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PAPER

Efficient synthesis of tetrahydronaphthalene- or isochroman-fused spirooxindoles using tandem reactions†

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The flexible and simple cascade reaction involving a Michael-aldol or vinylogous Henry-acetalization relay is described. We have used the cascade reaction to assemble functionalized tetrahydronaphthalene- or isochroman-fused spirooxindol and other drug-like spirocyclic scaffolds. The mild reaction condition, short reaction time, and high tolerance for various functional groups make this method attractive for constructing pharmacologically interesting architectures.

Introduction

Tetrahydronaphthalene and isochroman are scaffolds found in many natural products, pharmaceuticals and other compounds with biological activity (Figure 1).[1,2] Many efforts to synthesize tetrahydronaphthalene and isochroman derivatives have been made over the past 10 years.[3,4] Among them, the development of novel methods for the formation of medicinally important spirocyclic tetrahydronaphthalenes or isochromans is of importance but finitude; it is rarely explored if these methods give rise to the construction of quaternary carbons which is synthetically challenging in itself.[5]

Among indole derivatives, spirooxindoles bearing a tetrasubstituted stereogenic center at the 3-position are of particular interest, and efforts to prepare them have expanded rapidly in recent years.[6] The fact that the spirooxindoles NITD609[7] and MI-77301[8] have advanced into clinical trials (Fig. 2a) has made these compounds even more attractive synthetic targets. We believe that the unique architecture of spirooxindole contributes significantly to its drug potential, potentially by aiding target recognition and/or altering the overall drug's physicochemical or pharmacokinetic properties in vivo. This raises the question of whether fusing the oxindole core with other rings might alter the overall molecule's biological properties in pharmacologically useful ways.

Oxindole fusion has been achieved with various chemically complex rings, including cyclopropane, cyclopentane, cyclohexane, pyrrolidine, piperidine, tetrahydrofuran, tetrahydropyran, and oxazoline.[6] However, very few synthetic protocols have been reported for combining oxindole with pharmacologically interesting tetrahydronaphthalene[9] or isochroman[10] (Fig. 2b). The groups of Smith[9a] and Padwa[9b] independently reported the synthesis of tetrahydronaphthalene-fused spirooxindole bearing a quaternary carbon center at the 1-position of tetrahydronaphthalene, but we are unaware of reports with the quaternary carbon center at the 2-position.

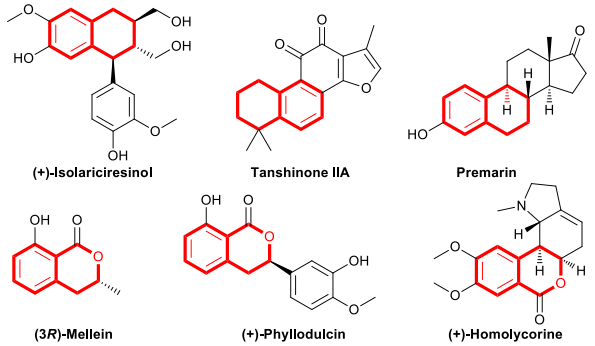

Fig. 1 Selected examples of pharmacologically active tetrahydronaphthalenes and isochromans.

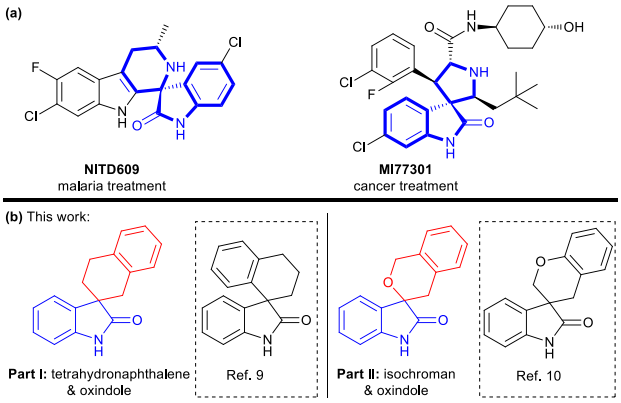

Fig. 2 (a) Examples of spirocyclic oxindoles and their pharmaceutical applications. (b) Combination of spirooxindole with tetrahydronaphthalene or isochroman.

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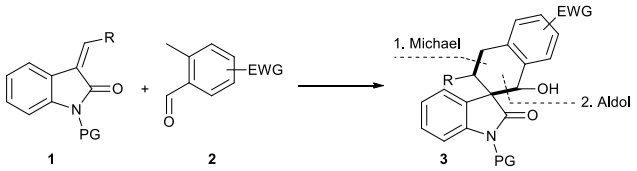
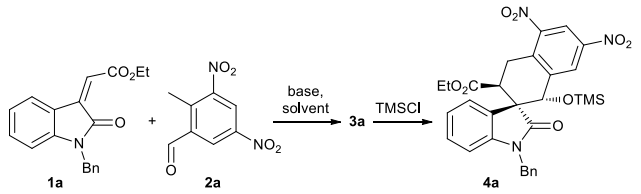


Scheme 1 Strategy for synthesizing tetrahydronaphthalene-fused spirooxindoles.

As part of our on-going efforts to design and synthesize new spirooxindole scaffolds as potential drug leads,[11] we aimed to develop a method to create a quaternary carbon center at the 2-position of tetrahydronaphthalene. We envisaged that a convenient Michael-aldol tandem reaction assembling 3-ylideneoxindole **1** and 2-methylbenzaldehyde **2** could afford the desired product **3** (Scheme 1). Since the benzene-tethered methyl group shows negligible nucleophilicity, we expected that we would be unable to perform the reaction under mild conditions. Drawing on the pioneering work of Wang,[12] Jørgensen[13] and Hong,[14] we planned to render the methyl group hydrogen atom acidic by introducing nitro groups at *ortho*- and/or *para*-positions of the benzene ring. This should facilitate methyl group deprotonation, generating a highly reactive nucleophilic species.

To test the feasibility of the proposed cascade process, we carried out a model reaction of 3-ylideneoxindole **1a** with 2-methyl-3,5-dinitrobenzaldehyde **2a** (1.2 equiv) in the presence of DBU in CH_2Cl_2 at rt for 2 h. To our gratification, the domino reaction proceeded smoothly to afford the desired compound.

Table 1 Optimization of reaction conditions[a]



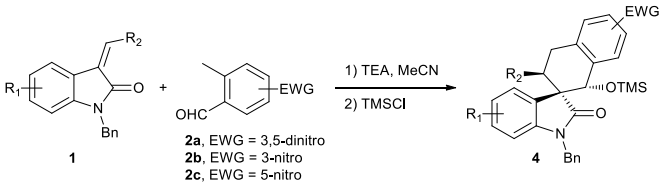
Entry	Solvent	Base	Time (h)	Yield (%)[b]	dr[c]
1	CH_2Cl_2	DBU	2	59	85:15
2	CH_2Cl_2	K_2CO_3[d]	6	25	78:22
3	CH_2Cl_2	NaOH[d]	6	20	75:25
4	CH_2Cl_2	DABCO	2	40	80:20
5	CH_2Cl_2	DMAP	2	45	84:16
6	CH_2Cl_2	DIPEA	2	65	88:12
7	CH_2Cl_2	TEA	1	70	80:20
8	Toluene	TEA	1	58	84:16
9	THF	TEA	1	38	85:15
10	DMF	TEA	1	45	80:20
11	MeCN	TEA	1	88	84:16
12[e]	MeCN	TEA	4	90	90:10

[a] Unless noted otherwise, reactions were performed with 0.3 mmol of **1a**, 0.36 mmol of **2a**, and 0.06 mmol of base in 4 mL of solvent at rt. [b] Yield of isolated **4a**. [c] Calculated based on ^{1}HNMR analysis of the crude reaction mixture. [d] H_2O (2.0 mL) and TBAB (0.03 mmol) were added. [e] The reaction was performed at 0 °C.

Direct protection of the hydroxyl with trimethylchlorosilane (TMSCl) gave the corresponding product **4a** in moderate yield and good diastereoselectivity (Table 1, entry 1). This compound is more soluble in $CDCl_3$ and easier to analyze than **3a**. Encouraged by these preliminary results, we sought to optimize reaction conditions. Our observation of low yield when using inorganic bases (entries 2-3) led us to screen organic bases (entries 4-7). Using TEA led to high yield of **4a** (entry 7). Screening various solvents revealed a strong influence on reaction efficiency (entries 8-11), with acetonitrile proving to be the best choice (entry 11). Performing the reaction at 0 °C slowed it down but slightly improved the dr value; extending the reaction time to 4 h led to similar yield as at rt (entry 12).

We then used these optimized conditions to examine the substrate scope for the synthesis of tetrahydronaphthalene-fused spirooxindole derivatives (Table 2). Incorporating different substituents at positions C4-C7 of 3-ylideneoxindole **1** did not substantially affect the efficiency of cyclization; the corresponding products were produced in good yields (entries 2-10). At the same time, the position and electronic properties of the substituents affected diastereoselectivity, which varied from 92:8 dr to 80:20 dr under the conditions tested.

Table 2 Synthesis of tetrahydronaphthalene-fused spirooxindole derivatives[a]



Entry	R^1	R^2	2	Product	Yield (%)[b]	dr[c]
1	H	CO_2Et	**2a**	**4a**	90	90:10
2	4-Br	CO_2Et	**2a**	**4b**	91	92:8
3	5-Cl	CO_2Et	**2a**	**4c**	88	90:10
4	5-Br	CO_2Et	**2a**	**4d**	86	85:15
5	5-F	CO_2Et	**2a**	**4e**	92	82:18
6	5-NO_2	CO_2Et	**2a**	**4f**	85	80:20
7	6-Cl	CO_2Et	**2a**	**4g**	85	88:12
8	6-Br	CO_2Et	**2a**	**4h**	81	92:8
9	7-F	CO_2Et	**2a**	**4i**	84	85:15
10	5-Me	CO_2Et	**2a**	**4j**	78	86:14
11[d]	H	Benzoyl	**2a**	**4k**	75	80:20
12	H	CO_2Et	**2b**	**4l**	n.r.	-
13	H	CO_2Et	**2c**	**4m**	n.r.	-
14[e]	H	CO_2Et	**2b**	**4l**	52	88:12
15[e]	H	CO_2Et	**2c**	**4m**	58	85:15
16[f]	H	CO_2Et	**2a**	**4a**	87	90:10

[a] See entry 12 and footnote *a* in Table 1. [b] Yields of isolated **4.** [c] Calculated from ^{1}H NMR analysis of the crude reaction mixture. [d] The reaction was performed at 40 °C for 2 h. [e] 0.03 mmol of Proazaphosphatrane (PAP) was used. [f] The scaled-up reaction contained **1a** (3.0 mmol), **2a** (3.6 mmol), and TEA (0.6 mmol).

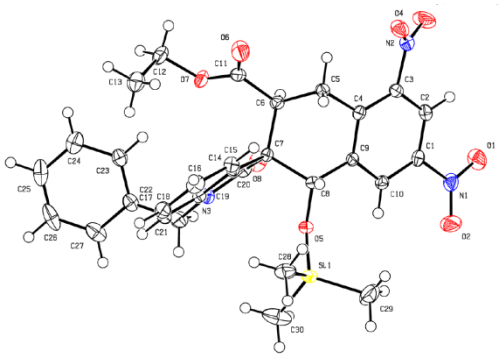
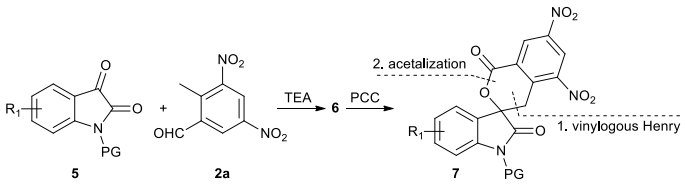


Fig. 3 ORTEP drwaing of compound **4a**.

An olefinic oxindole with a β-benzoyl group proved much less reactive than other olefinic oxindoles bearing ester group, necessitating slightly harsher conditions (entry 11). Mono-substituted nitrotoluenes displayed poor nucleophilicity, and our attempts to react **2b** or **2c** with 3-ylideneoxindole **1a** failed under optimized conditions (entries 12 and 13). However, when using Verkade's superbase (Proazaphosphatrane, PAP), the scope of the reaction could be successfully extended to **2b** and **2c**. To our satisfaction, the corresponding products **4l** and **4m** could be obtained in moderate yield (entries 14 and 15). The reaction scaled up well (entry 16). The relative configuration of **4a** was determined by X-ray crystallographic analysis (Fig. 3),[15] and the relative configurations of the other products were tentatively assigned by analogy.

Table 3 Synthesis of isochroman-fused spirooxindole derivatives[a]

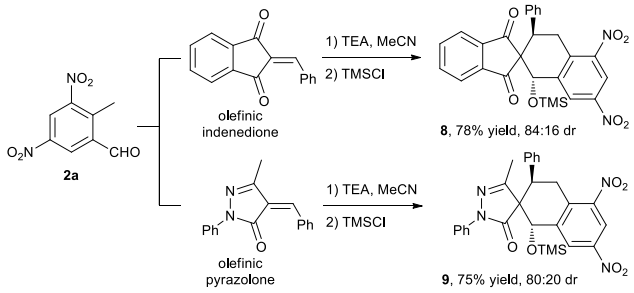


Entry	R^1	PG	Product	Yield (%)[b]
1	H	Bn	**7a**	79
2	4-Br	Bn	**7b**	81
3	5-Cl	Bn	**7c**	78
4	5-Br	Bn	**7d**	70
5	5-F	Bn	**7e**	80
6	5-NO_2	Bn	**7f**	79
7	6-Cl	Bn	**7g**	74
8	6-Br	Bn	**7h**	70
9	7-F	Bn	**7i**	80
10	5-Me	Bn	**7j**	65
11	H	Me	**7k**	72
12	H	Allyl	**7l**	78

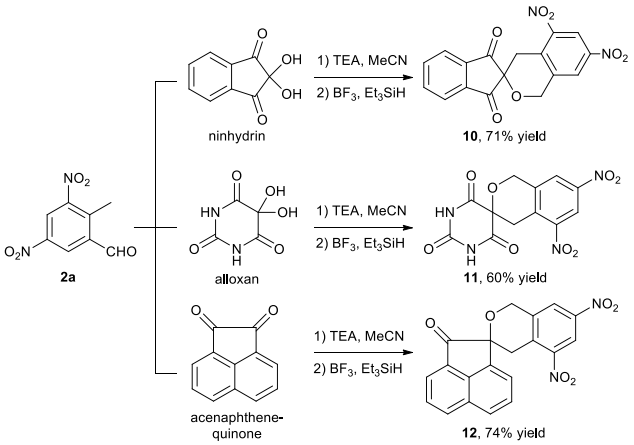
[a] Unless noted otherwise, reactions were performed with 0.3 mmol of **4**, 0.36 mmol of **2a**, and 0.06 mol of TEA in 4 mL acetonitrile at rt for 1 h. [b] Yield of isolated **7**.

Next we turned our attention to generating isochroman-fused spirooxindoles with multiple functional groups. The research groups of Zhu,[10a] Zhao[10b] and Ramachary[10c] have combined chroman and oxindole motifs, but the analogous combination of isochroman and oxindole has yet to be reported. Since 3-ylideneoxindole can undergo the Michael addition/aldol reaction sequence with 2-methylbenzaldehyde in Scheme 1, we reasoned that isatins could participate in an analogous [4+2] annulation reaction involving a vinylogous Henry reaction followed by acetalization. To our gratification, the domino reaction proceeded smoothly to afford the desired products **6a**-**6k** within 1 h (Table 3). Direct hemiacetal oxidation with pyridinium chlorochromate (PCC) gave the stabler spirocyclic lactone derivatives **7a**-**7j** in high yields. Methyl and allyl protecting groups on the isatins were well tolerated, affording the corresponding products **7k** and **7l**.

To further probe the usefulness of these domino reactions in diversity-oriented synthesis, we screened other activated trisubstituted olefins or cyclic carbonyl substrates (Schemes 2 and 3). Numerous synthetically useful substrates, including olefinic indenedione, olefinic pyrazolone, ninhydrin, alloxan and acenaphthenequinone, reacted smoothly to provide the corresponding drug-like spirocyclic products bearing tetrahydronaphthalene (**8** and **9**)[16] or isochroman (**10**-**12**) moieties in good yields.



Scheme 2 Synthesis of tetrahydronaphthalene-fused drug-like spirocyclic scaffolds via Michael-aldol tandem reaction.



Scheme 3 Synthesis of isochroman-fused drug-like spirocyclic scaffolds via vinylogous Henry-acetalization tandem reaction.

Conclusions

In summary, we have successfully developed a flexible and simple cascade reaction involving a Michael-aldol or vinylogous Henry-acetalization relay, and we have used the cascade reaction to assemble functionalized tetrahydronaphthalene- or isochroman-fused drug-like spirocyclic scaffolds. The mild reaction condition, short reaction time, and high tolerance for various functional groups make this method attractive for constructing pharmacologically interesting architectures. Our laboratory is now examining the bioactivity of the resulting spirocyclic compounds and developing organocatalytic asymmetric versions of these cascade reactions.[17]

Acknowledgements

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17 For the preliminary investigation on the catalytic asymmetric versions of these tandem reactions, see the ESI.