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Tandem Phospha-Michael Addition/*N*-Acylation/ Intramolecular Wittig Reaction of aza-*o*-Quinone Methides: Approaches to 2,3-Disubstituted Indoles

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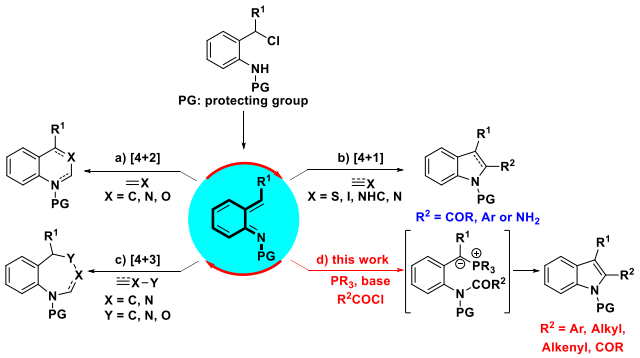
Abstract.A tandem phospha-Michael addition/*N*-acylation/intramolecular Wittig reaction of in situ formed aza-*o*-QMs is disclosed. This approach features high functional group tolerance and provides a convenient and practical access to biologically significant indole derivatives (37 examples, up to 91% yield) under mild reaction conditions.

Keywords:aza-*o*-Quinone Methides•Indoles•Intramolecular Wittig Reaction• Tandem Reaction•Phospha-Michael Addition

Aza-*ortho*-quinone methides (aza-*o*-QMs) are a versatilereactive intermediates which have found broad applications in synthetic chemistry.[1] To date, several strategies have been developed for the in situ generation of aza-*o*-QMs, including pyrolysis,[2] photolysis,[3] as well as Brønsted acid[4] or base[5-8] mediated 1,4-elimination. Pioneering works from the Corey and Steinhagen's group disclosed a formal [4+2] cycloaddition reaction of *N*-(*o*-chloromethyl)aryl amides with electron-rich olefins involving a Brønsted base promoted elimination step (Scheme 1a).[6a] After that, aza-*o*-QMs have been widely used for the construction of a variety of biologically important *N*-containing heterocycles through cycloaddition reactions, e.g., [4+1], [4+2], [4+3] cycloaddition reactions (Schemes 1a-c).[6-8] In this scenario, the [4+1] cycloaddition reactions of aza-*o*-QMs turn out to be an efficient and reliable method to indole derivatives,[9] which are privileged scaffolds in many natural isolates and therapeutic agents.[10] In this context, our group[7a],[7b] and Scheidt's group[7d],[7e] developed formal [4+1] cycloaddition reactions of aza-*o*-QMs with sulfur ylides or enolate equivalents *viaN*-heterocyclic carbene catalysis to access 2-acyl indole and 2-aryl indole scaffolds, respectively (Scheme 1b). Despite these advances, the further development of novel and efficient procedures towards the construction of indole skeletons with good functional group compatibility, through aza-*o*-QMs intermediates, remains highly desirable.

Phosphines, often served as nucleophiles, can react with a series of electron-deficient species. The resultant phosphonium zwitterions can subsequently participate in Wittig reactions by the interception of carbonyl electrophiles to form several heterocyclic compounds[11],[12] such as benzofurans and indoles. Based on these developments and our ongoing research interests in the development of heterocycle-oriented methodologies,[7a],[7b],[13] we envisioned that a phosphorus ylide can be first generated from the addition of phosphines to aza-*o*-QMs, and the following intramolecular Wittig reactions with the corresponding amide groups take place to produce highly funcitionalized indole compounds (Scheme 1d). To the best of our knowledge, there has hitherto been no known literatures related to the Michael additions of aza-*o*-QMs with phosphine nucleophiles and their further applications. Herein we report an efficient tandem phospha-Michael addition/*N*-acylation/intramolecular Wittig reaction of aza-*o*-

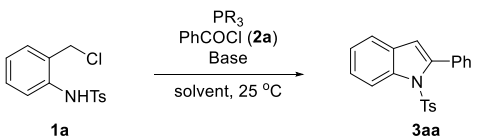
QMs, which allows the rapid access to 2,3-disubsituted indole derivatives (Scheme 1d).



Scheme 1. Cycloaddtion Reactions Involving aza-*o*-QMs from *N*-(*o*-chloromethyl)aryl amides.

We began our investigation by examining the reaction of *N*-(2-(chloromethyl)phenyl)-4-methylbenzenesulfonamide (**1a**) with PPh_3 and PhCOCl (**2a**) in the presence of Et_3N in CH_2Cl_2 at 25 °C. The desired indole product **3aa** was obtained in 55% isolated yield after 12 hours (Table 1, entry 1). Encouraged by these results, we then started to optimize the reaction conditions to improve the chemical yield (Table 1).[14] A brief survey of solvents revealed that CH_2Cl_2 was still the best choice in terms of yields (Table 1, entries 1-5). Next, we evaluated a series of bases, which were found to have a dramatic impact on the reaction efficiency (Table 1, entries 1 and 6-11). Notably, $CsOH·H_2O$ was identified as the optimal base for the formation of **3aa** (75% yield, Table 1, entry 11). Unfortunately, no positive result was observed with other phosphines (Table 1, entries 12-13). The protection group on the nitrogen of anilines plays an important role. When Bz group was employed as the protection group, the reaction is very slow at room temperature and only trace product was detected. In the case of Ns as the protection group, the isolated desired product contains the anhydride derived from benzoyl chloride. Finally, by prolonging reaction time to 72 hours, the yield of **3aa** was further improved to 89% (Table 1, entry 14)

Table1. Reaction Optimization [a]



Entry	Base	Solvent	PR_3	T(h)	Yield [%][b]
1	Et_3N	CH_2Cl_2	PPh_3	12	55
2	Et_3N	Et_2O	PPh_3	12	46
3	Et_3N	toluene	PPh_3	12	33
4	Et_3N	THF	PPh_3	12	52
5	Et_3N	CH_3CN	PPh_3	12	25
6	DABCO	CH_2Cl_2	PPh_3	12	trace
7	TMG	CH_2Cl_2	PPh_3	12	0
8	t-BuOK	CH_2Cl_2	PPh_3	12	12
9	NaOH	CH_2Cl_2	PPh_3	12	41
10	Cs_2CO_3	CH_2Cl_2	PPh_3	12	64
11	$CsOH·H_2O$	CH_2Cl_2	PPh_3	12	75
12	$CsOH·H_2O$	CH_2Cl_2	PBu_3	12	9
13	$CsOH·H_2O$	CH_2Cl_2	PPh_2Et	12	35
14[c]	$CsOH·H_2O$	CH_2Cl_2	PPh_3	24	81
15	$CsOH·H_2O$	CH_2Cl_2	PPh_3	72	89

[a] Reaction condition: **1a** (0.3 mmol), **2a** (0.36 mmol), PR_3 (0.33 mmol), and base (2.5 equiv.), solvent (3.0 mL).
[b] Isolated yield.
[c] 83% yield for 48 h.
Ts = 4-toluene-1-sulfonyl; DABCO: 1,4-diazabicyclo [2.2.2]octane; TMG: tetramethylguanidine.

With the optimal reaction conditions established, we then examined the substrate scope of this tandem reaction by employing a variety of *N*-(*ortho*-chloromethyl)aryl amides. As highlighted in Table 2, aside from **1a**, various *N*-(*ortho*-chloromethyl)aryl amides with electronically varied substituents, such as OMe, Me, OH, Br, Cl, at the para position relative to the sulfonamidenitrogen atom could readily participate in the tandem process, providing the corresponding cycloadducts in good yields (Table 2, **3ba**-**3fa**: 70%-89% yields). The tolerance of substituents at different positions on the benzene ring was also investigated (Table 2, **3ga**-**3ha**: 25%-83% yields). The low yield observed for **3ha** was probably due to the steric hindrance. The reaction of disubstituted *N*-(*ortho*-chloromethyl)aryl amide substrate **1i** also afforded the expected products **3ia** in 73% yield. Additionally, as shown in the reactions of **1j** and **1k**, variation of the protecting group can also be tolerated, and products **3ja** and **3ka** were obtained in 52%-90% yields. Notably, substrates bearing substituents at benzylic position were also suitable for this transformation and were converted to 2,3-disubstituted indole products **3la**-**3nb** (Table 2, 30%-85% yields). These results suggested that electronic variations of substituents at benzylic position affected the efficiency of the process owing to the stability of generated phosphorus ylides during the process.

The substrate scope with respect to acyl chloride 2 was also investigated. As summarized in Table 3, the reaction demonstrated wide scope and high functional group tolerance. An array of aromatic acyl chlorides (**2b**-**2h**) with various electron-donating (e.g., OMe, Me) or electron-withdrawing (e.g., NO_2, Br, Cl) substituents at the *para*-, *ortho*-, or *meta*-position of the phenyl ring were suitable substrates for the

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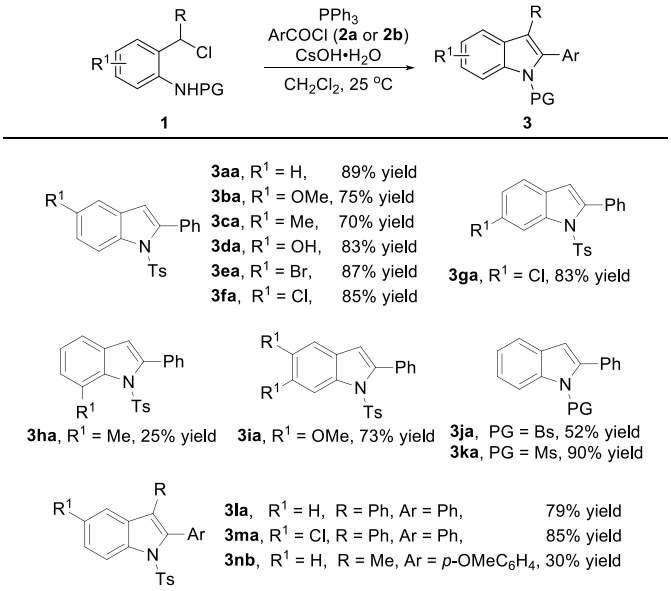
reaction And the corresponding products **3ab**-**3ah** were obtained in generally high yields (81-91%). The reaction of 2,4-disubstituted benzoyl chloride **2i** also provided the desired product **3ai** in 86% yield. Moreover, heteroaromatic acyl chlorides, such as **2j** and **2k**, could be tolerated under the reaction conditions, and cinnamoyl chloride (**2l**) and ester-substituted acyl chloride **2m** were also applicable in the reaction to give the products in 17-73% yields.

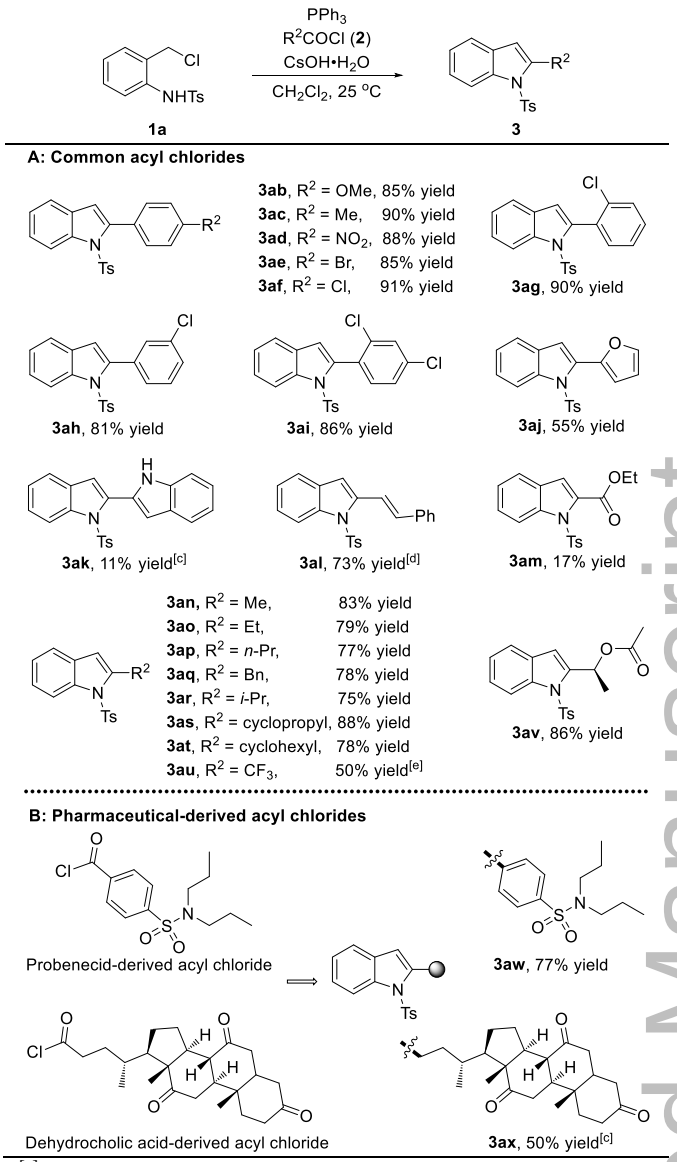
Table 2. Scope of *N*-(*ortho*-chloromethyl)aryl amides[a],[b]



[a]Reaction conditions: **1** (0.5 mmol), **2a** or **2b** (0.6 mmol),PPh_3 (0.33 mmol), and $CsOH{\cdot}H_2O$ (2.5 equiv.), anhydrous CH_2Cl_2 (5.0 mL) were used.
[b] Isolated yield.
Bs = benzenesulfonyl; Ms = methanesulfonyl.

Gratifyingly, the influence of aliphatic acyl chlorides with varying steric parameters on the reaction outcome was also examined. Methyl, ethyl, *n*-propyl,benzyl, *i*-propyl, cyclopropyl and cyclohexyl substituents are all well tolerated, leading to indole products **3an**-**3at** in good yields (75-88%). Additionally, trifluoroacetic acid anhydride (**2u**) smoothly underwent the developed reaction, and indole **3au** bearing a CF_3 substituent was delivered in 50% yield. Remarkably, reaction using chiral acyl chloride **2v** also furnished the desired product **3av** in 86% yield. To further demonstrate the synthetic utility of this method in a medicinal chemistry setting, we also tested the model reaction of pharmaceutical-derived acyl chlorides (Table 3B). To our delight, both probenecid- and dehydrocholic acid-derived acyl chlorides participated in the tandem reactions smoothly to give the coressponidng products (**3aw** and **3ax**) in 77% and 50% yields, respectively. These results showed the potential application of the current reaction in late-stage structural elaboration of drugs.

Table 3. Scope of acyl chlorides[a],[b]



[a]Reaction conditions: **1a**(0.5 mmol), **2** (0.6 mmol), PPh_3 (0.55 mmol), and $CsOH{\cdot}H_2O$ (2.5 equiv.) in anhydrous CH_2Cl_2 (5 mL) were used, 72 h.
[b] Isolated yield.
[c]The acyl chloride was freshly prepared and used directly, see the supporting information for details..
[d]4-Dimethylaminopyridine (0.05 mmol) was used.
[e]Trifluoroacetic acid anhydride (**2u**) (0.6 mmol) was used.

Furthermore, the reaction performed on a gram scale also worked well to furnish product **3af** in 80% yield (Scheme2a). As a proof of concept, we demonstrated an efficient tandem reaction of **1a** and **2a** and the deprotection of Ts group in a one-pot reaction, providing *N*-H indole **4aa** in 85% yield (Scheme 2b).

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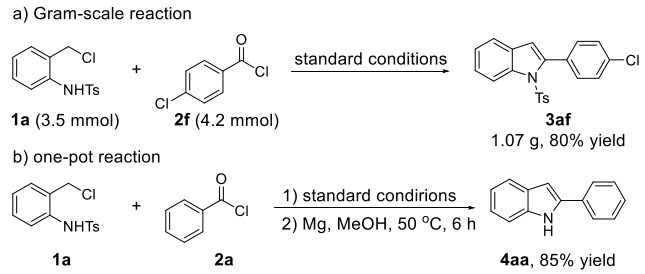
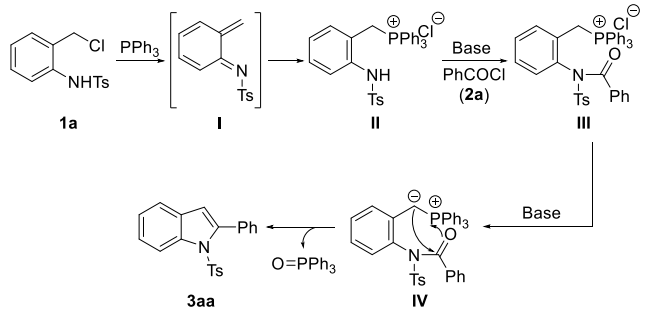


Scheme 2. Follow-up Chemistry.

Based on the above experimental results and previous reports,[1b],[6-8],[12g] a tentative mechanism for this model reaction of **1a**, **2a** as an example is exemplified in Scheme 3. Initially, the reaction of PPh_3 with **1a** generates the phosphonium salt **II***via* the *in situ* generated aza-*o*-QMs **I**. Then, the phosphonium salt **II** undergoes an acylation with benzoyl chloride **2a** under basic conditions to provide intermediate **III**, which could be further deprotonated by another equivalent of base to afford phosphorus ylide **IV**. This step is followed by intramolecular Wittig reaction with generation of triphenylphosphine oxide, completing the reaction process. On the basis of the proposed mechanism, we also wished to explore the possibility of employing catalytic phosphine in our protocol. Unfortunately, nosatisfactory results were obtained probably because of the stability of phosphonium intermediates.[14]



Scheme 3. Plausible Reaction Mechanism

In summary, we have developed a tandem phospha-Michael addition/*N*-acylation/intramolecular Wittig reaction of aza-*o*-QMs from *N*-(*ortho*-chloromethyl)aryl amides under mild conditions. This protocol features broad substrate scope, mild and simple reaction procedures, providing a practical access to valuable indole derivatives in moderate and good yields. Further studies of additional applications of aza-*o*-QMs toward the synthesis of heterocyclic compounds are currently underway in our laboratory.

Experimental Section

General procedure:A dry 10 mL Schlenk flask equipped with a magnetic stirring bar, was sequentially charged with *N*-(2-(chloromethyl)phenyl)-4-methylbenzenesulfonamide**1a** (0.5 mmol, 1.0 equiv.), dichloromethane (5.0 mL), PPh_3 (0.55 mmol, 1.1 equiv.), $CsOH{\cdot}H_2O$ (1.25 mmol, 2.5 equiv.) and acyl chloride**2a** (0.6 mmol, 1.2 equiv.). The reaction mixture was stirred for 72 h at 25°C, the reaction was monitored *via* TLC (petroleum ether/ethyl acetate =8:1). Thereafter, the reaction mixture was purified by flash chromatography on silica gel (petroleum ether/ ethyl acetate = 10:1-40:1) to give the desired product **3aa**as a white solid in 89% yield.

Acknowledgements

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[14]For more details, please see the supporting information

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Tandem Phospha-Michael Addition/*N*-Acylation/ Intramolecular Wittig Reaction of aza-*o*-Quinone Methides: Approaches to 2,3-Disubstituted Indoles

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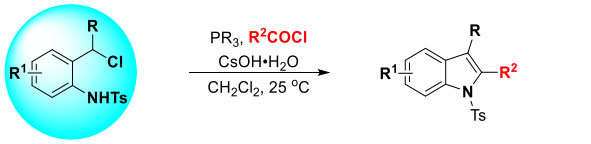

- application of aza-*o*-QMs
- high FG tolerance
- significant indole framework
- 37 examples with up to 91% yield