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Preparation of spiro[imidazolidine-4,3′-indolin]-2′-imines *via* copper(I)-catalyzed formal [2 + 2 + 1] cycloaddition of 3-diazoindolin-2-imines and triazines†

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We report a facile and efficient synthesis of spiro[imidazolidine-4,3′-indolin]-2′-imines *via* a copper(I)-catalyzed cascade reaction of 3-diazoindolin-2-imines with 1,3,5-triazines. The reaction proceeds under very mild conditions and tolerates a variety of functional groups. The cascade process involves the formation of a copper–carbene intermediate and a formal [2 + 2 + 1] cycloaddition.

Introduction

Indole and its derivatives are prevalent structures for medicinal chemistry.[1] Among them, many molecules with a spirocyclic framework at the 3-position of the indole ring exhibited a broad range of bioactivities (Fig. 1).[2] For example, SAR-405838 and several other spiro[3*H*-indole-3-3′-pyrrolidin]-2(1*H*)-ones are clinical and preclinical inhibitors of mouse double minute 2 (MDM2) proto-oncogene, as they are chemically stable and orally active against MDM2–TP53 (tumor protein p53) interaction.[2a] Additionally, spirooxindoles are common structural motifs and are often found in natural products. Hence, there is an increasing interest in the development of novel approaches to prepare architecturally challenging indole derivatives with a spirocyclic framework such as spirooxindoles both in organic synthesis and medicinal chemistry.[3]

In 2014, we reported two practical methods for the preparation of 3-diazoindolin-2-imines *via* a copper-catalyzed cascade reaction of *o*-ethynylanilines with sulfonyl azides[4] and a catalytic-free cascade 1,3-dipolar cycloaddition/dehydrogenation of indoles with sulfonyl azides.[5] Lately, we[4–6] and several other groups[7] demonstrated that this unique class of diazo compounds are valuable precursors of metal carbenes for the construction of a series of heterocyclic compounds with the indole ring system.

1,3,5-Triaryl-1,3,5-triazines show nucleophilic reactivity at the nitrogen, but have also been employed as stable precursors of formaldimines and have been used as effective aminomethylation reagents.[8] One elegant example was reported by Sun and co-workers for the gold-catalyzed formal [4 + 1] cycloaddition of diazo esters with 1,3,5-triazines, which provided imidazolidines.[9] In this transformation, 1,3,5-triazines acted as formal dipolar adducts. Inspired by these reports and in continuation with our ongoing interest in the 3-diazoindolin-2-imine chemistry,[4–6] we herein report a copper(I)-catalyzed cycloaddition of 1,3,5-triazines with 3-diazoindolin-2-imines, which resulted in the preparation of spiro[imidazolidine-4,3′-indolin]-2′-imines.

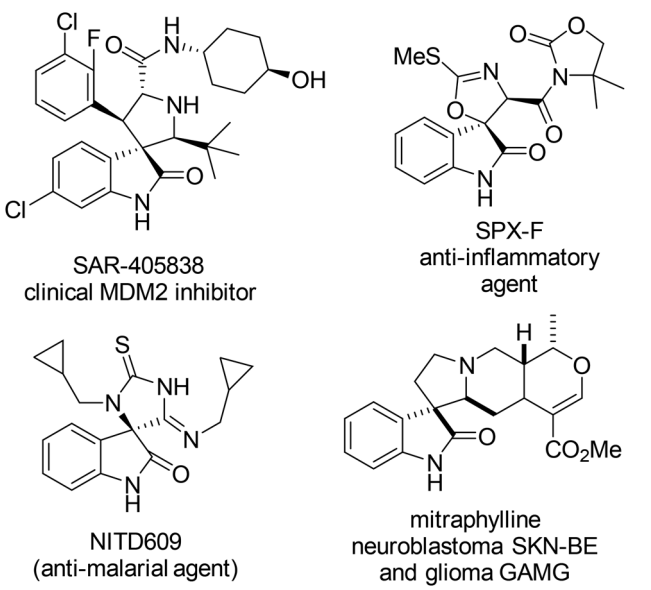

Fig. 1 Representatives of biologically active spirooxindoles.

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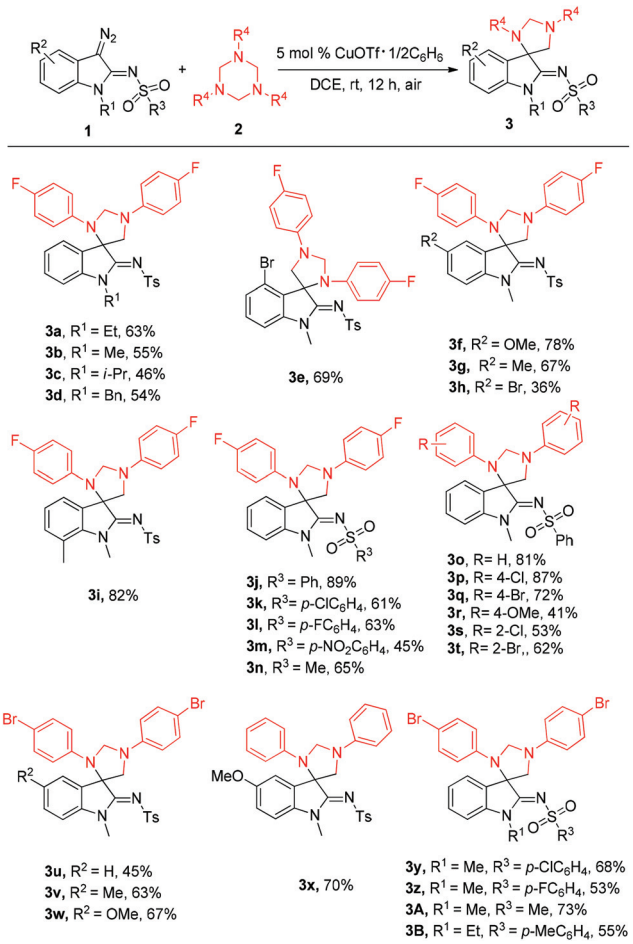
Results and discussion

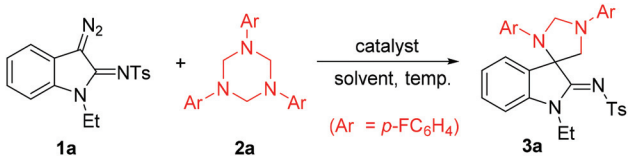
To begin with, the reaction between 3-diazoindolin-2-imine **1a** and 1,3,5-tris(4-fluorophenyl)-1,3,5-triazine (**2a**) was carried out in the presence of $Cu(OTf)_2$ in 1,2-dichloroethane (DCE) at room temperature under air. A [2 + 2 + 1] product **3a** was isolated in 56% yield (Table 1, entry 1) and its structure was confirmed by X-ray single-crystal analysis.[10] By screening across various Cu(I) and Cu(II) catalysts, $Cu(OTf)\cdot\frac{1}{2}C_6H_6$ was found to be optimal (Table 1, entries 2–5). No reaction occurred either with Rh(II) or Ag(I) as the catalyst (Table 1, entries 6 and 7). Using $Cu(OTf)\cdot\frac{1}{2}C_6H_6$ as the catalyst, we further screened several solvents including toluene, DCM, THF, and CH_3CN. Among these, DCE provided the highest yield (Table 1, entries 8–11). Finally, either decreasing or increasing the reaction temperature led to a slight decrease in the yield of **3a** (Table 1, entries 12–14).

With the optimized conditions in hand, we explored the scope of the reaction with respect to variation of diazo compounds and the triazine component (Scheme 1). Beginning with the alternation of substituents on diazo compounds **1**, the R^1 group at the 1 position on the indole ring could be ethyl (**1a**), methyl (**1b**), isopropyl (**1c**), and benzyl (**1d**). The corresponding products **3a–3d** were obtained in 46–63% yields. The substituent R^2 on the indole ring could be 4-Br (**1e**), 5-MeO (**1f**), 5-Me (**1g**), 5-Br (**1h**) and 7-Me (**1i**). Thus, the corresponding products **3e–3i** were isolated in 36–82% yields. The R^3 group on the diazo compounds could be any one among phenyl (**3j**), *p*-chlorophenyl (**3k**), *p*-fluorophenyl (**3l**), *p*-nitrophenyl (**3m**), and methyl (**3n**). In these cases, the yields of the desired products ranged from 45% to 89%. Then, we investigated the scope of 1,3,5-triaryl-1,3,5-triazines **2**. 1,3,5-Triphenyl-1,3,5-triazine (**2b**), 1,3,5-tris(4-chlorophenyl)-1,3,5-triazine (**2c**) and 1,3,5-tris(4-bromophenyl)-1,3,5-triazine (**2d**) proceeded smoothly to give the corresponding products **3o–3q** in high yields (72–87%). In the cases where 1,3,5-tris(4-methoxyphenyl)-1,3,5-triazine (**2e**), 1,3,5-tris(2-chlorophenyl)-1,3,5-triazine (**2f**) and 1,3,5-tris(2-bromophenyl)-1,3,5-triazine (**2g**) were used, products **3r–3t** were obtained in relatively lower yields (41–62%). Finally, various 3-diazoindolin-2-imines and 1,3,5-triaryl-1,3,5-triazines were subjected to this reaction and the corresponding products **3u–3B** were obtained in 45–73% yields.



Scheme 1 Substrate scope.

Table 1 Optimization of the reaction conditions[a]

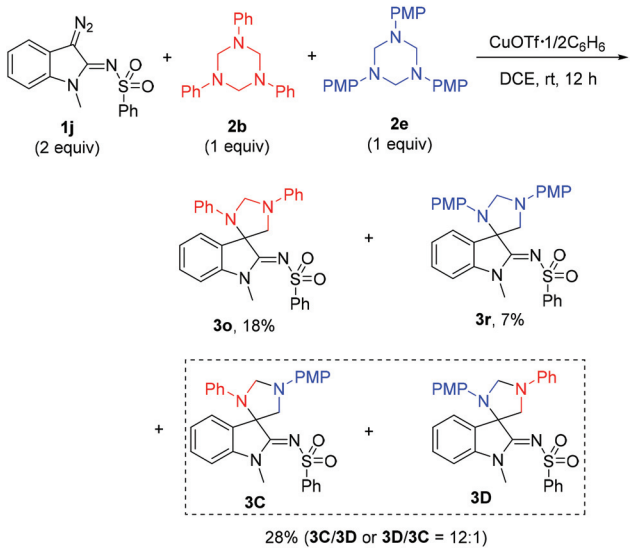


Entry	Catalyst	Solvent	Temp. (°C)	Yield[b] (%)
1	$Cu(OTf)_2$	DCE	rt	56
2	$Cu(OTf)\cdot\frac{1}{2}C_6H_6$	DCE	rt	63
3	$Cu(OAc)_2$	DCE	rt	Trace
4	CuCl	DCE	rt	Trace
5	$Cu(CH_3CN)_4PF_6$	DCE	rt	46
6	$Rh_2(Oct)_4$	DCE	rt	N.R
7	AgOTf	DCE	rt	Trace
8	$Cu(OTf)\cdot\frac{1}{2}C_6H_6$	Toluene	rt	27
9	$Cu(OTf)\cdot\frac{1}{2}C_6H_6$	DCM	rt	62
10	$Cu(OTf)\cdot\frac{1}{2}C_6H_6$	THF	rt	N.R
11	$Cu(OTf)\cdot\frac{1}{2}C_6H_6$	CH_3CN	rt	N.R
12	$Cu(OTf)\cdot\frac{1}{2}C_6H_6$	DCE	0	52
13	$Cu(OTf)\cdot\frac{1}{2}C_6H_6$	DCE	50	55
14	$Cu(OTf)\cdot\frac{1}{2}C_6H_6$	DCE	75	50

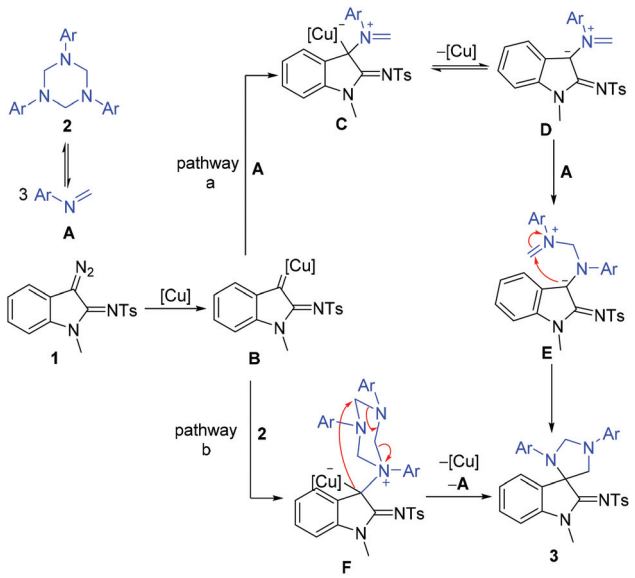
[a] Reaction conditions: **1a** (0.3 mmol), **2a** (0.2 mmol), catalyst (0.01 mmol), solvent (2 mL), 12 h. [b] Isolated yields.

To further understand the reaction mechanism, control experiments were conducted (Scheme 2). The reaction of **1j** (2 equiv.) with **2b** (1 equiv.) and **2e** (1 equiv.) was carried out under standard conditions. In this case, the cross-cycloaddition products **3C** and **3D** were isolated as a mixture with a ratio of 12 : 1 and characterized by ^1H and ^{13}C NMR as well as HRMS analyses.

Based on these results and the published studies,[8,9,11] we propose two plausible reaction mechanisms, as shown in Scheme 3. First, the copper–carbene intermediate **B** is generated from diazo compound **1**. In the next step, there are two possible pathways to obtain product **3**. In pathway a, the nucleophilic addition of 1,3,5-triazine derived formaldimine **A** to copper–carbene **B** generates ylide **C**, which releases Cu(I) to



Scheme 2 Control experiments.



Scheme 3 Proposed reaction mechanism.

form ylide **D**. Subsequent addition with another formaldimine gives intermediate **E**. Finally, **E** undergoes an intramolecular nucleophilic addition to furnish the final product **3**. Although the cross-cycloaddition products were isolated in our control experiment, a direct reaction between triazine **2** and metal–carbene intermediate **B**, as shown in pathway b, cannot be exclusively excluded.

Conclusions

In conclusion, we demonstrated that spiro[imidazolidine-4,3′-indolin]-2′-imines could be synthesized from 3-diazoindolin-2-imines through a copper(I)-catalyzed reaction with 1,3,5-triazines as precursors of formaldimines. The reaction proceeded under mild conditions and provided spiro products in moderate to good yields. The cascade process involves the formation of a copper–carbene intermediate and a formal [2 + 2 + 1] cycloaddition.

Experimental section

Typical procedure for the synthesis of (*Z*)-*N*-(1′-ethyl-1,3-bis(4-fluorophenyl)spiro[imidazolidine-4,3′-indolin]-2′-ylidene)-4-methylbenzenesulfonamide (3a)

To an over-dried flask equipped with a magnetic stirrer were added sequentially **1a** (0.3 mmol), **2a** (0.2 mmol), Cu(OTf)·$\frac{1}{2}C_6H_6$ (0.01 mmol) and dry DCE (2 mL) under air. The reaction mixture was stirred at room temperature for 12 h. Upon completion, the solvent was evaporated under vacuum. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 5 : 1–3 : 1, v/v) to give 70 mg (63% yield) of pure **3a** as a white solid. M. p. 195.0–196.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, J = 7.9 Hz, 2H), 7.36 (t, J = 7.7, 1.2 Hz, 1H), 7.28 (d, J = 7.3 Hz, 1H), 7.08–6.97 (m, 6H), 6.73–6.61 (m, 4H), 6.00 (dd, J = 9.2, 4.0 Hz, 2H), 5.20 (s, 1H), 5.14 (s, 1H), 4.61 (d, J = 7.9 Hz, 1H), 4.13 (dq, J = 14.2, 7.1 Hz, 1H), 3.91 (dq, J = 14.1, 7.0 Hz, 1H), 3.72 (d, J = 8.0 Hz, 1H), 2.30 (s, 3H), 1.34 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 156.5 (d, J_{C-F} = 235.7 Hz), 155.9 (d, J_{C-F} = 235.1 Hz), 142.5 (d, J_{C-F} = 1.9 Hz), 142.0, 140.03, 139.99, 139.6 (d, J_{C-F} = 1.9 Hz), 132.6, 129.6, 128.8, 125.9, 124.6, 123.2, 115.8 (d, J_{C-F} = 22.3 Hz), 115.7, 115.5 (d, J_{C-F} = 22.2 Hz), 114.4 (d, J_{C-F} = 7.5 Hz), 112.8 (d, J_{C-F} = 7.3 Hz), 109.6, 71.6, 68.9, 60.3, 37.6, 21.3, 11.6; IR (film): 3057, 2979, 2933, 1574, 1515, 1469, 1229, 1151, 1086 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{31}H_{28}F_2N_4NaO_2S$ ([M + Na]$^+$): 581.1793; found: 581.1797.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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