05 mmol, 0.5 eq.). [f] DBU (0.2 mmol, 2 eq.). [g]The reaction was carried out at 40 °C. [h]The reaction was carried out at 0 °C. DCM = Dichloromethane, DCE = 1,2-dichloroethane, n.d. means not detected.

Further optimization of the DBU loading showed that 1.5 equivalents maximized the yield to 96 % and, notably, also improved the dr to 2.7:1 (Entry 11). However, increasing the loading beyond this point led to a decreases in both yield and dr, while lower, sub-stoichiometric amounts of DBU diminished the reaction efficiency. Temperature screening indicated that room temperature remained optimal. A key observation throughout the optimization process was the relative stability of the dr value, which fluctuated within a narrow range (1.4:1 to 2.7:1). This suggests that the diastereoselectivity is largely insensitive to reaction conditions—including the nature of the base, solvent polarity, temperature, and catalyst loading. Such consistency implies

that the stereochemical outcome is governed by the transition state of the DBU-promoted pathway rather than by external parameters. Since the dr could not be significantly enhanced by modifying the conditions, the focus of the optimization shifted to maximizing reaction efficiency. Ultimately, the conditions of Entry 11 (1.5 equiv DBU, CH_3CN, rt, 3 h) were adopted as the standard, providing the desired product in 96 % isolated yield with a dr of 2.7:1.

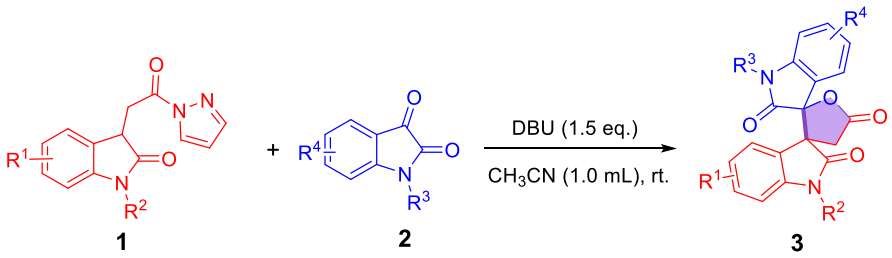
With the optimal conditions established, we employed 1-methylindoline-2,3 -dione (2a) as model electrophile to investigate the substrate scope. The effects of the R^1 and R^2 substituents on the 3-pyrazolyl oxindole derivatives 1, as well as the R^3 and R^4 substituents on isatin 2, were examined (Scheme 2). The results demonstrated that all reactions proceeded smoothly, furnishing the corresponding products (3a–3q) in good yields (83–96 %) with moderate diastereomeric ratios (dr = 1.5:1–4.7:1).

Substrate scope exploration revealed that 3-pyrazolyl oxindole derivatives 1 tolerated a wide range of substituents on the phenyl ring. Irrespective of their electronic nature (electron-withdrawing or -donating), the reactions proceeded smoothly to afford products 3b–3g in high yields (85–96 %) with good diastereoselectivities (dr = 1.9:1–3.7:1). Notably, the 7-methyl substrate (3e) was an exception, delivering a markedly lower yield (85 %) and dr (1.9:1). This is rationalized by the steric congestion of the ortho-methyl group, which disrupts the cyclization transition state, thereby concomitantly eroding both reaction efficiency and stereocontrol.

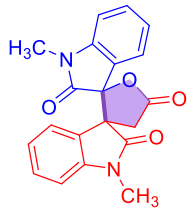
The scope was then extended to isatin partners 2. Isatins bearing electron-donating groups (e.g., Me, OMe) proved to be excellent substrates, furnishing products 3h, 3i, and 3n with high yields and diastereoselectivities. In contrast, while electron-withdrawing substituents (e.g., halogens, NO_2) caused a slight diminution in yield, the diastereoselectivity remained consistently high (>3:1).

Furthermore, the N-protecting group emerged as a critical parameter. Employing an N-Bn group on isatin significantly enhanced the diastereoselectivity to 4.7:1, albeit with a modest reduction in yield to 84 %. Conversely, the reaction proved highly sensitive to strongly electron-withdrawing N-substituents. Replacing the N-Bn group on isatin with an acetyl (-Ac) group, or the N-substituent on oxindole 1 with a p-toluenesulfonyl (-Ts) group, rendered the reaction unviable, with no desired product detected. This complete inhibition is attributed to the profoundly destabilizing effect of these groups on the requisite transition state.

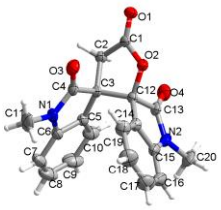
scheme 2: Substrate Scope[a]



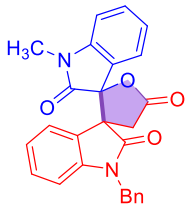
1 + 2 → 3



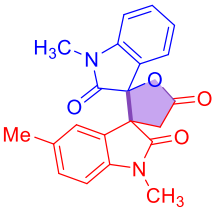
3a dr 2.7:1, 96% yield



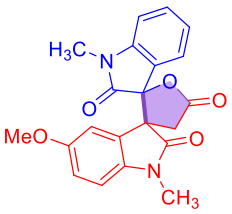
3a *X-ray*



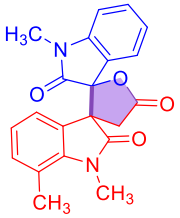
3b dr 2.5:1, 95% yield



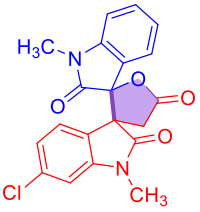
3c dr 2.8:1, 96% yield



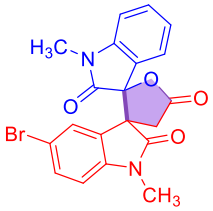
3d dr 2.6:1, 92% yield



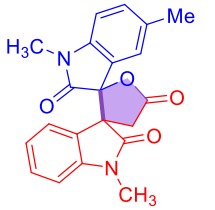
3e dr 1.9:1, 85% yield



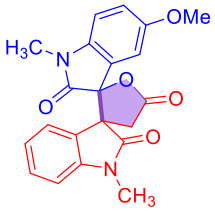
3f dr 1.7:1, 90% yield



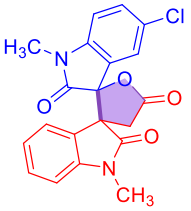
3g dr 3.7:1, 91% yield



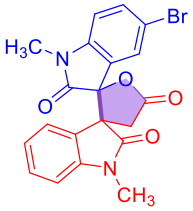
3h dr 3.1:1, 94% yield



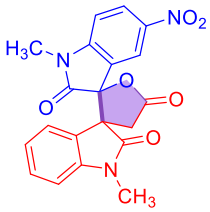
3i dr 2.8:1, 92% yield



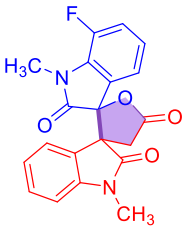
3j dr 3.3:1, 88% yield



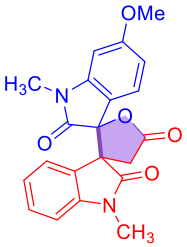
3k dr 3.1:1, 87% yield



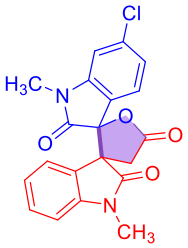
3l dr 3.2:1, 85% yield



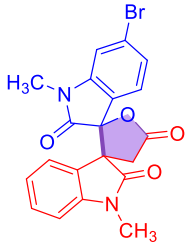
3m dr 3.0:1, 83% yield



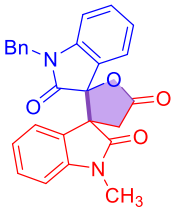
3n dr 3.8:1, 90% yield



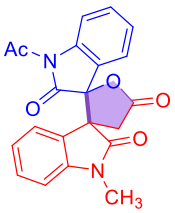
3o dr 3.7:1, 87% yield



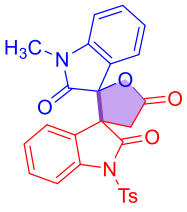
3p dr 3.2:1, 90% yield



3q dr 4.7:1, 84% yield

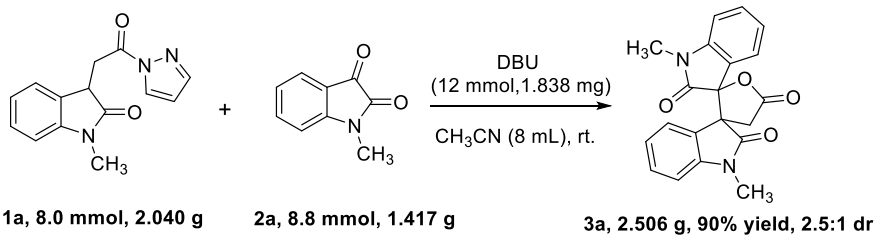


3r ND.



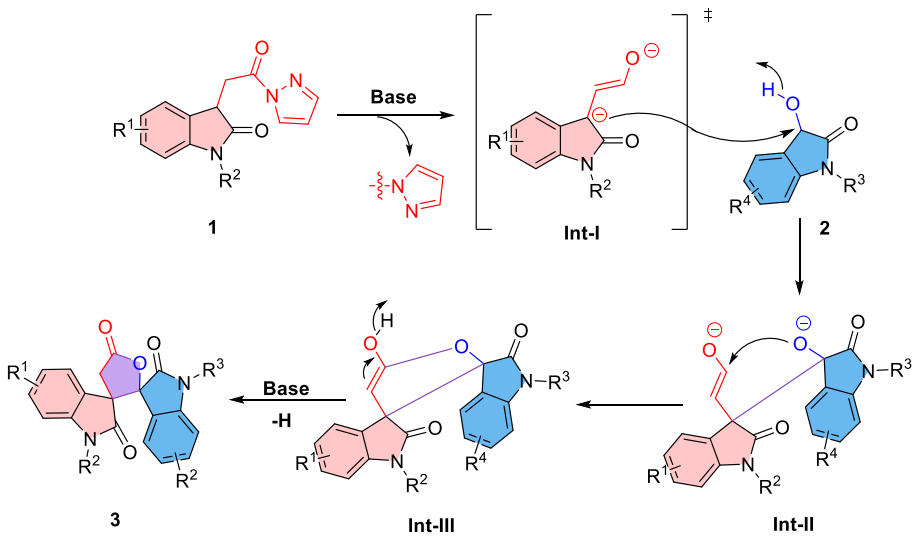
3s ND.

[a]Unless otherwise specified, reactions were carried out with 1 (0.10 mmol), 2 (0.11 mmol), and DBU (0.15 mmol) in 1.0 mL of CH_3CN and stirred at room temperature for specified time. [b]The diastereomeric ratio (dr) was determined from the isolated yields of the diastereomers. [c]Isolated yields.



scheme 3: Gram-Scale Experiment

To demonstrate the synthetic practicality of this strategy, the gram-scale cascade [3+2] cycloaddition of 1a and 2a was performed under the optimal conditions, affording product 3a in 92 % yield with 2.5:1 dr (Scheme 3). Based on the structural features of the 3-pyrazolyl oxindole and the general pathway of [3+2] cycloaddition, a plausible mechanism is proposed as follows (Scheme 4). Initially, under basic conditions, deprotonation of the α-carbon of substrate 1 facilitates the cleavage of the C-N bond, leading to the departure of the pyrazolyl group and the formation of a key zwitterionic intermediate, Int-I. Subsequently, the negatively charged C-3 atom of Int-I acts as a nucleophile, performing an intermolecular nucleophilic addition to the C-3 carbonyl carbon of isatin 2. This key bond-forming event establishes the crucial C3-C3' bond, yielding the alkoxide intermediate Int-II. Next, under the basic environment, the alkoxide in Int-II undergoes intramolecular cyclization by attacking the ester carbonyl, constructing the spiro-tetrahedral intermediate Int-III. Finally, this intermediate collapses, eliminating the pyrazole moiety and restoring the conjugated system to afford the desired polyspiro oxindole-γ-butyrolactone product 3.



scheme 4: Proposed Reaction Mechanism

Conclusion

In summary, we have developed a novel and efficient DBU-promoted [3+2] cycloaddition strategy for the synthesis of unprecedented trispiro heterocycles. This

method utilizes newly synthesized 3-pyrazolyl oxindole derivatives as highly reactive C3 synthons, which undergo formal annulation with substituted isatins under mild, metal-free conditions. The protocol provides direct access to a diverse library of novel 3,3'-polyspiro oxindole-γ-butyrolactone scaffolds, a privileged structural motif in bioactive compounds, in excellent yields (up to 96 %) with moderate diastereoselectivity (dr up to 4.7:1). Key advantages include operational simplicity, broad substrate scope encompassing various electronic and steric substitutions, scalability (demonstrated on gram scale), and the avoidance of metal catalysts. The mechanistic pathway involves base-induced generation of an amphiphilic intermediate from the 3-pyrazolyl oxindole, followed by sequential C–C bond formation and intramolecular cyclization. This work significantly expands the synthetic toolbox for constructing complex spirocyclic architectures relevant to drug discovery. Future efforts will focus on enhancing enantioselectivity for the spiro quaternary stereocenter.

Supporting Information

Details of optimization experiments, full characterization

data, X-Ray data, and NMR spectra (^{1}H, ^{13}C) for all products.

Funding

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