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Communication

Allylation and alkylation of oxindoleketimines *via* imine umpolung strategy

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ABSTRACT

When treated with an alkoxide base like *t*-BuOK in aprotic solvent, *N*-diphenylmethyl imino oxindoles, made conveniently through condensation of corresponding isatins with *N*-diphenylmethyl amine, are deprotonated to form azaallyl anions. Allylation and alkylation of this type of intermediates proceed smoothly with diverse C-electrophiles. Acidic work up finishes 3-amino-3-allyl/alkyl oxindoles. The overall transformation equals to an umpolung process at the C3 of isatins.

Occurring widely both in nature products and synthetic agents of biologic significance, the structurally unique 3-substituted 3-amino-2-oxindole moiety is becoming a popular and privileged substructure in medicinal chemistry [1–7], as embodied by Chartellines A–C [8], gastrin receptor antagonist **AG-041R** [9], anti-bacterial agent spirooxindole **1** [10], anti-cancer agent **2** [11] and HIV protease inhibitor **3** [12] (Fig. 1). In the past 15 years, developing new protocols for the construction of this framework has constituted an active topic among synthetic chemists leading to a plethora of creative methods [1,2]. Almost all of literature syntheses fall in roughly three strategies (Scheme 1). Firstly, 3-alkyl oxindolate anion **5** reacts with appropriate electrophilic nitrogen sources leading to the formation of tetra-substituted oxindoles **4** (path a) [13]. Alternatively, alkylation of 3-amino oxindolate anion **6** with C-electrophiles can afford 3-amino-2-oxindole as well (path b) [14–32]. The addition of alkyl nucleophiles over the convenient oxindole imines **7** provides the third and probably the most widely adopted tactic (path c) [33–54]. Impressed by the umpolung reaction of imines [55–60], which could construct a C(sp^3)-C(sp^3) and a C(sp^3)-N bond simultaneously on a single carbon through the immediacy of azaallyl anion [61–69], we argued that this chemistry, if effective with oxindole (**8**) derived ketimine **9**, would provide a facile access to 3-alkyl-3-amino-2-oxindole considering the readily available oxindoles (path d). Herein, we would like to disclose our progress along this direction and report on a new preparative protocol for the core substructure under discussion.

Our studies began with exploring the reaction of *N*-diphenylmethyl ketimine **9a** with cinnamyl bromide **11a** (Table 1). Almost no reaction was detected after the introduction of **11a** into a premixed solution of **9a** with 2 equiv. Cs_2CO_3 in dichloromethane followed by stirring for 48 h at room temperature (entry 1). Employment of NaOH powder in place of Cs_2CO_3 resulted in a mixture with gradually deepened red color in 30 min. Upon addition of the allyl bromide, the red color faded away in 2 days and the desired 3-allyl-3-amino oxindole **4a** was obtained in a 10% yield after hydrolysis (entry 2). Impressively, an immediate color change to dark red took place with KOH as the base and a remarkable increment in the yield to 52% was observed (entry 3), manifesting the noticeable beneficial effects of the potassium counter ion on the reaction in comparison with its sodium congener. By using *t*-BuOK instead, instantaneous color change took place resulting in a further yield improvement to 67% (entry 4). Evaluation of several common solvents spanning a range of polarity (PhMe, THF, dioxane, MeCN, DMF) enabled the quick identification of THF as the optimal reaction medium, furnishing a clean reaction with a yield as high as 85% in only 12 h (entries 5–9). Cutting down the quantity of electrophile **11a** to 1.2 equiv. led to a slight drop in yield (entry 10). On the other hand, base deduction to

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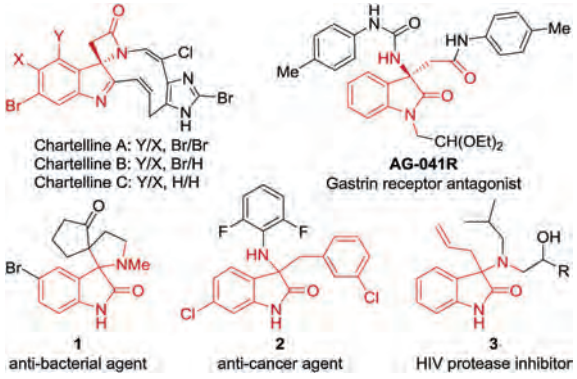
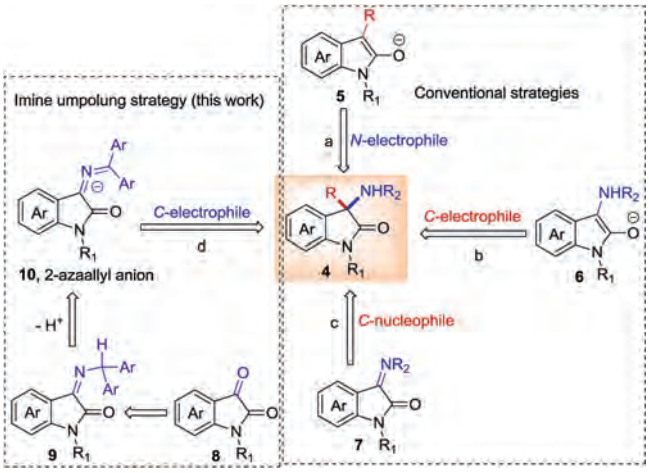
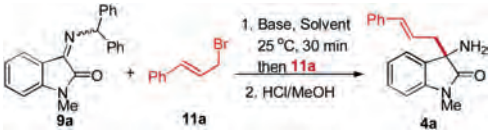


Fig. 1. Selected 3-alkyl-3-amino oxindoles of biological importance.



Scheme 1. Conventional and imine umpolung strategies toward 3-alkyl-3-amino oxindole.

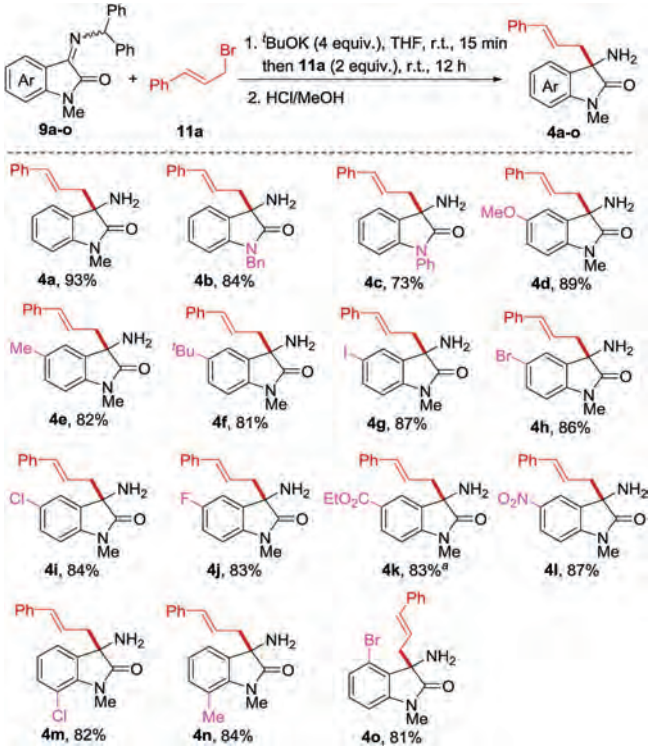
Table 1
Proof of concept and condition optimization.[a]



Entry	Ratio of **9a**/**11a**	Base (equiv.)	Solvent	Time (h)	Yield (%)[b]
1	1/2	Cs_2CO_3 (2.0)	CH_2Cl_2	48	< 5
2	1/2	NaOH (2.0)	CH_2Cl_2	48	10
3	1/2	KOH (2.0)	CH_2Cl_2	48	52
4	1/2	*t*-BuOK (2.0)	CH_2Cl_2	48	67
5	1/2	*t*-BuOK (2.0)	PhMe	48	48
6	1/2	*t*-BuOK (2.0)	THF	12	85
7	1/2	*t*-BuOK (2.0)	dioxane	48	56
8	1/2	*t*-BuOK (2.0)	MeCN	48	45
9	1/2	*t*-BuOK (2.0)	DMF	48	63
10	1/1.2	*t*-BuOK (2.0)	THF	12	78
11	1/2	*t*-BuOK (1.2)	THF	12	52
12	1/2	*t*-BuOK (4.0)	THF	12	93

[a] Conditions: **9a** (0.2 mmol), **11a**, base, solvent (2 mL), in a sealed tube, r.t., monitored by TLC.
[b] Isolated yield.

1.2 equiv. caused a drastic yield decline (entry 11), while triple-fold excess of *t*-BuOK could further promote the yield to 93% (entry 12). The appearance of the characteristic red color proved the formation and persistence of the corresponding 2-azaallyl anion

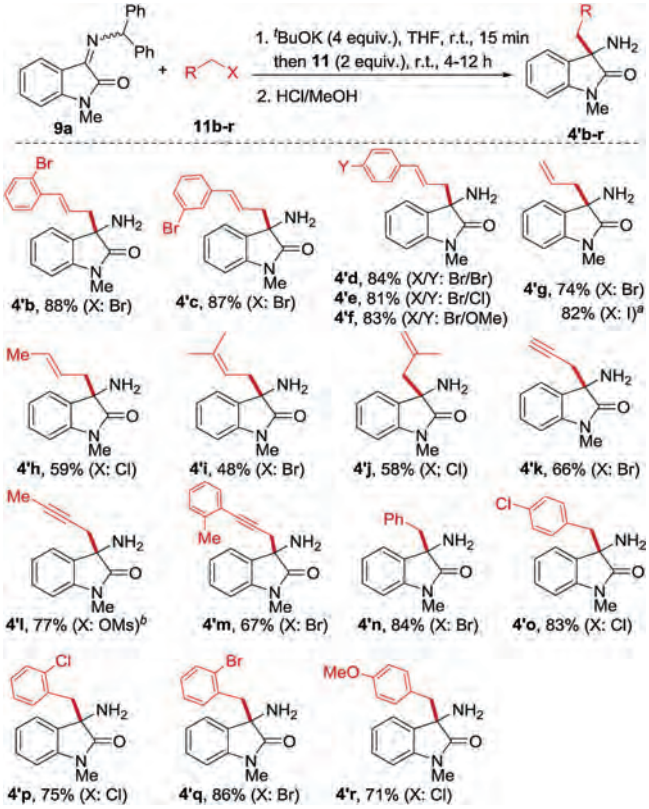


Scheme 2. The scope of oxindole ketimines. On a 0.25 mmol scale, isolated yields were reported. [a]Hydrolyzed with AcOH in MeOH.

10a. By now, the proof-of-concept reaction for umpolung alkylation of oxindole ketimine with C-electrophile was realized.

With optimized conditions in hand for the C3-alkylation of oxindole imine, we proceed to explore the scope of the ketimines (Scheme 2). As expected, **9b** with NBn group reacted smoothly to give **4b** in a high yield (84%) after column chromatography. The reaction of **9c** afforded product **4c** in a yield of 73%, and this perceptible yield decrease might attribute to the less stable NPh lactam group. Oxindole imines **9d-f** carrying electron releasing substituents MeO, Me and *t*-Bu at C5 reacted equally well with cinnamyl bromide to give **4d-f** in excellent yields (81%–89%). Halogenation at the same position did not exert any adverse effects on this process as evidenced by constantly high conversions of **9g-j** to products **4g-j**. Gratifyingly, with strong electron withdrawing ester and nitro groups at C5, **4k** and **4l** were obtained in 83% and 87% yield respectively from corresponding substrates **9k** and **9l**. These results shown that not only halides but also ester and nitro groups are compatible with the current basic conditions. The high yields of **4m** and **4n** indicated that substitution at C7 could barely affect the reaction outcomes. 4-Br oxindole derived ketimine **9o** achieved **4o** in 81% yield as well, in spite of the potential hindrance around the reacting site. These functionalities provide convenient handles for further chemical manipulations of these useful products.

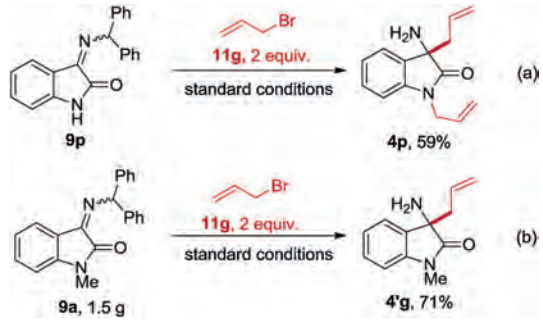
Next, with **9a** as the azaallyl anion precursor, we turned to explore the scope of electrophiles for this coupling process (Scheme 3). *ortho*-, *meta*- and *para*-Brominated cinnamyl bromides **11b-d** as well as the *para*-chloro homologue **11e** all reacted equally well as their parent bromide **11a**, delivering **4′b-e** in high yields (81%–88%). With 4-methoxylated cinmmyl bromide **11f**, a similar yield of **4′f** was obtained. In the comparison with allyl bromide (**11g**), allyl iodine (**11g'**) served as a better electrophile in terms of reaction yield (74% *vs.* 82%). Other aliphatic allyl halides such as (*E*)-crotyl chloride (**11h**), prenyl bromide (**11i**) and methylallyl chloride (**11j**) are all viable electrophiles affording 3-allyl-3-amino



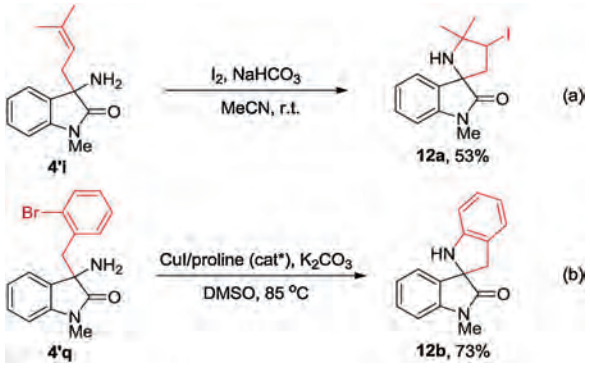
Scheme 3. The scope of electrophiles. On a 0.25 mmol scale, isolated yields were reported.[a]2 h. [b]6 equiv. of *t*-BuOK was used.

oxindoles **4′h-j** without any difficulties. The modest yields observed in these cases might be due to the relatively more labile alkenyl groups in the strong acidic hydrolyzing conditions. 3-Amino-3-propargyl oxindoles **4′k-m** were obtained all in good yields under the same conditions by coupling with related propargyl electrophiles **11k-m** (66%–77%). Besides halides, sulfonate could also serve as a good leaving group as evidenced by the efficient coupling reaction of **9a** with 2-butynyl mesylate (**11l**, 77% yield). At last, the azaallyl anion mediated nucleophilic C-alkylation of **9a** with a series of benzyl halides also proceeded smoothly, giving rise to **4′n-r** in high to excellent yields (71%–86%). The hindrance imposed by the *o*-Cl group in **11p** might account for the 10% drop in yield of **4′p** when compared with that observed for **4′o**.

In order to figure out the viability of N-unprotected substrates for this protocol, NH free ketimine **9p** was submmitted to the standard conditions employing allyl bromide **11g** (2 equiv.) as the electrophile. Double allylated product **4p** was isolated in a nice yield of 59% (Scheme 4a). To further demonstrate the usefulness of



Scheme 4. Reaction of NH substrate and gram-scale synthesis.



Scheme 5. Examples of application of products in synthesis.

the current reaction in organic synthesis [70,71], gram-scale reaction was carried out with **9a**. Pleasingly, **4′g** was smoothly collected in 71% yield (Scheme 4b).

The presence of the versatile allyl and propargyl groups endues the product with diverse potential transformations (Scheme 5). For example, treatment of 4′**i** with I_2 in the presence of $NaHCO_3$ in MeCN accomplished spirooxindole **12a** successfully (Scheme 5a) [72]. By applying Ullman-Ma coupling reaction [73,74], **4′q** was also smoothly converted into benzofused spiroxindole **12b** (Scheme 5b). It is worth to note that spirooxindoles make up a significant and highly wanted class of indole derivatives in the medicinal chemistry perspective [75–77]. These showcases underscore the usefulness of current reactions.

In summary, a convenient method for the synthesis of important 3-amino-3-allyl/alkyl oxindoles has been developed by using an imine umpolung strategy. *N*-Diphenylmethyl imino oxindoles can be allylated or alkylated successfully with carbon based electrophiles at the C3 position after treating with an appropriate base. This strategy of construction of oxindole quaternary C3 is realized through the intermediacy of azaallyl anions and provide a complementary access to 3-substituted 3-amino-oxidoles. Moreover, the products are also versatile molecules for further transformations, for example, biological important spirooxindoles can be obtained readily by one-step reactions.

Declaration of competing interest

The authors report no declarations of interest.

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