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A practical one-pot procedure for the synthesis of N–H isoquinolones

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ABSTRACT

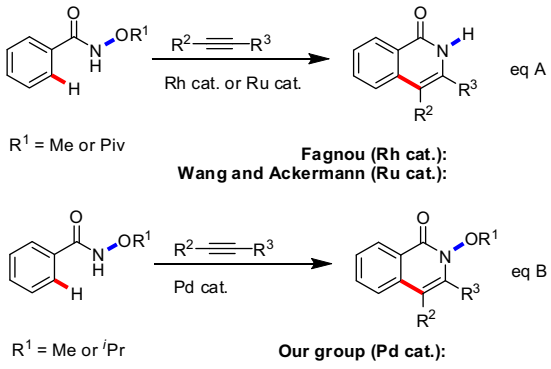
A practical one-pot procedure for the preparation of N–H isoquinolones has been developed. This 2-step process via C–H activation of *N*-alkoxyl benzamides and NaH-mediated dealkoxylation reaction has been demonstrated to be a high yielding alternative methodology for the efficient synthesis of a wide range of representative N–H isoquiolones. In addition, the experimental precedent supported mechanism of the dealkoxylation reaction was also proposed.

1. Introduction

There have been a considerable number of syntheses of isoquinolones using modern directing group associated direct C–H functionalization reactions in the last 3 years.[1,2] Among these amide directed and associated isoquinolone syntheses, when alkoxyl benzamide was utilized as the substrate, both C–H bond activation (Scheme 1, Eq. A, marked in red) and N–O bond cleavage (Scheme 1, Eq. A, marked in blue) were observed for Rh[3a,b]- and Ru[4b,d]-catalysed N–H isoquiolone syntheses.[2,3]

More recently we have reported new approaches using relatively cheap Pd-catalysts for the tailoring of these isoquinolones.[5a,b] Interestingly, we have found that under our Pd-catalysed conditions, when alkoxyl benzamides reacted with alkynes, the alkoxyl groups were retained without N–O bond cleavage detected and N–OR[1] isoquinolones were achieved instead of N–H isoquiolones. (Scheme 1, Eq. B)

As an alternative methodology to Rh[3]- and Ru[4]-catalysed N–H isoquiolone syntheses, our research interests have moved to the developement of a Pd-catalysed approach for the access of these versatile intermediates. Herein we report our latest discovery towards the practical synthesis of N–H isoquinolones via a two-step one-pot procedure from N-alkoxybenzamides. After Pd-catalysed isoquinolone ring formation, the reaction mixture was treated with NaH for deprotection to give N-unsubstituted isoquinolone. In addition, a plausible N–O bond cleavage reaction mechanism was also proposed at the end of the article.



Scheme 1. Rh-, Ru- and Pd-catalysed isoquinolone syntheses.

2. Results and discussion

2.1. Base screening for the demethoxylation reaction

Initial attempts on the direct one step synthesis of N–H isoquinolone by the introduction of inorganic bases were not successful. Only less than 10% of demethoxylated product was obtained in most of the cases when cheap readily available inorganic bases KOH, Na_2CO_3, NaOAc, K_3PO_4 and NaH were employed.

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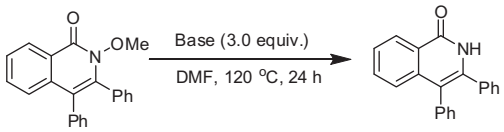


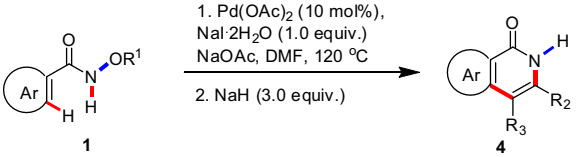
3a **4a**

Base		
NaOAc		16 %
Na_2CO_3		7%
NaOH		16%
K_3PO_4		20%
KOH		17%
Et_3N		14%
NaH	0.5 h	99%

Scheme 2. Base screening for the demethoxylation of isoquinoline.

Our attention was then moved to the demethoxylation of isoquinolone **3a** and we were attempting to develop a 2-step sequence instead of direct synthesis of N–H isoquinolone **4a**. Different from Cheng's photolysis for the demethoxylation of NN–OMe phenanthridinone for the synthesis of crinasiadine,[6] we serendipitously observed that the N–O bond cleavage occurred when isoquinolone **3a** was treated with inorganic bases. A base screening was then carried out and a number of readily available bases were examined. We were pleased to find that all the bases examined have shown positive results for the bond cleavage although some of the bases have resulted in slow conversion which gave rise to the desired product in low yields. As depicted in Scheme 2, inorganic bases such as NaOAc, NaOH, K_3PO_4 and KOH provided the N–H isoquinolinone **4a** in nearly 20% yield while Na_2CO_3 led to the product in

Table 1
One-pot synthesis of N–H isoquinolone **4**



R^2—≡—R^3 (**2**, 3.0 equiv.)

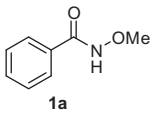
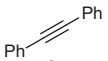
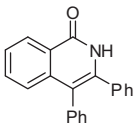
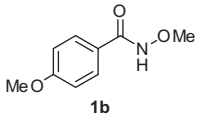
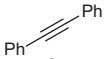
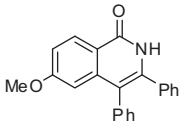
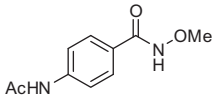
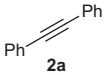
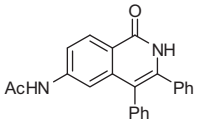
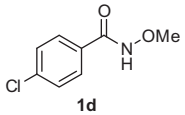
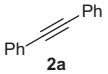
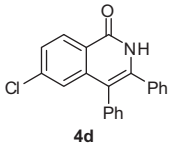
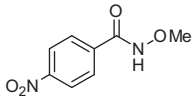
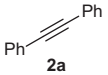
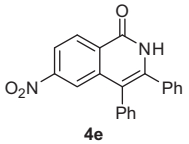
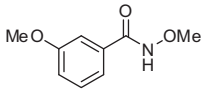
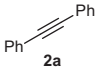
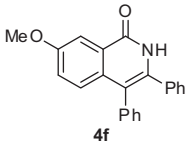
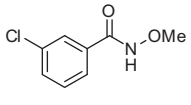
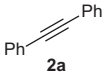
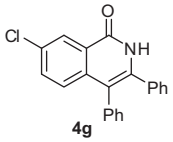
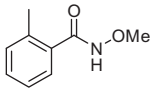
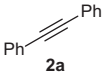
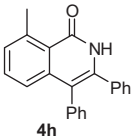
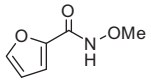
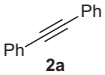
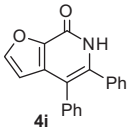
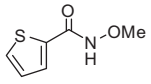
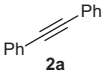
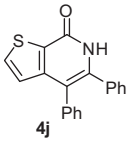
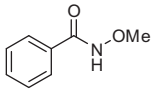
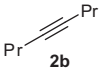
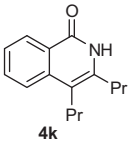
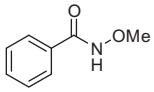
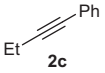
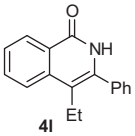
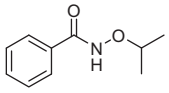
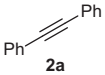
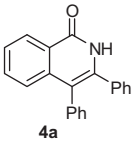
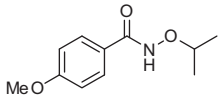
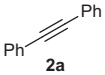
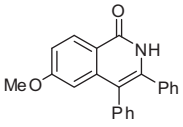
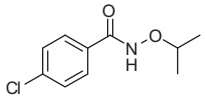
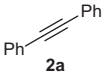
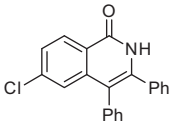
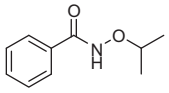
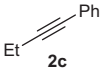
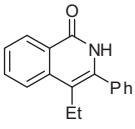
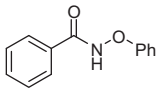
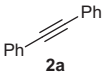
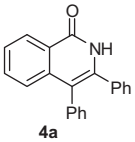
Entry	Benzamide **1**	Alkyne **2**	Isoquinolone **4**	Yield %
1	 **1a**	 **2a**	 **4a**	96
2	 **1b**	 **2a**	 **4b**	99
3	 **1c**	 **2a**	 **4c**	57
4	 **1d**	 **2a**	 **4d**	70
5	 **1e**	 **2a**	 **4e**	26
6	 **1f**	 **2a**	 **4f**	87
7	 **1g**	 **2a**	 **4g**	44[a]

Table 1 (*continued*)

Entry	Benzamide **1**	Alkyne **2**	Isoquinolone **4**	Yield %
8	 **1h**	 **2a**	 **4h**	80
9	 **1i**	 **2a**	 **4i**	90
10	 **1j**	 **2a**	 **4j**	81
11	 **1a**	 **2b**	 **4k**	76
12	 **1a**	 **2c**	 **4l**	94 (85)[b]
13	 **1h**	 **2a**	 **4a**	81
14	 **1i**	 **2a**	 **4b**	83
15	 **1j**	 **2a**	 **4d**	57
16	 **1k**	 **2c**	 **4l**	62 (56)[b]
17	 **1l**	 **2a**	 **4a**	89

[a] N–H isoquinolone **4a** was also isolated in 22% yield.
[b] The overall yield of 2 regioisomers and the yields in the parentheses are the yields for the major regioisomers.

less than 10%. Organic base, Et_3N also facilitated the desired product in 14% yield. NaH surprisingly, however, delivered the corresponding isoquinolone in an excellent 99% yield with much shorter reaction time.

2.2. One-pot procedure for the synthesis of N–H isoquinolones

On the basis of previous discovery of amide directed C–H activation synthesis of isoquinolones, modified reaction conditions

were utilized. In the presence of catalytic amount of $Pd(OAc)_2$, halide salt as well as NaOAc, under air conditions, the ring construction went fluently. After the reaction was completed, 3.0 equiv of NaH was added and the reaction underwent N–O bond cleavage to give our desired N–H isoquinolinones in good to excellent yields as illustrated in Table 1.

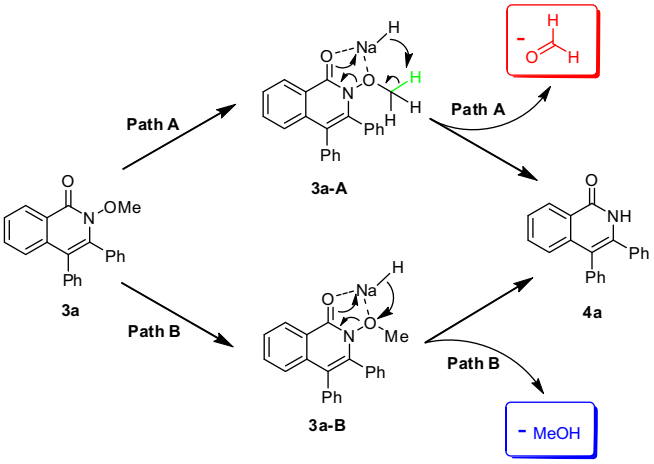
The reaction scope is wide enough which covered various benzamides, alkynes as well as N-substituents. Electron rich benzamide **1b** has shown excellent reactivity to give isoquinolone **4b** in 99% yield and the electron rich benzamide **1c** bearing another directing group also provided our desired product **4c** in a good 57% yield (Table 1, entries 2 and 3). Electron-deficient *para*-chloro benzamide **1d** is also tolerant for this type of transformation; the corresponding isoquinolone was obtained in 70% yield. Even benzamide with a strong electron-withdrawing nitro group *para* to the benzamide, the product was also formed albeit with a low yield (Table 1, entry 5). When benzamide with a *meta*-substituted halogen atom was subjected into the reaction system, we do find that during the cyclization and demethoxylation, dechlorination reaction occurred and the corresponding dechlorinated isoquinolone **4a** was isolated in 22% yield as well as 44% of our desired product **4g** (Table 1, entry 7). The introduction of *ortho*-substituent did not affect the reactivity; isoquinolone **4h** was successfully prepared in 80% yield. Different from Wang's Ru-catalysed reaction of thiophenyl amide reaction (a low 35% yield of desired product was isolated),[3d] under our conditions, heterocyclic amides are also demonstrated to be good substrates where the corresponding isoquinolones were accessed fluently with good 90% and 81% yields (entries 9 and 10). Symmetrical aliphatic alkyne behaved similarly as diphenyl acetylene to facilitate the dialkyl substituted isoquinolone **4k** in 76% yield. It is worth noting that when unsymmetrial alkyne **2c** was utilized, a mixture of 10:1 mixture of **4l** and **4l′** was observed and the major isomer **4l** was isolated in 85% yield (entry 12). The regioselectivity outcome has been rationalized in our previous Letter during the ring formation studies.[4a] Different N-substituents are also compared, hindered secondary alkyl substituted benzamides have demonstrated similar reactivity as well as regioselectivity as they gave the corresponding N–H isoquinolones in comparable good yields with good regioselectivity compared to N–OMe benzamides (Table 1, entries 13–16 versus entries 1, 2, 4 and 12). In addition, we were pleased to find that the reaction of N–OPh **1l** also facilitated our desired isoquinolone **4a** in a good 89% yield (Table 1, entry 17).

2.3. Mechanistic investigation of N–O bond cleavage process

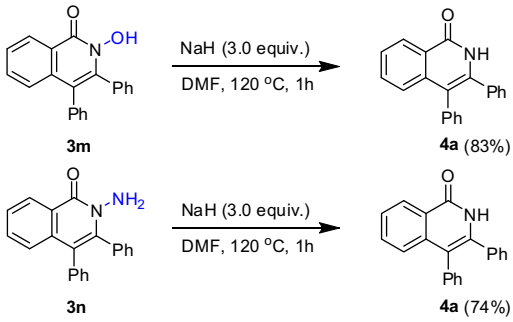
With respect to the reaction mechanism, we have proposed 2 possible reaction pathways. As illustrated in Scheme 3, take N–OMe isoquinolone **3a** for example, under pathway A, the N–O bond cleavage undergoes amide directed hydride deprotonation via intermediate **3a-A**, to give N–H isoquinolone **4a** with the loss of formaldehyde. Alternatively, the direct attack of hydride to the oxygen atom gives desired free N–H product with the elimination of MeOH.

Elucidating the appropriate reaction mechanism over the 2 possible pathways can be viable by choosing an isoquinolone without the α-proton (the proton marked green in colour) as shown in Scheme 3a-A. The treatment of isoquinolones **3m** and **3n**[7,8] with 3.0 equiv of NaH, gave our desired isoquinolone **4a** in good 83% and 74% yields respectively, after the reaction mixture was heated at 120 °C in DMF for 1 h (Scheme 4).

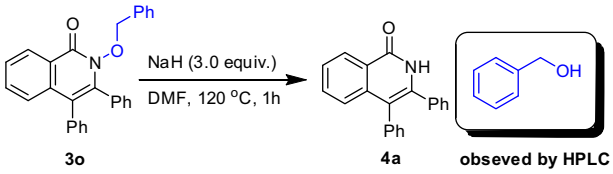
Theses experimental results as well as the results from the reaction of N–OPh (Table 1, entry 17) suggests that path B is likely to be the appropriate reaction pathway for the dealkoxylation reaction which is different from what Nikitin[9] had proposed in his earlier communication. This has also been further proved by the HPLC



Scheme 3. Proposed reaction pathways.



Scheme 4. The control reactions on the N–O bond cleavage



Scheme 5. HPLC analysis.

analysis of the crude reaction mixture, where we have successfully observed the formation of benzyl alcohol during the cleavage of N–OBn bond of isoquinolone **3o** (Scheme 5).

3. Conclusions

In summary, we have developed a practical one-pot procedure for the synthesis of a wide range of N–H isoquinolones in good to excellent yields. In addition, a plausible reaction pathway was proposed with experimental precedents. These would allow the synthesis of isoquinolones in an alternative high yielding protocol.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.02.003.

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