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Z-Selective synthesis of *o*-bromoacetophenone *N*-tosylhydrazones and formation of 3-methylindazoles in aqueous ethanol

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ABSTRACT

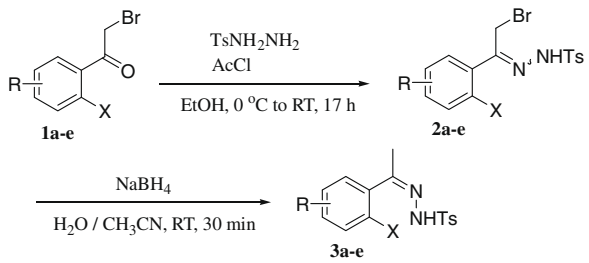
A practical and effective *Z*-selective synthesis of *o*-bromoacetophenone *N*-tosylhydrazones is developed. Subsequent cyclization of *Z*-tosylhydrazones to furnish 3-methylindazoles is accomplished with the aid of copper and DMEDA in aqueous ethanol. Cyclization reactions are complete at ambient temperature in 10 min to afford the desired compounds in excellent yields.

Among the myriad methods for the preparation of indazoles,[1] one of the most elegant routes is the catalytic cyclization of hydrazones derived from *o*-halogenated aromatic carbonyl compounds.[2] Although modern methods offer several advantages over classical indazole syntheses, there is still a demand for improvement when taking reaction time, reaction temperature, and yields into account. Recently, Inamoto et al.[2d] examined the reactivity of *N*-tosylhydrazones in Pd-catalyzed indazole formation. The desired indazole was obtained from the *Z*-isomer in excellent yield while the *E*-isomer was totally decomposed under the same conditions. The decomposition pathway was not further investigated, but the possibility of a base-mediated Bamford–Stevens reaction cannot be ruled out.[3]

When *o*-bromoacetophenone was treated with *p*-toluenesulfonyl hydrazide in the presence of acid, *Z*- and *E*-isomers were obtained in a ratio of 1:4.6.[2d] The predominance of the *E*-isomer was also reported by Bunnel and Fuchs.[4] To avoid the loss of starting material and to take full advantage of the rapid cyclization of the *Z*-isomer we decided to investigate the *Z*-selective synthesis of *o*-bromoacetophenone *N*-tosylhydrazones. Recently, we reported a *Z*-selective synthesis of *o*-bromoacetophenone oximes[5] and a similar approach was attempted for *N*-tosylhydrazones (Scheme 1). To our delight, this route was found to be also suitable for *N*-tosylhydrazones and probably proceeds in an analogous manner.[6] Formation of the *Z*-hydrazone is initiated by abstraction of the acidic proton leading to an *N*-tosyl-vinyl-diazene. Subsequent Michael addition of a hydride nucleophile then provides the desired *Z*-hydrazone (Scheme 2).

We decided to prepare four *o*-brominated *N*-tosylhydrazones adorned with electron-donating substituents and one *o*-fluorinated *N*-tosylhydrazone (Table 1). We reasoned that if catalytic cyclization of these electron-rich starting materials (**3a–d**→**4a–d**) occurred then the possible S_NAr-pathway would be minimized. On the other hand, the fluorinated hydrazone **3e** would favor the S_NAr-mechanism and disfavor the catalytic pathway.

After successful preparation of the *Z*-tosylhydrazones **3a–e**, we began screening the cyclization conditions as indicated in Table 2. Our goal was to develop a cyclization which occurs at ambient temperature, thus all the reactions were carried out without external heating, in air. At first the non-catalytic pathway was ruled out (entries 1 and 2). When *N*-tosylhydrazones **3a** and **3e** were treated with base and DMEDA in the absence of CuI, no formation of **4a**



Scheme 1. *Z*-Selective synthesis of *N*-tosylhydrazones.

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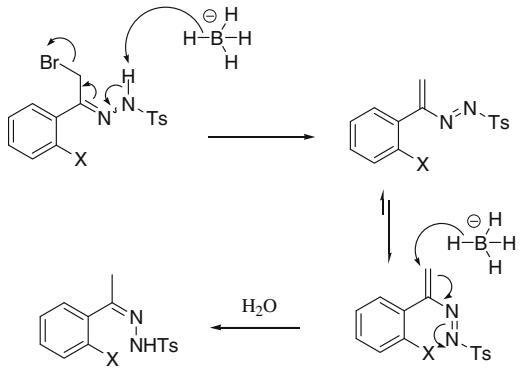
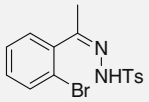
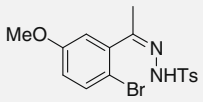
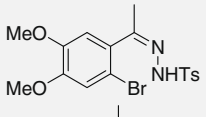
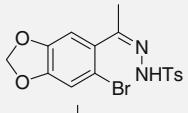
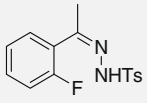


Scheme 2. Mechanism for the *Z*-selective formation of *N*-tosylhydrazones.

was observed even after 12 h. According to TLC and the ^{1}H NMR spectrum of the recovered starting material no isomerization took place under these conditions. Several reports in which fluorine has been used as a leaving group exist, but all involve external heating or the use of excess hydrazine.[7] Palladium-catalysts were found to be inefficient for our model reaction (entries 3–5). However, when **3a** was treated with DMEDA and CuI without *t*-BuONa the desired indazole **4a** was detected after 12 h (entry 6). As expected there was no evidence of cyclization when **3e** was subjected to similar conditions (entry 7).

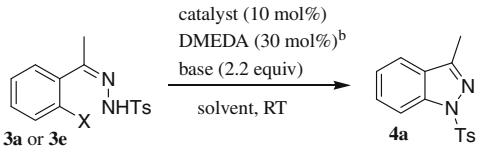
Next we used the conditions employed for benzisoxazoles[5] (entry 8) and the reaction proceeded smoothly and was complete in 10 min. After work-up, compound **4a** was obtained in 96% yield with no need for chromatographic purification. Comparison of the estimated pK_a values of hydrazone **3a** and the corresponding oxime[8] indicated that a milder base could be utilized. Thus, *t*-BuONa was replaced with Cs_2CO_3 and Na_2CO_3 (entries 9 and 10), respectively, and to our delight, our assumption was correct and the desired indazoles were formed in 10 min and in excellent yields. Finally, we wanted to see if THF could be replaced by safer and environmentally friendly solvents. Indeed, the reaction was rapid when EtOH was used as the solvent (entry 11). Despite the fact that conversion was fast and the yields were excellent we were still concerned about the heterogeneity of the reaction media. This could cause problems when the reaction is performed on larger scale. To enhance the solubility of the inorganic reagents we used aqueous ethanol as the solvent (entry 12). The reaction proceeded as a clear solution and **4a** was isolated as the sole product in 98% yield. Full conversion was achieved in this case in 10 min. When only water was utilized as the solvent the reaction did not proceed to completion (entry 13). Finally, *E*-tosylhydrazone **3a-*E*** was subjected to the optimized conditions to examine the possible

Table 1
Synthesized *o*-halogenated *N*-tosylhydrazones

Entry	Product		Yield%[a]
1		**3a**	98
2		**3b**	66
3		**3c**	90
4		**3d**	82
5		**3e**	76

[a] Isolated yield after two steps.

Table 2
Screening of the cyclization conditions[a]

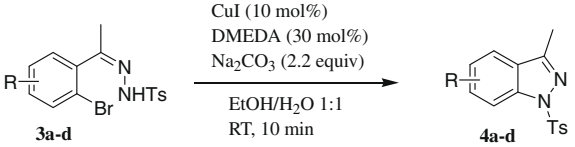


3a or **3e** **4a**

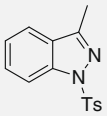
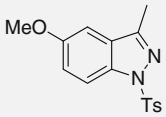
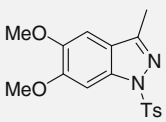
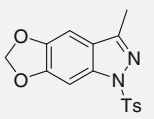
Entry	X	Solvent	Base	Catalyst	Yield%[c]
1	Br	THF	*t*-BuONa	—	—
2	F	THF	*t*-BuONa	—	—
3	Br	THF	*t*-BuONa	$PdCl_2$	6[d]
4	Br	THF	*t*-BuONa	$Pd(OAc)_2$	—
5	Br	THF	*t*-BuONa	Pd/C	—
6	Br	THF	—	CuI	26[d]
7	F	THF	—	CuI	—
8	Br	THF	*t*-BuONa	CuI	96
9	Br	THF	Cs_2CO_3	CuI	95
10	Br	THF	Na_2CO_3	CuI	96
11	Br	EtOH	Na_2CO_3	CuI	95
12	Br	EtOH/H_2O (1:1)	Na_2CO_3	CuI	98
13	Br	H_2O	Na_2CO_3	CuI	54[d]
14[e]	Br	EtOH/H_2O (1:1)	Na_2CO_3	CuI	—

[a] See the Supplementary data for details concerning the reaction conditions.
[b] 0.7 M solution in THF or EtOH.
[c] Isolated yield.
[d] Determined by ^{1}H NMR spectroscopy of the crude reaction mixture.
[e] Compound **3a-*E*** was used as the reactant.

Table 3
Preparation of 5- and 6-substituted indazoles



3a-d **4a-d**

Entry	Product		Yield%[a]
1		**4a**	98
2		**4b**	98
3		**4c**	99
4		**4d**	95

[a] Isolated yield.

equilibrium[9] between **3a-*E*** and **3a-*Z***, however, formation of **4a** was not observed after 12 h at room temperature (entry 14).

The substituted *N*-tosylhydrazones **3a–d** were subjected to the optimized conditions and the results are collected in Table 3. In all entries the reaction was complete in 10 min and the pure indazoles were isolated without chromatography.

In summary, we have developed a facile strategy for the preparation of *Z*-configured *N*-tosylhydrazones. These compounds can be utilized efficiently as precursors for the copper-catalyzed synthesis of 3-methylindazoles under mild conditions. We believe that this easy access to *Z*-hydrazones will open new possibilities for metal-catalyzed C–H activation protocols. Further investigations to extend this strategy to other substituents at the 3-position are currently in progress in our laboratory and the results will be presented in due course.

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Supplementary data

Supplementary data (experimental procedures, characterization data, and ^{1}H and ^{13}C NMR spectra for new compounds are available) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.05.024.

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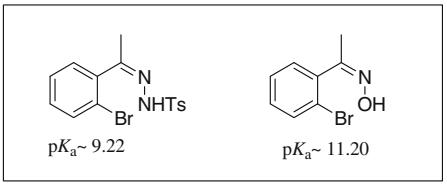
8. Estimation was made by ACD/Labs extension for *CS ChemDraw (v 8.0)*; Advanced Chemistry Development, Inc.; Toronto, Canada; http://www.acdlabs.com.



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