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Stereoselective synthesis of oxazino[4,3-*a*]indoles employing the oxa-Pictet–Spengler reaction of indoles bearing N-tethered vinylogous carbonate†

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A one-pot, sequential 2,3-bis-functionalization of indoles bearing N-tethered vinylogous carbonates employing an intramolecular oxa-Pictet–Spengler reaction followed by electrophilic substitution is developed for the stereoselective synthesis of oxazino[4,3-*a*]-indoles.

The indole nucleus is ubiquitous in nature and is an integral part of various alkaloid families and several pharmacologically attractive synthetic targets.[1] N-fused indoles have attracted considerable attention due to the varied biological activity associated with them. Mitomycin C and cryptaustoline possessing an N-fused indole unit have been associated with antitumour[2] and tubulin polymerization inhibitory activities.[3] Pyrazino[1,2-*a*]indoles are reported to be 5-HT_{2c} receptor agonists,[4] whereas oxazino[4,3-*a*]indole systems have been studied for their antidepressant and antitumor properties.[5] Given the biological significance of N-fused indoles, various methods have been reported for the synthesis of N-fused indole derivatives over the last several years. Recently, pyrazinoindoles have drawn significant attention from synthetic chemists.[6] However, methods for the synthesis of oxazinoindoles are scarcely available in the literature. Very recently, Chen and Xiao *et al.* reported synthesis of oxazino[4,3-*a*]indoles by cascade addition–cyclization reactions of (1*H*-indol-2-yl)methanols and vinyl sulfonium salts.[7] Though useful, this elegant method was largely limited to an unsubstituted or monosubstituted oxazine core and the stereoselective synthesis of the oxazine core was not discussed. Herein, we now describe a new approach for the stereoselective synthesis of oxazinoindoles employing an intramolecular oxa-Pictet–Spengler reaction of an indole moiety with N-tethered vinylogous carbonate.[8] The intramolecularity of the reaction ensures preferential electrophilic substitution of indole at a less nucleophilic C2 position. We further demonstrate that one-pot, electrophilic, bis-functionalization of indoles at C2 followed by the C3 position can also be achieved by sequencing the reaction judiciously.[9]

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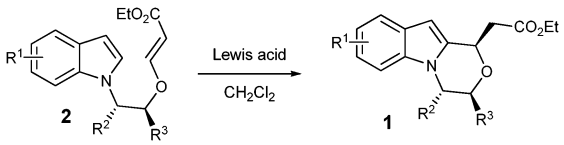


Scheme 1 Oxa-Pictet–Spengler cyclization for the synthesis of oxazinoindoles.

Vinylogous carbonates have been extensively used in the synthesis of cyclic ethers under radical conditions.[10] Recently, it has been demonstrated that they can act as Michael acceptors under anionic conditions.[11] It has also been shown that vinylogous carbonates can function similar to enol ethers and can act as a source of oxo-carbenium in the Prins type cyclization reaction.[12] However, these reports not withstanding, their utility under Lewis acidic conditions is still not well explored.

In a program directed at using vinylogous carbonates in the synthesis of cyclic ethers,[13] particularly under non-radical conditions,[14] we envisaged that the oxazinoindole derivative **1** can be readily assembled *via* an intramolecular oxa-Pictet–Spengler reaction on the indole derivative **2** bearing an N-tethered vinylogous carbonate moiety (Scheme 1). The requisite indole derivative **2** in turn could be readily prepared from the substituted indoles and appropriate epoxides (see ESI†).

To test the hypothesis, the vinylogous carbonate **2a** was subjected to the oxa-Pictet–Spengler reaction with various Lewis and Bronsted acids as catalysts. The results are summarized in Table 1. Lewis acids like $BF_3{\cdot}OEt_2$, $BiBr_3$, $TiCl_4$, $SnCl_4$ and $FeCl_3$ gave the oxazinoindole **1a** in poor to moderate yields albeit with excellent diastereoselectivity (Table 1, entries 1–5). Interestingly, when TMSOTf was used as the Lewis acid, the oxazinoindole **1a** was obtained in excellent yield and diastereoselectivity (Table 1, entry 6). On the other hand, Bronsted acids like TFA gave only a moderate yield due to partial decomposition (Table 1, entry 7). Milder Bronsted acid like (±)-binolphosphoric acid was found to be ineffective and only starting material was recovered even after prolonged reaction time (Table 1, entry 8). The *cis* stereochemistry of the oxazinoindole **1a** was ascertained by NOE experiments and by the single crystal X-ray diffraction studies (see, ESI†).

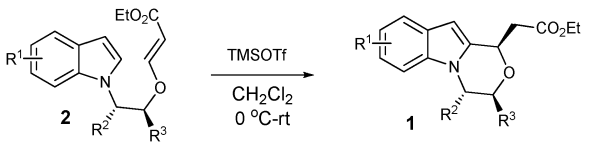
Table 2 outlines the scope of this oxa-Pictet–Spengler reaction of indole to vinylogous carbonates for the stereoselective synthesis of the oxazinoindoles **1**. The reaction was found to work well

Table 1 Optimization of the oxa-Pictet–Spengler cyclization for the synthesis of oxazinoindole **1a** using indole **2a** (R^1 = R^2 = H, R^3 = Me)

Entry	Catalyst	Equiv.	Temp./°C	Time/h	Yield[a,b] (%)
1	$BF_3{\cdot}OEt_2$	1.1	0–rt	1.5	30
2	$BiBr_3$	1.1	rt	1.5	54
3	$TiCl_4$	1.1	0-rt	1.5	42
4	$SnCl_4$	1.1	0-rt	3.5	56
5	$FeCl_3$	1.1	rt	0.5	53
6	*TMSOTf*	*1.1*	*0–rt*	*0.5*	*91*
7	CF_3CO_2H	2.0	rt	1.2	42
8	(±)-BPA[c]	1.1	rt	24	0

[a] Isolated yield. [b] In all the cases, dr was determined on the crude reaction mixtures by ^{1}H NMR and was found to be ≥ 19 : 1. [c] (±)-Binolphosphoric acid.

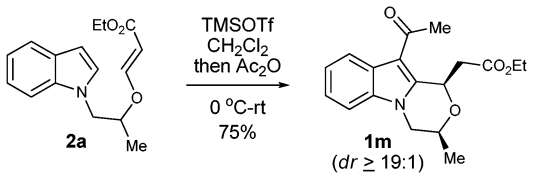
Table 2 Scope of the oxa-Pictet–Spengler cyclization for the synthesis of oxazinoindoles



Entry	R^1	R^2	R^3		Product	Yield[a,b] (%)	dr[c]
1	H	H	Ph	**2b**	**1b**	85	≥ 19 : 1
2	H	H	CH_2OBn	**2c**	**1c**	60	≥ 19 : 1
3	H	–$(CH_2)_4$–		**2d**	**1d**	56	≥ 19 : 1
4	H	–$(CH_2)_3$–		**2e**	**1e**	32	≥ 19 : 1
5	5-OMe	H	Me	**2f**	**1f**	92	≥ 19 : 1
6	5-OMe	H	Ph	**2g**	**1g**	72	≥ 19 : 1
7	5-Br	H	Me	**2h**	**1h**	54	≥ 19 : 1
8	5-Br	H	Ph	**2i**	**1i**	64	≥ 19 : 1
9	3-Me	H	Me	**2j**	**1j**	85	10 : 1
10	3-Me	H	Ph	**2k**	**1k**	75	7 : 1
11	3-Ph	H	Ph	**2l**	**1l**	74	5 : 1
12	3-Ac	H	Me	**2m**	**1m**	0	—

[a] Isolated yield. [b] In all the cases, reaction was conducted for 0.5–1.5 h (TLC control). [c] In all the cases, dr was determined on the crude reaction mixtures by ^{1}H NMR.

with alkyl and aryl substitutions leading to the formation of the product oxazinoindoles **1b–c** in good to excellent yields and diastereoselectivities (Table 2, entries 1 and 2). When an additional ring, either a six-membered or a five-membered, was present, reaction gave only a moderate yield of the corresponding oxazinoindoles **1d–e**, albeit with excellent diastereoselectivity (Table 2, entries 3 and 4). Substitution on the phenyl ring of the indole moiety did not have any detrimental effect on this reaction (Table 2, entries 5–8). Interestingly, in the cases where an alkyl or aryl substitution was present at the C3 position of indole, the products were formed in good yields but only with moderate diastereoselectivity (Table 2, entries 9–11). This could be attributed to the steric interaction similar to 1,3-allylic strain. Presence of an electron withdrawing acetyl group at the C3 position of indole, however, deactivated the indole moiety and the desired product could not be obtained (Table 2, entry 12). Prolonging the reaction time only led to decomposition of the starting material. Formation of the *cis* isomer as the major product in all the cases is consistent with the preference of the substituent R^3 and the incipient bulkier substituent (CH_2CO_2Et) to occupy the pseudo-equatorial as opposed to pseudo-axial orientation in the transition state in order to avoid 1,3-diaxial interaction.

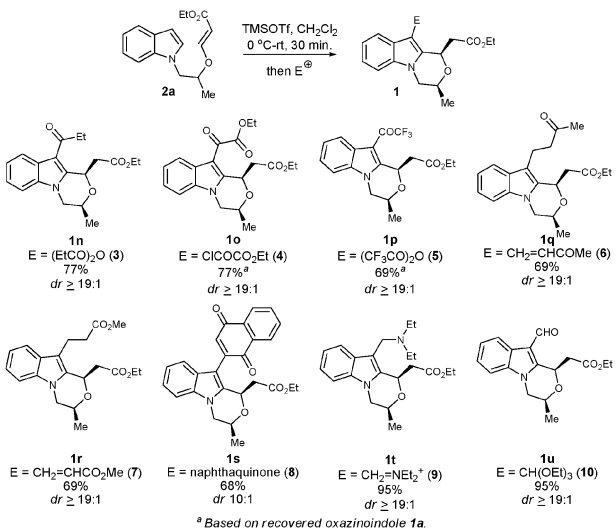


Scheme 2 One-pot, tandem oxa-Pictet–Spengler cyclization Friedel–Crafts acylation for the synthesis of oxazinoindoles.

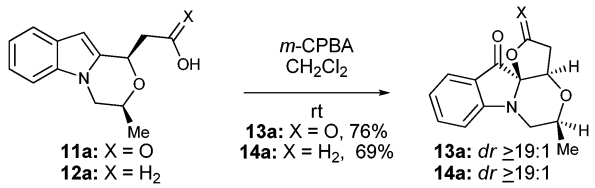
Inability of the 3-acetyl substituted indole derivative to undergo cyclization prompted a rethink of the strategy. It was envisaged that an acetyl group can be introduced at the C3 position of the indole in a tandem fashion *via* a Lewis acid mediated Friedel–Crafts acylation reaction post facto *i.e.* after the oxa-Pictet–Spengler cyclization of the indole moiety to vinylogous carbonate is effected at the C2 position to generate oxazinoindole. To test the hypothesis, the vinylogous carbonate **2a** was reacted with TMSOTf to generate the oxazinoindole **1a** (TLC control) which was acylated *in situ* in a tandem fashion by introducing Ac_2O to the reaction mixture. Gratifyingly, the reaction indeed furnished the acylated oxazinoindole derivative **1m** in excellent overall yield and diastereoselectivity (Scheme 2).

A careful survey of the literature revealed that there are very few reports available for *the sequential electrophilic substitution of C2 and C3 positions of indoles, particularly cases where C2 is functionalized prior to the C3 position.*[1] Hence, we decided to expand the scope of this tandem oxa-Pictet–Spengler electrophilic substitution reaction by trapping the C3 position of the indole moiety with various electrophiles leading to the synthesis of the substituted oxazinoindoles (Scheme 3).

Various anhydrides and acid chlorides like propionic anhydride (**3**), ethyl chlorooxoacetate (**4**), trifluoroacetic anhydride (**5**) were added to the reaction mixture after complete conversion of vinylogous carbonate **2a** to furnish the requisite 3-substituted oxazinoindoles **1n–p** in good yields and excellent diastereoselectivity (Scheme 3). Not only acyl equivalents but also Michael acceptors like methyl vinyl ketone (**6**) and methyl acrylate (**7**) were found to be useful electrophiles in this tandem oxa-Pictet–Spengler-electrophilic substitution reaction



Scheme 3 Scope of the one-pot, tandem oxa-Pictet–Spengler cyclization electrophilic substitution for the synthesis of oxazinoindoles.



Scheme 4 Tandem oxidative cyclization for the synthesis of spirooxindoles.

sequence furnishing the corresponding 3-substituted oxazinoindoles **1q** and **1r**, respectively, in good yields and diastereoselectivity. When 1,4-napthaquinone (**8**) was employed as the Michael acceptor, *in situ* oxidation of the substituted oxazinoindole was observed, thus regenerating the quinone moiety to form the oxazinoindole **1s** in good yield with respectable diastereoselectivity favouring the *cis* isomer. It's noteworthy that iminium **9** (formed by reacting diethyl amine and formalin) could also be employed in this one-pot synthesis to form the biologically important grammine type oxazinoindole **1t** in commendable yield and diastereoselectivity. The formylation at the C3 position could be accomplished employing triethylorthoformate (**10**) as the electrophile precursor furnishing the 3-formylated oxazinoindole **1u** in excellent yield and diastereoselectivity. It is pertinent to mention here that under the conditions employed for effecting the formylation, formation of the bis-indolyl methanes was not observed which is a problem in many related addition of indoles to aldehydes and ketones.

Spirooxindoles are part structures of various biologically important molecules and natural products.[15] We envisioned that elaboration of the oxazinoindole derivatives to spirooxindole derivatives will further expand the scope and utility of this strategy. Thus, the oxazinoindole **1a** was saponified to form the corresponding acid **11a**. Alternatively, it was reduced to the alcohol **12a** using lithium aluminium hydride. Tandem oxidative cyclization of the acid **11a** using *m*-CPBA furnished the lactone bearing spirooxindole **13a** in good yields.[16] Similarly, the alcohol **12a** gave the oxa-spirooxindole derivative **14a** in very good yields (Scheme 4). The stereochemistry of the oxa-spirooxindole derivative **14a** was unambiguously ascertained based on the NMR and the single crystal X-ray diffraction studies (see ESI†).

In summary, we have developed a general methodology for a highly stereoselective synthesis of the N-fused oxazinoindoles employing a TMSOTf mediated oxa-Pictet–Spengler reaction to vinylogous carbonate. We have also demonstrated a novel strategy for the 2,3-bis-functionalization of N-tethered indoles leading to disubstituted oxazinoindoles *via* a one pot, tandem oxa-Pictet–Spengler-electrophilic substitution reaction. Further, the oxazinoindole derivatives were efficiently elaborated into the oxa-spirooxindole derivatives using oxidative cyclization reaction.

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