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PAPER

Aryne [3 + 2] cycloaddition with *N*-sulfonylpyridinium imides and *in situ* generated *N*-sulfonylisoquinolinium imides: a potential route to pyrido[1,2-*b*] indazoles and indazolo[3,2-*a*]isoquinolines†

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The aryne [3 + 2] cycloaddition process with pyridinium imides breaks the aromaticity of the pyridine ring. By equipping the imide nitrogen with a sulfonyl group, the intermediate readily eliminates a sulfinate anion to restore the aromaticity, leading to the formation of pyrido[1,2-*b*]indazoles. The scope and limitation of this reaction are discussed. As an extension of this chemistry, *N*-tosylisoquinolinium imides, generated *in situ* from *N*′-(2-alkynylbenzylidene)-tosylhydrazides *via* an AgOTf-catalyzed *6-endo-dig* electrophilic cyclization, readily undergo aryne [3 + 2] cycloaddition to afford indazolo [3,2-*a*]-isoquinolines in the same pot, offering a highly efficient route to these potential anticancer agents.

Introduction

During the past five years, the aryne [3 + 2] dipolar cycloaddition has received significant interest among the synthetic community. With the introduction of 2-(trimethylsilyl)aryl triflates as a modernized aryne precursor,[1] old processes have been re-visited and renovated,[2] difficult processes have been realized,[3] and new reactivities have been observed.[4] Now, the aryne [3 + 2] dipolar cycloaddition has been increasingly considered as a synthetic tool toward medicinally relevant heterocycles, and aryne considered as a synthetic building block instead of a simple reactive intermediate. With our growing interest in aryne [3 + 2] cycloaddition chemistry, a few "non-traditional" dipoles started to catch our attention.[5]

Pyridinium imide (**1**, Fig. 1), also called *N*-iminopyridinium ylide or pyridin-*N*-imine,[6] has been traditionally recognized as a masked azomethine imine.[7] Historically, it has been reported to undergo [3 + 2] cycloaddition[8] with a wide range of dipolarophiles, including electron-poor alkynes[6,9] nitriles,[10] and others. However, despite the knowledge gained during the study, the humble yields of these reactions made them poorly respected as synthetic tools. This is because: i) pyridinium imide is unstable and has to be generated *in situ* from *N*-aminopyridinium halides (**2**, Fig. 1) with a base, and side-reactions such as dimerization may occur; ii) the initial [3 + 2] cycloaddition (Scheme 1, process A) breaks the aromaticity of the pyridine ring and thus

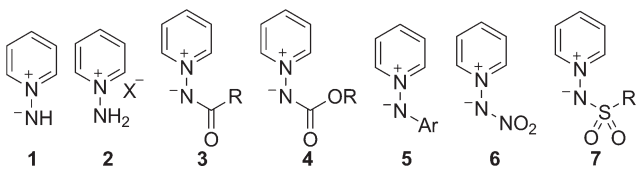
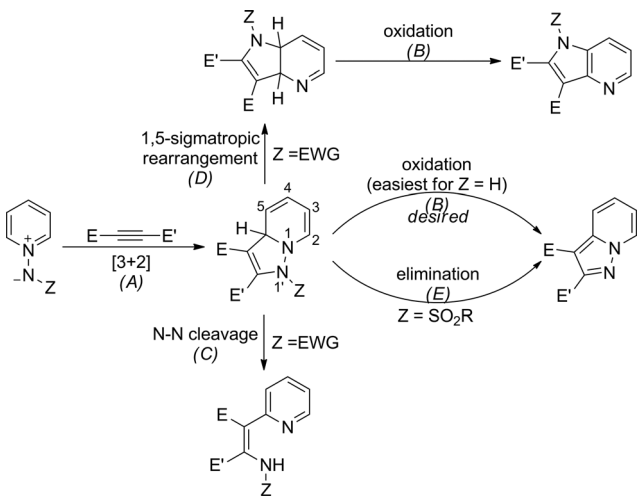


Fig. 1 Pyridinium imides and related structures.



Scheme 1 [3 + 2] Cycloaddition of pyridinium imides with dipolarophiles: different process after the cycloaddition.

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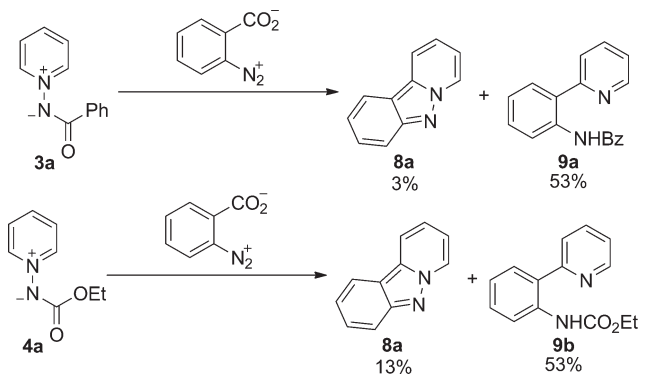
leads to an unstable intermediate, which has to be oxidized to afford the final "desired" product (Scheme 1, process B).

To solve the first problem, *N*-substituted pyridinium imides (**3–6**, Fig. 1) were introduced, where the exocyclic nitrogen was equipped with electron-withdrawing groups such as acyl (**3**),[11] alkoxycarbonyl (**4**),[12] aryl (**5**),[13] and even nitro groups (**6**).[14] Such modification indeed brought the desired stability of the starting material, but the process B now may involve an additional step (such as hydrolysis of the alkoxycarbonyl or acyl groups) and becomes even more problematic. Other unwanted processes such as N–N bond cleavage (Scheme 1, process C)[12] and sigmatropic rearrangement (Scheme 1, process D)[15] started to compete, making the entire reaction outcome heavily dependent on the exact structural nature of the substrates and dipolarophiles. The overall yields of the "desired" product often became even worse.

This problem remained unaddressed until *N*-sulfonyl derivatives (**7**, Fig. 1) were introduced.[16] Unlike aryl, acyl or alkoxycarbonyl groups, a sulfonyl group can behave as a leaving group.[17] Therefore, the [3 + 2] cycloaddition intermediate can readily eliminate a sulfinate group (Scheme 1, process E) to restore the aromaticity and afford the desired product.[18] This modification has been used to afford the "desired" products much more cleanly, although the yields remained to be optimized.

As a research group focusing on aryne chemistry, we considered that the "desired" reaction between aryne and those pyridinium imide derivatives shown in Fig. 1 should be of great value as it produces a structurally interesting yet under-presented pyrido[1,2-*b*]indazole scaffold **8**.[19] However, we were surprised to find that there was only one single report in the literature describing this cycloaddition with disappointing results (Scheme 2).[20] Thus, imide **1** was found to react directly with diazotized anthranilic acid prior to the formation of benzyne. Imide **3a** or **4a** reacted to produce **9** as the major products after the N–N bond cleavage, and the desired [3 + 2] adduct **8a** was formed in only trace quantities in both cases. Inspired by Ellis and Sundberg's work,[16] we envisioned that employing *N*-sulfonylpyridinium imides **7** as the starting material should lead to a smooth reaction to pyrido[1,2-*b*]indazoles (**8**), and hopefully will provide a synthetically useful approach to this scaffold. To our pleasure, we have demonstrated the preliminary success of this proposed approach in an earlier communication,[21] and herein we wish to disclose in full our investigation, including an expansion in the reaction scope.



Scheme 2 Aryne [3 + 2] cycloaddition with pyridinium imide derivatives.

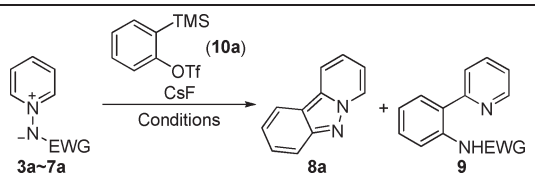
Results and discussion

Choice of the imide nitrogen substitution

Our first effort was to examine different electron-withdrawing groups on the imide nitrogen to test our hypothesis. Considering the ease of synthesis, acyl, alkoxycarbonyl, and sulfonyl groups were of major interest (Table 1).

Not surprisingly, substrates equipped with acyl groups, such as Bz (entry 1) and Piv (entry 2), were found to afford poor yields of **8a**. Those with alkoxycarbonyl groups such as Cbz (entry 3) and Boc (entry 4) were no better, although the latter offered a much cleaner reaction with a high yield of **9**. Varying the solvent, temperature, or the fluoride source did not change this product distribution (entries 5–7), and addition of either base (Cs_2CO_3, for easier hydrolysis of the Boc–N bond) or oxidant (I_2, for easier oxidation) resulted in even more complex mixtures (not shown).[22] In sharp contrast, imide **7a** with a Ts group afforded a 65% yield of **8a** cleanly (entry 8). Upon changing the reaction conditions to refluxing THF, the yield increased to 85% with only 1.2 equiv of aryne precursor **10a** used (entry 10). Thus, it can be clearly and safely concluded that the sulfonyl group on the imide nitrogen was superior to arguably any acyl or alkoxycarbonyl group regarding the formation of the desired product **8** and was the key solution to the successful synthesis of pyrido[1,2-*b*]indazoles this way. Noticeably, an

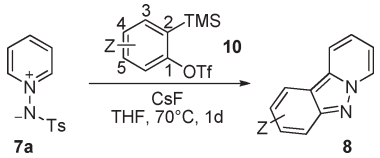
Table 1 Influence of different electron-withdrawing groups[a]

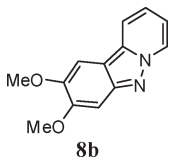
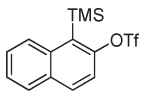
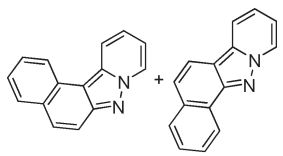


Entry	EWG	Reaction conditions	Yield of **8a** (%)[b]	Yield of **9** (%)[b]
1	Bz (**3a**)	MeCN, 50 °C, 16 h	24	0
2	Piv (**3b**)	MeCN, 50 °C, 16 h	complex mixture	
3	Cbz (**4b**)	MeCN, 50 °C, 16 h	30	7
4	Boc (**4c**)	MeCN, 50 °C, 16 h	10	86
5		MeCN, rt, 24 h	39	59
6		THF, 70 °C, 24 h	30	62
7[c]		THF, −78 °C to rt, 24 h	16	33
8	Ts (**7a**)	MeCN, 50 °C, 16 h	65	0
9		THF, 70 °C, 24 h	83	0
10[d]		THF, 70 °C, 24 h	85	0
11[d,e]		THF, 70 °C, 24 h	34	0

[a] Reaction conditions: 0.3 mmol of imide, 0.45 mmol of **10a**, 0.9 mmol of CsF in 4 mL of solvent. [b] Isolated yields. [c] TBAF (3.0 equiv) was used instead of CsF. [d] 1.2 Equiv of **10a**. [e] 1.5 Equiv of CsF.

Table 2 Scope of arynes[a]



Entry	10	Yield of 8 (%)[b]	Yield (%)[b]
1	Z = 4,5-(MeO)$_2$ (**10b**)	 **8b**	88
2	Z = 3-(MeO) (**10c**)	 **8c**	77[c]
3	 **10d**	 **8d+8d'**	<40[d]

[a] Reaction conditions: 0.3 mmol of **7a**, 0.36 mmol of **10**, 0.9 mmol of CsF in 4 mL of THF. [b] Isolated yields. [c] The regiochemistry was assigned by NOESY experiment. See ref. 21. [d] Low conversions of both **7a** and **10d**. Regioselectivity ~1 : 2, but we were unable to tell which one is the major isomer.

additional equivalent of CsF was necessary to promote the elimination of Ts^-, as a control experiment with only 1.5 equiv of CsF led to significantly lower conversions of both **7a** and **10a** and the yield dropped to 34% (entry 11). Thus, the reaction conditions described in entry 10, Table 1 were used as the standard conditions for the subsequent study.

Reaction scope of *N*-tosylpyridinium imides

The scope of aryne precursors (**10**)[23] was examined next (Table 2). The symmetrical aryne generated from **10b** afforded the desired product **8b** in an 88% yield (entry 1). The unsymmetrical aryne from **10c** gave a 77% yield of **8c** as a single regioisomer *via* the attack of the imide nitrogen at the *meta* position (with respect to the OMe group) (entry 2). Unfortunately, attempts to employing α-naphthalyne as the aryne partner under the standard reaction conditions resulted in low conversions of both starting materials (entry 3), and both a low yield (<40%) and a poor regioselectivity were obtained. This might suggest that the scope of the current reaction is limited to substituted benzynes only.

A range of *N*-tosylpyridinium imides was subsequently examined (Table 3), which varied in substitution patterns and electronics. It should be pointed out beforehand that most *N*-tosylpyridinium imides with a leaving group at the 2-position are not accessible[24] and thus are not in the scope of our investigation. 2-Alkyl variants such as **7b** (entry 1) worked well and cycloaddition took place cleanly at the 6 position. 4-Substituted pyridinium imides worked as well but satisfactory yields were only observed when the substitution was an alkyl (entry 2) or electron-withdrawing groups (entries 3 and 4). Imide **7f** derived from DMAP afforded a very modest 40% yield (entry 5). A few polysubstituted pyridinium imides were also examined. Symmetrical 3,5-dimethyl substrate **7g** afforded a 73% yield of the desired product **8j** (entry 6),[25] and a 2,6-dimethyl substrate **7h** was even reactive, leading to a low yield of **8e** where one methyl was lost (entry 7). The 2,4-dimethyl substrate **7i** (entry 8) and the 2,3,5-trimethyl substrate **7j** (entry 9) were also successfully transformed to the desired products in 54% and 75% yields, respectively.

We next paid attention to substrates monosubtituted at the 3-position. Clearly, the reaction still worked well for substrates equipped with electron-withdrawing groups (entries 10–12) or an alkyl group (entry 13), but not with strong electron-donating groups such as a morpholino group (entry 14). Regretfully, despite the high yields obtained for these substrates, the cycloaddition did not provide reasonable regioselectivity between the 2- and 6-positions. Although it can be seen that there is a slight preference for the 2-position over the 6-position (especially for 3-halo substrates as shown in entries 10 and 11), no apparent trends for electronic or steric factors can be generally concluded. Given that similarly poor regioselectivity has been reported for the [3 + 2] dipolar cycloaddition of pyridinium imides (series **1** in Fig. 1) with ethyl propiolate,[26] these results are at least not surprising.

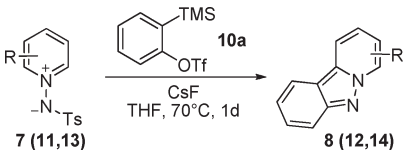
Beyond pyridine-derived imides, those derived from related fused heterocycles, such as quinoline (compound **11a**) and isoquinoline (compound **13a**), were also tested. As can be seen, quinolinium imide **11a** afforded a 92% yield of **12a** (entry 13), and isoquinolinium imide **13a** afforded an 87% yield of **14a** (entry 14) with good regioselectivity favoring the α position.

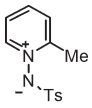
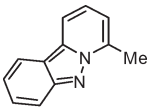
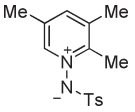
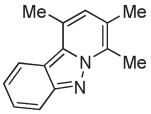
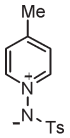
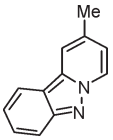
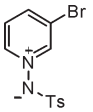
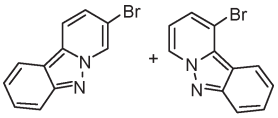
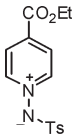
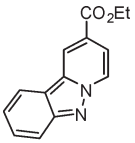
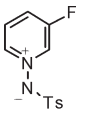
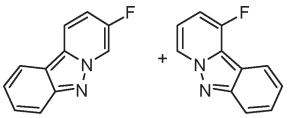
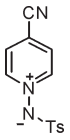
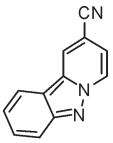
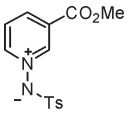
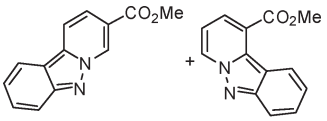
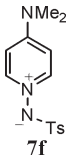
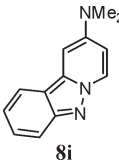
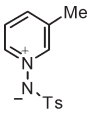
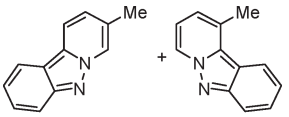
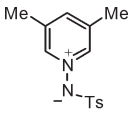
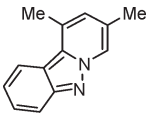
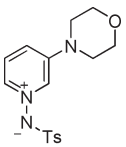
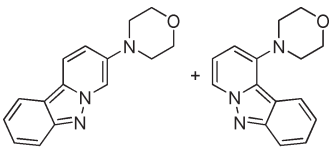
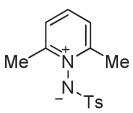
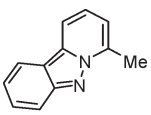
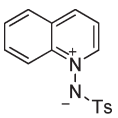
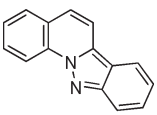
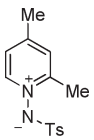
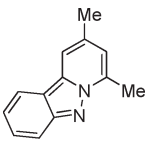
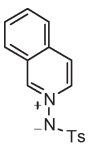
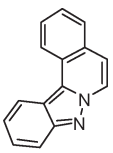
One substrate that is particularly worth mentioning is the imide **7p** derived from 3-bromo-5-methoxypyridine (see Scheme 3). This substrate was chosen because its electronics fell in between **7k** and **7o** and thus could provide more information as to the scope and limitation of the reaction with respect to the electronics of the pyridine ring. Meanwhile, its unsymmetrical substitution pattern would also bring an interesting regioselectivity issue for further discussion. Unfortunately, **7p** was found to react with benzyne to afford **15a** and **15b** in a 93% combined yield.[27] Neither **8r** nor **8r′** was observed. Apparently, the elimination did not occur but a sigmatropic rearrangement (process D in Scheme 1) took place that eventually led to the products **15a** and **15b**. While what exactly caused this change in reactivity remained elusive,[15b] the product distribution again suggested that the initial [3 + 2] cycloaddition took place without apparent regioselectivity.

Employment of *N*-nosylpyridinium imides

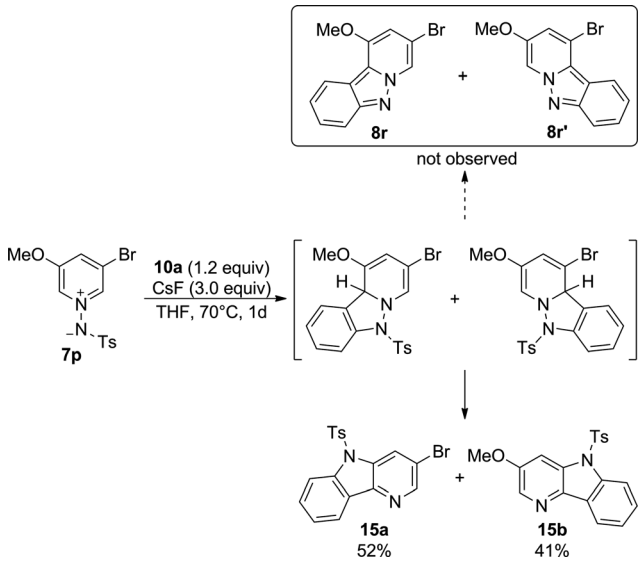
With the successful development of the [3 + 2] cycloaddition–elimination process, we wished to further improve the chemistry. Since the elimination of the sulfinate anion is the key to this reaction, replacement of the tosyl group with a more electronegative analogue, and thus a better leaving group, might perhaps

Table 3 Scope of *N*-tosylpyridinium imides[a]



Entry	7	Product	Yield (%)[b]	Entry	7	Product	Yield (%)[b]
1	 **7b**	 **8e**	93	9	 **7j**	 **8l**	75[c]
2	 **7c**	 **8f**	90	10	 **7k**	 **8m+8m'**	29 + 62[d]
3	 **7d**	 **8g**	90	11[d]	 **7l**	 **8n+8n'**	24 + 45[e,f]
4	 **7e**	 **8h**	66	12	 **7m**	 **8o+8o'**	52 + 47[d]
5	 **7f**	 **8i**	40	13	 **7n**	 **8p+8p'**	88[d,g] (0.8 : 1)
6	 **7g**	 **8j**	73	14	 **7o**	 **8q+8q'**	complex mixture
7	 **7h**	 **8e**	18	15	 **11a**	 **12a**	92
8	 **7i**	 **8k**	54[c]	16	 **13a**	 **14a**	87[h]

[a] Reaction conditions: 0.3 mmol of **7** (or **11**, **13**), 0.36 mmol of **10a**, 0.9 mmol of CsF in 4 mL of THF. [b] Isolated yields. [c] This product is slightly contaminated with a trace quantity of phenyl *p*-toluenesulfinate. The ^{1}H NMR spectrum is clean, but the ^{13}C NMR spectrum contains the signals of phenyl *p*-toluenesulfinate. [d] The two regioisomers can be distinguished by ^{1}H NMR spectroscopy. The H at 7-position has no *ortho* coupling for the 8-substituted isomer, but has one *ortho* coupling for 10-substituted isomer. [e] 2.0 Equiv. of **10a** was employed. [f] The two regioisomers can be distinguished by ^{13}C NMR spectroscopy. See ref. 21. [g] The two regioisomers were inseparable, and the ratio was obtained by ^{1}H NMR spectroscopy. [h] The crude ^{1}H NMR spectrum revealed a trace quantity of the other regioisomer, but it was not isolable.



Scheme 3 Reaction with *N*-tosyl-3-bromo-5-methoxypyridinium imide.

help to address some of the existing problems. The nosyl group (2-nitrobenzenesulfonyl, Ns) came into our view (Table 4). Indeed, the 2,6-lutidine-derived *N*-nosyl imide **16a** reacted with benzyne to afford a much higher 34% yield of **8e** (entry 1, Table 4, compare with entry 7, Table 3), suggesting that a better leaving group indeed provided a stronger driving force for the reaction. The same trend was observed with substrate **16b** (entry 2). While the Ts-derived imide **7p** afforded no product **8**, the Ns-derived imide furnished a modest 34% yield of **8r′**, albeit that the rearranged product **15c** was still formed. Surprisingly, these two products combined may indicate a good regioselectivity of the cycloaddition taking place only at the position *ortho* to bromine.

However, further study revealed that the employment of Ns failed to provide improvements in either the yield or the regioselectivity in general, as both compounds **16c** and **16d** afforded lower yields compared with the Ts counterparts, and a poorer regioselectivity in the former case as well (entries 3 and 4, compare with entries 10 and 12, Table 3). Imide **16e** also afforded product **8j** in a much lower 55% yield (entry 5, compare with entry 6, Table 3). These data, taken together with the fact that we were unable to prepare the Ns version of substrates **7f** and **7o**, further showed that the Ns-derivatives are inferior to the Ts-derivatives, despite the improved results obtained for **16a** and **16b** compared with those for **7h** and **7p**.

Reaction scope with *in situ* generated *N*-tosylisoquinolinium imides

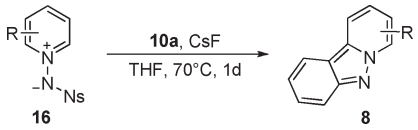
The success in the reaction of *N*-tosylisoquinolinium imide **13a** with benzyne (entry 16, Table 3), especially its good regioselectivity, encouraged us to make a further study of this cycloaddition. Its product, indazolo[3,2-*a*]isoquinoline, has been recognized as an effective DNA intercalator in the literature and exhibits anticancer activities.[28] However, due to the lack of synthetic methods,[20,29] derivatives thereof in the literature remained limited and therefore SAR studies remained to be done. With our [3 + 2] cycloaddition of arynes with *N*-tosylisoquinolinium imides as a tool, we hoped that a simple and effective method for the synthesis of such scaffold could be established and a library of structurally diverse derivatives could be constructed.

However, we have realized and have to point out that *N*-tosylisoquinolinium imides such as **13a** are not always easily prepared. Not only may multi-step synthesis of substituted isoquinolines be required,[25e,30] but also the *N*-amination step[24] may have possible issues of variable yields and functional group compatibility. Thus, alternative approaches needed to be sought. The AgOTf-catalyzed electrophilic cyclization of *N*′-(2-alkynylbenzylidene)hydrazides (**17**) (Scheme 4, first step), developed by Wu and others,[30b,31] caught our attention. Not only can this cyclization afford the desired *N*-tosylisoquinolinium imides *in situ* directly from readily available starting materials, but the mildness of this reaction would also potentially allow for telescoping these two reactions as a one-pot protocol from **17** directly to **14** without separation and isolation of the intermediate **13** (Scheme 4). Encouraged by this idea, we started the investigation of this one-pot protocol.

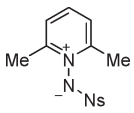
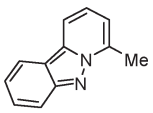
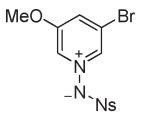
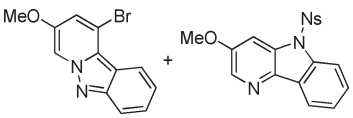
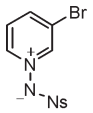
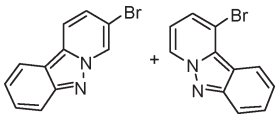
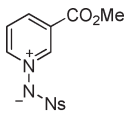
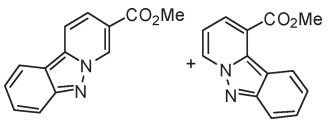
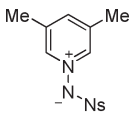
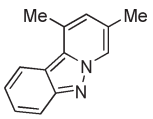
Our first effort was to optimize the reaction conditions of this sequence (Table 5). Since the AgOTf-catalyzed cyclization has been successfully performed in various solvents, including THF and MeCN which are most often used in aryne chemistry, we started our optimization with THF, which was optimal in the cycloaddition. Indeed, treatment of hydrozone **17a** with 10 mol % of AgOTf in refluxing THF led to a complete conversion to imide **13b**. Without isolation and purification, benzyne precursor **10a** and CsF were added directly to the reaction mixture and it was again heated to reflux. At the end of the reaction, a satisfactory 92% yield of **14b** was isolated (entry 1), demonstrating the smoothness of the reaction. However, subsequent studies led to the finding that this protocol gave capricious and somewhat irreproducible yields as low as 55%.[32] Nonetheless, switching the solvent to MeCN was found to give a reliable yield with good reproducibility (entry 2). Regrettably, all attempts to achieve a true one-step protocol without the batchwise addition of reagents failed.

Next, we examined a range of *N*′-(2-alkynylbenzylidene)-tosylhydrazides (**17**) under the standard protocol (Table 6). As can be seen, the reaction tolerated different R^1 groups including alkyl (entry 1), ether (entry 3), and halogens (entries 2 and 4) and was insensitive to electronics. High yields (>80%) could be almost always achieved. In terms of the R^2 group, substituted phenyl groups were suitable (entries 6 and 7) and again, electronic factors did not seem to play an important role. However, heteroaromatic groups showed different compatibilities. While a thiophenyl group was well tolerated and gave an 89% yield of the product **14j** (entry 8), a pyridyl group was detrimental to the reaction (entry 9). Closer investigation led to the finding that it was the electrophilic cyclization step that failed. Alkyl groups were also examined and showed no adverse effects on the overall reaction under these conditions. Not only was an unfunctionalized pentyl group completely compatible (entry 10), but a substrate containing a fairly acid-sensitive acetal group led to the successful formation of **14m** in a 60% yield (entry 11). Finally, substrate **17m** with a silyl group was tested (entry 12). Needless to say, the TMS group would not survive the aryne cycloaddition step due to the presence of fluoride. Thus, the aryne

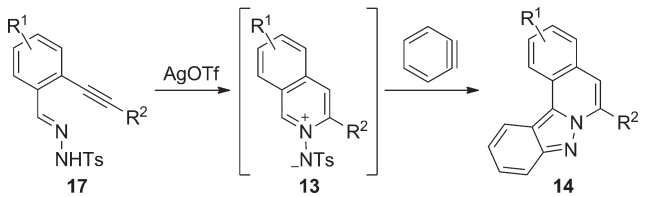
Table 4 Employment of *N*-nosylpyridinium imides[a]



16 8

Entry	16	Product	Yield (%)[b]
1	 16a	 8e	34
2	 16b	 8r'+15c	34[c]+22
3	 16c	 8m+8m'	28 + 41
4	 16d	 8o+8o'	25 + 26
5	 16e	 8j	55

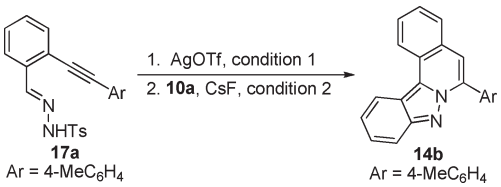
[a] Reaction conditions: 0.3 mmol of **16**, 0.36 mmol of **10a**, 0.9 mmol of CsF in 4 mL of THF. [b] Isolated yields. [c] Regiochemistry was assigned by NOESY experiment. See ESI.†



Scheme 4 One-pot cyclization–cycloaddition sequence from *N*′-(2-alkynylbenzylidene)hydrazides to indazolo[3,2-*a*]isoquinolines.

cycloaddition step was carried out with one additional equiv. of CsF, as well as 10 vol% of MeOH in the solvent to facilitate the protodesilylation. Although this reaction proceeded as desired, we noticed that the presence of the silyl group seriously retarded the electrophilic cyclization step, likely because the TMS group created large steric bulk around the cyclization site. Therefore, more AgOTf had to be employed and a longer reaction time was necessary. Even so, the overall yield was still modest. It should be mentioned that the electrophilic cyclization from **17** to **13**, as shown in Scheme 4 (first step), is limited to aldehyde-derived hydrazides. Hydrazides derived from ketones, even 2′-alkynylacetopheones, did not work and did not afford any meaningful products.

Table 5 Optimization of the one-pot protocol[a]

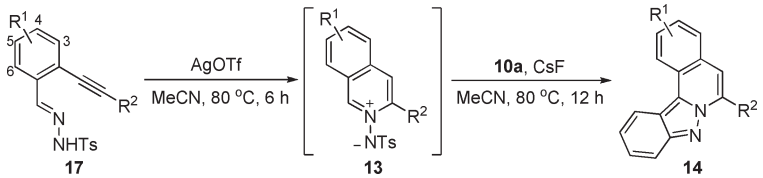


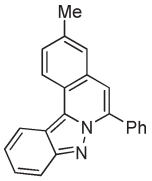
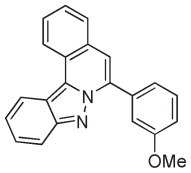
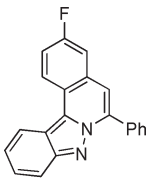
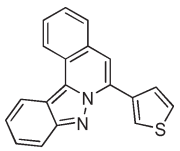
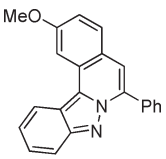
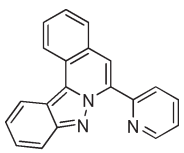
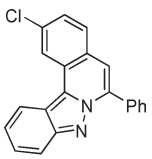
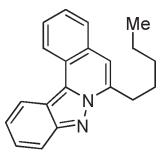
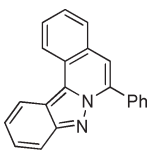
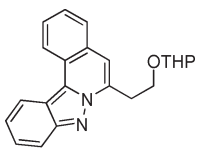
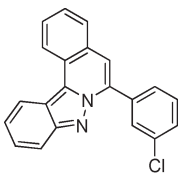
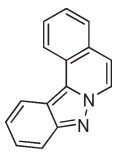
Entry	Condition 1	Condition 2	Yield (%)[b]
1	THF, 70 °C, 8 h	THF, 70 °C, 16 h	55–92[c]
2	MeCN, 80 °C, 6 h	MeCN, 80 °C, 12 h	87[d]

[a] Reaction conditions: 0.3 mmol of **17a**, 0.03 mmol of AgOTf in 4 mL of solvent, then 0.36 mmol of **10a**, 0.9 mmol of CsF. [b] Isolated yield. [c] Capricious. Yield varied from run to run. [d] Reproducible.

Besides possible modifications of R^1 and R^2 groups, the reagent initiating the electrophilic cyclization can also be modified. It is well known that in addition to those π-acidic coinage metal catalysts such as AgOTf, I_2 and equivalents also

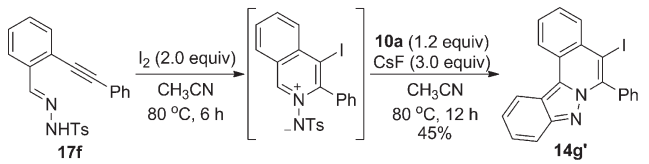
Table 6 Scope of *N′*-(2-alkynylbenzylidene)-tosylhydrazides[a]



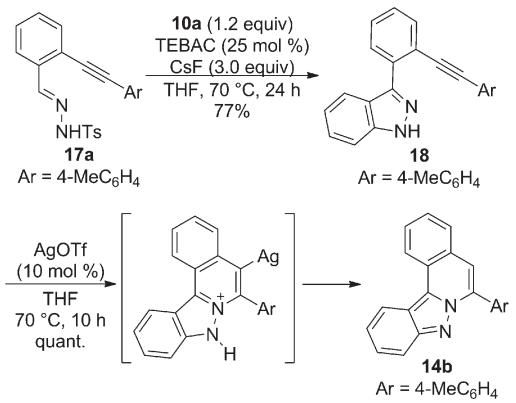
Entry	17	R^1, R^2	Product	Yield (%)[b]	Entry	17	R^1, R^2	Product	Yield (%)[b]
1	**17b**	R^1 = 4-Me R^2 = Ph	 **14c**	83	7	**17h**	R^1 = H R^2 = 3-(MeO)C_6H_4	 **14i**	81
2	**17c**	R^1 = 4-F R^2 = Ph	 **14d**	82	8	**17i**	R^1 = H R^2 = 3-thiophenyl	 **14j**	89
3	**17d**	R^1 = 5-MeO R^2 = Ph	 **14e**	88	9	**17j**	R^1 = H R^2 = 2-pyridyl	 **14k**	0[c]
4	**17e**	R^1 = 5-Cl R^2 = Ph	 **14f**	86	10	**17k**	R^1 = H R^2 = pentyl	 **14l**	76
5	**17f**	R^1 = H R^2 = Ph	 **14g**	85	11	**17l**	R^1 = H R^2 = $(CH_2)_2$OTHP	 **14m**	60
6	**17g**	R^1 = H R^2 = 3-ClC_6H_4	 **14h**	81	12	**17m**	R^1 = H R^2 = TMS	 **14a**	40[d]

[a] Reactions conditions: 0.3 mmol of **17a**, 0.03 mmol of AgOTf in 4 mL of MeCN, then 0.36 mmol of **10a**, 0.9 mmol of CsF. [b] Isolated yields. [c] The cyclization failed to work. [d] The cyclization was carried out with 30 mol% of AgOTf for 5 d, and the cycloaddition was carried out with 4 equiv of CsF, and an additional 0.4 mL of MeOH in a sealed tube for 16 h.

exhibit good affinity to triple bonds and can initiate similar electrophilic cyclizations.[33] Thus, we employed I_2 as the electrophile in the first step and carried out the reactions under otherwise identical conditions (Scheme 5). Delightfully, the reaction worked well with substrate **17f** and the iodinated product **14g′** could be isolated in a moderate 45% yield without additional optimization. Clearly, products obtained this way will have an additional handle for further manipulation under Pd-catalyzed cross-coupling events, potentially leading to a diverse library of functionalized indazolo[3,2-*a*]isoquinolines.



Scheme 5 One-pot iodocyclization–cycloaddition sequence to 5-iodoindazolo[3,2-*a*]isoquinolines.



Scheme 6 A cycloaddition–cyclization sequence from **17** to **14**.

Another route from 17 to 14: a cycloaddition–cyclization sequence

The potential application of the [3 + 2] cycloaddition of arynes with *in situ* generated *N*-tosylisoquinolinium imides intrigued us to move yet another step forward. The *N*-tosylhydrazone moiety of the structure **17** has been demonstrated to react with arynes in a [3 + 2] annulation fashion, partly through an *in situ* generated diazo intermediate.[34] If the same event could occur to compound **17** in the presence of the internal alkyne, compound **18** could be obtained. A subsequent yet unprecedented electrophilic cyclization[35] could lead to the same product **14** as obtained from the aforementioned cyclization–cycloaddition sequence (see Scheme 6). This new protocol might provide another option for the synthesis of the indazolo[3,2-*a*]isoquinoline scaffold.

Thus, substrate **17a** was first examined under the reaction conditions optimized for the annulation between arynes and *N*-tosylhydrazones.[34] Delightfully, the process afforded a 77% yield of product **18**, where the internal alkyne moiety was unreactive. Compound **18**, upon treatment with catalytic quantity of AgOTf, smoothly and cleanly cyclized to **14b** in a quantitative yield (Scheme 6). Thus, this second route to indazolo[3,2-*a*]isoquinoline proved also successful.

Conclusions

In conclusion, we have demonstrated that aryne [3 + 2] cycloaddition with *N*-tosylpyridinium imides can be a facile, effective, and operationally simple route to pyrido[1,2-*b*]indazoles and analogues. The sulfonyl group on the imide nitrogen was the key to this reaction. The reaction can be well extended to *N*-tosylisoquinolinium imides generated *in situ* from *N*′-(2-alkynylbenzylidene)tosylhydrazides, and a one-pot cyclization–aryne [3 + 2] cycloaddition sequence to prepare indazolo[3,2-*a*]isoquinolines has been realized. At this minute, certain limitations still exist and need to be addressed in future studies, including the poor results obtained from electron-rich pyridinium imides, as well as the poor regioselectivity for the 3-substituted substrates. Nonetheless, these methods provide a reasonable approach to the pyrido[1,2-*b*]indazole and indazolo[3,2-*a*]isoquinoline scaffolds, and potential applications in library synthesis can be expected.

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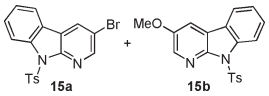

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