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In(OTf)$_3$-mediated synthesis of substituted pyridazines

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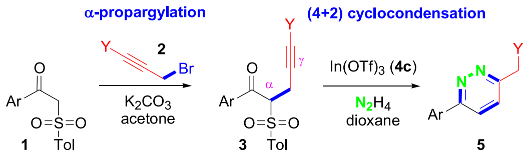
ABSTRACT

In(OTf)$_3$ (**4c**)-mediated one-pot (4+2) cyclocondensation of γ-alkynones **3** with $N_2H_{4(aq)}$ in dioxane affords substituted pyridazines **5** in good yields via a sequential desulfonative or dehydrogenative aromatization. The facile transformation proceeds by a facile synthetic sequence starting with an α-propargylation of β-ketosulfones **1** and a cyclocondensation of γ-alkynones **3** with $N_2H_{4(aq)}$. The method provides a mild and efficient condition. Moreover, this route can be enlarged to multigram scale.

1. Introduction

For transformation from terminal alkynes to methyl ketones, mercuric salts mediating the hydration of alkynes is a classic method used in the presence of acids via Markovnikov regioselectivity.[1,2] However, new catalysts to the synthetic routes of methyl ketones from non-activated alkynes still represent continuing needs in the organic field. Among these protocols, transition-metal complexes (Au,[3] Ag,[4] Ag/Au,[5] Ru,[6] Rh,[7] Pt,[8] Os,[9] Ir,[10] Pd,[11] Fe,[12] Hg,[13] Cu,[14] or In[15]) promoting hydration of alkynes is the major pathway. Notably, few examples have been performed for metal triflates-promoted reactions. Nishizawa et al. reported the traditional synthesis of 2-methylfurans via the Hg(OTf)$_2$-catalyzed cyclization of 1-alkyn-5-ones.[13] Jha et al. reported a microwave-assisted hydration of arylacetylene with Cu(OTf)$_2$.[14a] AgOTf-mediated hydration of alkynes has been developed by Chakraborty and co-workers.[4a] There are only two In(III)-mediated examples of synthesis of substituted furans via the hydration of nonactivated alkynes by Tan[15a] and Nakamura.[15b] To the best of our knowledge, no examples for In(OTf)$_3$-mediated one-pot (4+2) annulation of γ-alkynone with $N_2H_{4(aq)}$ have been reported. In continuation of our investigation on the applications of β-ketosulfones **1** (e.g., 2-arylpyrroles, vinylcyclopropanes, 2,6-diaryltetrahydropyrans, 2-arylfurans and substituted benzenes),[16,17] a facile one-pot synthesis of 2-arylpyridazines **5** is developed, including (1) α-propargylation of **1** with propargylic bromides **2**, and (2) In(OTf)$_3$-promoted cyclocondensation of the resulting γ-alkynones **3** with $N_2H_{4(aq)}$ (see Scheme 1). Pyridazine is a versatile building block in the synthesis of natural products and a useful synthetic intermediate.[18] A number of articles have highlighted fascinating developments based on two C–N bond formations.[19] 2-Arylpyridazines are also known to exhibit versatile biological activities, such as antibacterial activity, antibiotic or anti-depressant activity.[20] After further comparing literature reports on the preparation of substituted pyridazines, herein, we describe one-pot route on the cyclocondensation of the γ-alkynones with $N_2H_{4(aq)}$.



Scheme 1. Synthetic route of **5**.

2. Results and discussion

According to previous literature on metal triflate-mediated hydration of alkynes,[16d] catalytic amounts (2 mol %) of AgOTf (**4a**), Hg(OTf)$_2$ (**4b**), In(OTf)$_3$ (**4c**) or Cu(OTf)$_2$ (**4d**) were first examined for the transformation of model substrate **3a** (R=Tol, Ar=Ph, Y=H) from γ-alkynone to a skeleton of 2-arylpyridazine **5a** in dioxane at 25 °C for 4 h. As shown in Table 1 and entries 1–4, **4c** provided a better yield (80%) than **4a** (72%), **4b** (69%) and **4d** (25%) for generating **5a**. On the basis of a higher yield and activity, low toxicity and relatively low price, **4c** was chosen as the appropriate catalyst for synthesizing **5** via one-pot mild (4+2) cyclocondensation of **3a**

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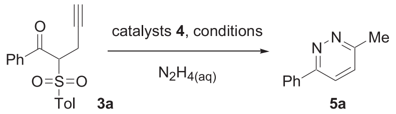
Table 1
One-pot conditions[a]



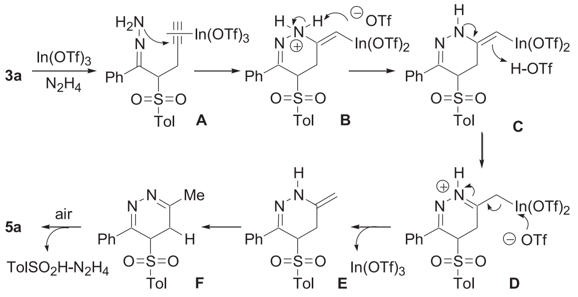
Entry	Catalyst 4 (mol %), solvent (mL), temp (°C)	Yield (%)[b]
1	AgOTf **4a** (2), dioxane (5), 25	72
2	$Hg(OTf)_2$ **4b** (2), dioxane (5), 25	69
3	$In(OTf)_3$ **4c** (2), dioxane (5), 25	80
4	$Cu(OTf)_2$ **4d** (2), dioxane (5), 25	25[c]
5	$InCl_3$ **4e** (5), dioxane (5), 25	60
6	$InBr_3$ **4f** (2), dioxane (5), 25	68
7	In_2O_3 **4g** (2), dioxane (5), 25	12[d] (20)[e]
8	$In(OTf)_3$ **4c** (0), dioxane (5), 25	—[f]
9	$In(OTf)_3$ **4c** (5), dioxane (5), 25	79
10	$In(OTf)_3$ **4c** (10), dioxane (5), 25	77
11	$In(OTf)_3$ **4c** (2), dioxane (10), 25	75
12	$In(OTf)_3$ **4c** (2), dioxane (5), 50	70
13	$In(OTf)_3$ **4c** (2), dioxane (5), 100	63
14	$In(OTf)_3$ **4c** (2), $MeNO_2$ (5), 25	75
15	$In(OTf)_3$ **4c** (2), $(CH_2Cl)_2$ (5), 25	63
16	$In(OTf)_3$ **4c** (2), benzene (5), 25	51
17	$In(OTf)_3$ **4c** (2), EtOH (5), 25	58

[a] Reactions were run on a 1.0 mmol scale with **3a**, $N_2H_{4(aq)}$ (80%, 1 mL), 4 h.
[b] Isolated yields.
[c] 46% of a hydrazone mixture was isolated.
[d] 48% of a hydrazone mixture was isolated.
[e] 40 h and 40% of a hydrazone mixture was isolated.
[f] 88% of a hydrazone mixture was isolated.

in the presence of $N_2H_{4(aq)}$. Then, the use of other In(III) salts was examined (see entries 5–7). In comparison with these In(III) complexes, such as $InCl_3$ (**4e**), $InBr_3$ (**4f**) and In_2O_3 (**4g**), **4c** was still a better catalyst for the generation of **5a**. **4e-f** produced **5a** in 60% and 68% yields, respectively. For **4g**, only 12% of **5a** was isolated along with 48% of a hydrazone mixture. To elongate the reaction time (4 → 40 h), similar results were observed. Furthermore, controlling **4c** as the catalyst, catalyst equivalents, reaction solvents and temperature were further studied. Without the addition of **4c**, no **5a** was yielded (entry 8). When using 5 or 10 mol % of **4c**, the isolated yield was similar to 2 mol % (entries 9–10). By adjusting reaction concentrations (entries 11) or temperature (entries 12–13), poorer yield occurred. To change the reaction solvents from dioxane to $MeNO_2$, dichloroethane, benzene and EtOH, dioxane provided a better yield of **5a** due to good solubility with water (entries 14–17). Based on the above results, we envisioned that 2 mol % of $In(OTf)_3$/dioxane/$N_2H_{4(aq)}$ should be an optimal combination for forming **5a** via one-pot reaction of **3a**.

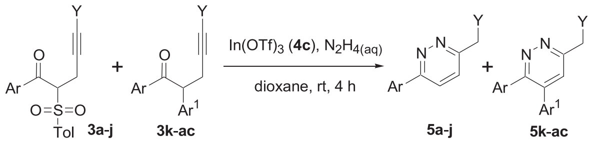
Based on the results, a possible reaction mechanism is shown in Scheme 2. How is **5a** produced? The mechanism should be initiated to form **A** by complexation of an alkynyl motif of a hydrazone skeleton (in situ generated from condensation of **3a** with N_2H_4) with **4c**, and participation of an amino group of hydrazone could lead to an ammonium ion **B** via intramolecular 6-*exo-dig* annulation. Deprotonation of **B** should give vinyl indium intermediate **C**. Then, protonation by in situ generated HOTf leads to an alternative iminium cation **D**, which, following loss of $In(OTf)_3$, is able to provide **E** and the recovery of $In(OTf)_3$. Tautomerization of **E** affords **F**. Subsequently, desulfonylative aromatization of the resulting **F** generates **5a** under air atmosphere.

With optimized conditions in hand (Table 1, entry 3), we further explored the substrate scope of the reaction, and the results are shown in Table 2. For adjusting the Ar and Y substituents of α-sulfonyl γ-alkynones **3a–j**, arylpyridazines **5a–j** (Ar=Ph, 4-FC_6H_4, 4-$MeOC_6H_4$, 4-MeC_6H_4, 4-$CF_3C_6H_4$, 4-PhC_6H_4, 2-naphthalene, 2-thiophene; Y=H, Me, Et) were provided in 72–85% yields (entries 1–10). To demonstrate the utilization of the route, α-aryl γ-arylalkynones **3j–ab** were prepared from α-propargylation of substituted deoxybenzoins with propargyl bromide. By this combination of $In(OTf)_3$/dioxane/$N_2H_{4(aq)}$, diarylpyridazines **5j–ab** (Ar=Ph, 4-$MeOC_6H_4$, 3,4-$(MeO)_2C_6H_3$, 2,3,4-$(MeO)_3C_6H_2$; Ar^1=Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-FC_6H_4, 4-$CF_3C_6H_4$, 3,5-$F_2C_6H_3$, 4-PhC_6H_4, 2-naphthalene, 4,7-$(MeO)_2$-1-naphthalene, Y=H) were isolated in 75–85% yields under the above conditions (entries 11–28). Changing a sulfonyl group to an aryl group, no obvious yield changes were observed for the generation of **5**. For the Ar and Ar^1 groups of **3**, the phenyl ring, with both electron-withdrawing and electron-donating substituents, was well tolerated, providing the desired product **5** in moderate to good yields. The structures of **5h**, **5n**, **5p**, **5u**, **5w**, **5z** and **5aa** were determined by single-crystal X-ray crystallography.[21] However, treatment of **3ac** (Ar=Ar^1=Y=Ph) with the α-phenylacetylene group (an internal alkyne) afforded the



Scheme 2. Possible mechanism.

Table 2
Synthesis of **5**[a]



Entry	**3**, Ar=, Ar^1=, Y=,	**5**, yield%[b]
1	**3a**, Ph, —, H	**5a**, 80
2	**3b**, 4-FC_6H_4, —, H	**5b**, 82
3	**3c**, 4-$MeOC_6H_4$, —, H	**5c**, 85
4	**3d**, 4-MeC_6H_4, —, H	**5d**, 83
5	**3e**, 4-$CF_3C_6H_4$, —, H	**5e**, 82
6	**3f**, 4-PhC_6H_4, —, H	**5f**, 81
7	**3g**, 2-naphthalene, —, H	**5g**, 75
8	**3h**, 2-thiophene, —, H	**5h**, 72
9	**3i**, Ph, —, Me	**5i**, 73
10	**3j**, Ph, —, Et	**5j**, 72
11	**3k**, Ph, Ph, H	**5k**, 85
12	**3l**, 4-$MeOC_6H_4$, Ph, H	**5l**, 83
13	**3m**, 4-$MeOC_6H_4$, 4-MeC_6H_4, H	**5m**, 83
14	**3n**, 4-$MeOC_6H_4$, 4-$MeOC_6H_4$, H	**5n**, 80
15	**3o**, 4-$MeOC_6H_4$, 4-FC_6H_4, H	**5o**, 78
16	**3p**, 4-$MeOC_6H_4$, 4-$CF_3C_6H_4$, H	**5p**, 75
17	**3q**, 4-$MeOC_6H_4$, 3,5-$F_2C_6H_3$, H	**5q**, 82
18	**3r**, 4-$MeOC_6H_4$, 4-PhC_6H_4, H	**5r**, 83
19	**3s**, 4-$MeOC_6H_4$, 2-naphthalene, H	**5s**, 84
20	**3t**, 3,4-$(MeO)_2C_6H_3$, Ph, H	**5t**, 85
21	**3u**, 3,4-$(MeO)_2C_6H_3$, 4-MeC_6H_4, H	**5u**, 80
22	**3v**, 3,4-$(MeO)_2C_6H_3$, 4-$MeOC_6H_4$, H	**5v**, 82
23	**3w**, 3,4-$(MeO)_2C_6H_3$, 4-FC_6H_4, H	**5w**, 81
24	**3x**, 3,4-$(MeO)_2C_6H_3$, 4-PhC_6H_4, H	**5x**, 82
25	**3y**, 3,4-$(MeO)_2C_6H_3$, 3,5-$F_2C_6H_3$, H	**5y**, 75
26	**3z**, 2,3,4-$(MeO)_3C_6H_2$, Ph, H	**5z**, 80
27	**3aa**, 2,3,4-$(MeO)_3C_6H_2$, 4-FC_6H_4, H	**5aa**, 82
28	**3ab**, 4,7-$(MeO)_2$-naphthalene, 2,3-$CH_2O_2C_6H_3$, H	**5ab**, 75
29	**3ac**, Ph, Ph, Ph	**5ac**, —[c]

[a] The pyridazine synthesis was run on a 1.0 mmol scale with **3**, $In(OTf)_3$ (**4c**) (2 mol %), dioxane (5 mL), $N_2H_{4(aq)}$ (80%, 1 mL), 4 h at 25 °C.
[b] Isolated yield.
[c] Complex mixture was observed.