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Base-Catalyzed Diastereoselective [3 + 3] Annulation of 3-Isothiocyanatooxindoles and Azomethine Imines

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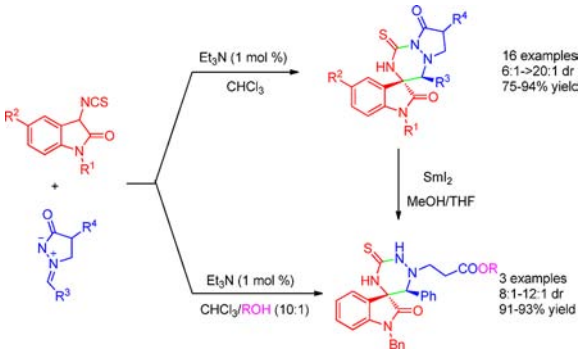
ABSTRACT



An unprecedented diastereoselective [3 + 3] annulation of 3-isothiocyanatooxindoles and azomethine imines was catalyzed by Et_3N, affording 3,3′-triazinyl spirooxindoles in excellent yields and diastereoselectivities under mild conditions.

Spirocyclicoxindoles are the structural valuable motifs frequently existing in many natural products and synthetic compounds.[1−3] In particular, some spiro heterocyclic oxindoles have drawn considerable interest from medicinal chemists, as they contain two biological and pharmaceutical characteristics of both oxindoles and heterocycles.[4,8b]

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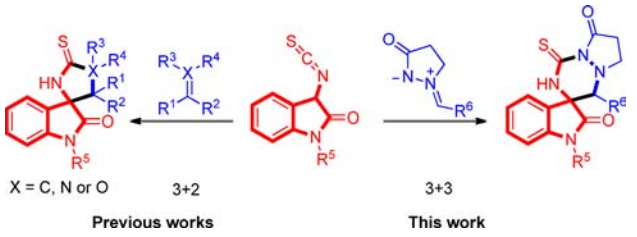
Azomethine imines have been employed as efficient 1,3-dipoles in various metal-catalyzed and organocatalytic [3 + 2] cycloadditions.[5] However, the [3 + 3] cycloadditions have been much less studied, and only a few examples have been reported to date. Hayashi,[6a] Toste,[6b] Guo,[6c] and Doyle[6d] reported metal-catalyzed [3 + 3] annulations of azomethine imines with trimethylenemethanes, propargyl esters, allenoates, and enol diazoacetates. Scheidt[6e] also described an N-heterocyclic carbene-catalyzed formal [3 + 3] annulation of azomethine imines with enals. Despite these efforts, the use of an organic molecule to catalyze a [3 + 3] annulation of azomethine imines has yet to be realized.

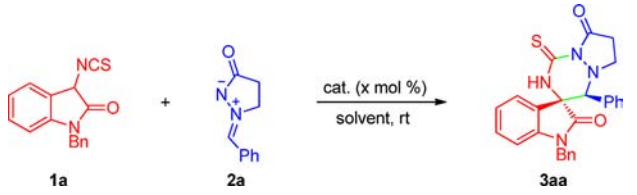
Recently, we[7] and others[8] have disclosed that 3-isothiocyanato oxindoles could be used as an efficient C−N−C trio of atom synthons in formal [3 + 2] annulations with electron-deficient olefins, aldehydes, ketones, or imines. As a continuation of our research interest in construction of spirocyclic oxindoles,[2f,5f,7,9] we wondered whether 3-isothiocyanato oxindoles could be involved in a formal [3 + 3] cyclization with azomethine imines to provide 3,3′-triazinyl spirooxindole (Scheme 1).

Scheme 1



Initially, we examined the base-catalyzed reaction employing 3-isothiocyanato oxindole **1a** and azomethine imine **2a** as the substrates in dichloromethane (DCM) at room temperature.[10] We found that the reaction swiftly went to completion with 10 mol % Et_3N to obtain the desired product **3a** in 77% isolated yield and more than 20:1 diastereoselectivity within 5 min (Table 1, entry 1). In view of reaction time, yield and diastereoselectivity, the catalysis of Et_3N was better than that of DBU, DIPEA, DABCO and Na_2CO_3 (Table 1, entries 2−5).

Table 1. Condition Optimization of the Reaction[a]



entry	cat.	*x* (mol %)	solvent	time (min)	yield[b] (%)	dr[c]
1	Et_3N	10	CH_2Cl_2	5	77	>20:1
2	DBU	10	CH_2Cl_2	30	43	5:1
3	DIPEA	10	CH_2Cl_2	30	44	8:1
4	DABCO	10	CH_2Cl_2	30	50	10:1
5	Na_2CO_3	10	CH_2Cl_2	40	59	>20:1
6	Et_3N	10	$CHCl_3$	5	92	>20:1
7	Et_3N	10	THF	10	87	>20:1
8	Et_3N	10	PhMe	10	80	>20:1
9	Et_3N	10	MTBE	10	42	2:1
10	Et_3N	10	MeOH	5	84	5:1
11	Et_3N	10	EtOAc	5	n.d	1:1
12	Et_3N	10	$ClCH_2CH_2Cl$	20	78	>20:1
13	Et_3N	5	$CHCl_3$	5	92	>20:1
14	Et_3N	1	$CHCl_3$	5	92	>20:1

[a] Unless otherwise specified, the reaction was carried out with **1a** (0.10 mmol) and **2a** (0.12 mmol) in the presence of catalyst (*x* mol %) in solvent (1.0 mL) at room temperature. [b] Isolated yield. [c] Determined by ^1H NMR spectroscopy of the crude mixture.

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(10) We also tested the reaction of 3-isothiocyanato oxindole and azomethine ylide, but it only afforded the [3 + 2] annulation product.

Subsequently, we attempted to optimize the reaction conditions by screening several solvents (Table 1, entries 6–12). As can be seen, $CHCl_3$ was found to be the most suitable solvent for this reaction. Finally, when the catalyst loading was reduced to 5 or 1 mol % respectively, the same excellent results were obtained (Table 1, entries 13 and 14).

With the optimal conditions in hand, we next investigated the scope of the reaction. In general, all the reactions proceeded well to completion within 5 min to afford the desired products in high yields and diastereoselectivities (Table 2). For the 3-isothiocyanato oxindoles **1**, the substitution, whether electron-withdrawing or -donating, on the 3-isothiocyanato oxindole aromatic ring afforded the respective products in excellent yields (91–94%) and diastereoselectivities (>20:1) (Table 2, entries 1–3). *N*-Me-protected 3-isothiocyanato oxindole could also be involved in the reaction in excellent isolated yield albeit with modest diastereoselectivity (Table 2, entry 4). Afterward, further exploration of the substrate scope was focused on N,N′-cyclic azomethine imines **2**. It appeared that aromatic groups on N, N′-cyclic azomethine imines with both electron-withdrawing and electron-donating substituents, as well as heterocyclic analogues, were compatible under the optimized reaction conditions and provided the products in good to high yields (75–92%) and diastereoselectivities (10:1→ 20:1) (Table 2, entries 5–15). In addition, azomethine imines bearing substituents on the pyrazolidinone ring could also be used in the present [3 + 3] annulation with high efficiency (Table 2, entry 16).

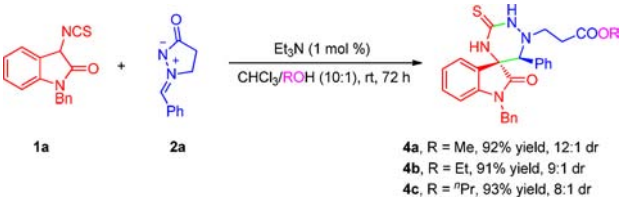
Table 2. Scope of the Reaction[a]

entry	**1**, R^1, R^2	**2**, R^3, R^4	**3**	yield[b] (%)	dr[c]
1	**1a**, Bn, H	**2a**, Ph, H	**3aa**	92	>20:1
2	**1c**, Bn, Me	**2a**, Ph, H	**3ca**	91	>20:1
3	**1d**, Bn, F	**2a**, Ph, H	**3da**	94	>20:1
4	**1b**, Me, H	**2a**, Ph, H	**3ba**	90	10:1
5	**1a**, Bn, H	**2b**, 2-ClC_6H_4, H	**3ab**	88	18:1
6	**1a**, Bn, H	**2c**, 2-BrC_6H_4, H	**3ac**	90	>20:1
7	**1a**, Bn, H	**2d**, 2-FC_6H_4, H	**3ad**	92	10:1
8	**1a**, Bn, H	**2e**, 2-MeC_6H_4, H	**3ae**	89	15:1
9	**1a**, Bn, H	**2f**, 4-$MeOC_6H_4$, H	**3af**	90	>20:1
10	**1a**, Bn, H	**2g**, 4-BrC_6H_4, H	**3ag**	89	15:1
11	**1a**, Bn, H	**2h**, 4-ClC_6H_4, H	**3ah**	86	17:1
12	**1a**, Bn, H	**2i**, 4-FC_6H_4, H	**3ai**	83	>20:1
13	**1a**, Bn, H	**2j**, 4-MeC_6H_4, H	**3aj**	85	>20:1
14	**1a**,Bn, H	**2k**, 1-Nap, H	**3ak**	75	>20:1
15	**1a**, Bn, H	**2l**, 2-furyl, H	**3al**	80	>20:1
16	**1a**, Bn, H	**2m**, Ph, Me	**3am**	90	6:1

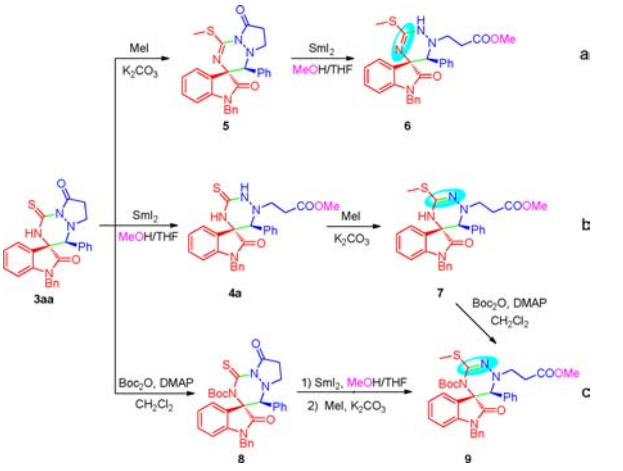
[a] All reactions were carried out with **1** (0.10 mmol) and **2** (0.12 mmol) in the presence of 1 mol % Et_3N in $CHCl_3$ (1.0 mL) at room temperature for 5 min. [b] Isolated yield. [c] Determined by ^1H NMR spectroscopy of the crude mixture.

During screening of the solvents of the reaction, an interesting phenomenon was observed: the ring-opening product **4a** was obtained in a mixture of $CHCl_3$ and MeOH (10:1) rather than in $CHCl_3$ or MeOH alone. When more complex alcohols (such as EtOH, ^{n}PrOH) were tested, the

Scheme 2



Scheme 3



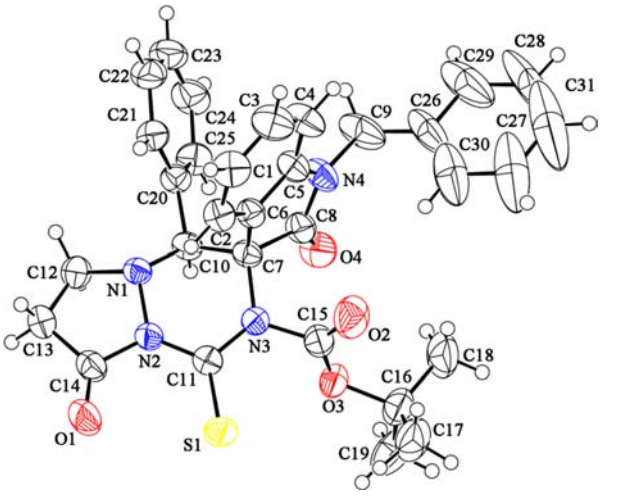


Figure 1. X-ray of **8**.

same satisfactory results were achieved, albeit with the longer reaction time (Scheme 2).

To further expand the versatility of our work, some conversions of the above cycloadduct were examined as shown in Scheme 3. Methylation of **3aa** with MeI, followed by ring-opening of **5** with SmI_2, led to the formation of **6**. Interestingly, using the same reaction conditions, but with the different pipetting sequence delivered another product **7**, which was determined by comparing with the NMR spectroscopic data of compound **9** whose configuration was unambiguous in the process. The relative configuration of the major of **8** was determined by X-ray crystallographic analysis (Figure 1).

In conclusion, we have developed a new base-catalyzed formal [3 + 3] annulation of 3-isothiocyanatooxindoles and *N*,*N*′-azomethine imines for the synthesis of novel 3,3′-triazinylspirooxindoles in excellent yields and diastereoselectivities. The synthetic procedure proved to be general, operationally simple, high-yielding, and highly diastereoselective.

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Supporting Information Available. Experimental details, characterization data for new compounds, and X-ray crystal structure. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.