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Solvent-free rhodium(III)-catalyzed synthesis of 2-aminoanilides *via* C–H amidation of *N*-nitrosoanilines under ball-milling conditions

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ABSTRACT

A solvent-free rhodium(III)-catalyzed C–H amidation of *N*-nitrosoanilines with 1,4,2-dioxazol-5-ones has been successfully developed under ball-milling conditions. This protocol provides an efficient and green access to a variety of 2-aminoanilide derivatives with low catalyst loading, remarkable functional group compatibility and excellent yields. In addition, the products allow convenient access to pharmaceutically valuable benzimidazole derivatives through a one-pot two-step synthesis.

1. Introduction

Over the past decades, mechanochemical organic transformations have aroused the tremendous interest of chemists because of their common features of high reaction efficiency, the ability to use poorly soluble reactants, and excellent stoichiometric control of reagents compared with the classical solvent-based protocols [1]. Among them, a series of metal-catalyzed reactions have been reported, and some of them even exhibited different selectivities from the liquid-phase reactions [1g,2]. Recently, after the report on the monitoring of palladium-mediated ligand-directed C–H activation under ball-milling conditions by solid-state Raman spectroscopy [3], direct C–H functionalizations under ball-milling conditions were achieved by Bolm and others, who successfully developed solvent-free C–H olefination, halogenation, amidation, arylation, allylation and oxidative annulation with alkynes [4]. These C–H functionalizations under ball-milling conditions demonstrated the advantages of shorter reaction times as well as the avoidance of high reaction temperatures and toxic organic solvents.

The *N*-nitroso moiety is a good directing group to realize C–H functionalizations in transition-metal-catalyzed reactions owing to its moderate coordination ability to transition-metal catalysts [5], and can be easily removed or transformed into other functional groups [6–15]. In 2013, the Zhu group developed the rhodium(III)-catalyzed *N*-nitroso-directed *ortho*-olefination of *N*-nitrosoanilines [6]. Later on, the catalytic *N*-nitroso-directed synthesis of indoles from *N*-nitrosoanilines was reported by the Zhu [7], Huang [8] and Jiao [9] groups, respectively. The alkynylation [10], alkoxylation [11], acyloxylation [12], acylation [13], cyanation [14] and other functionalizations [15] of *N*-nitrosoanilines were also demonstrated. Given our continued interest in mechanochemical organic reactions [16] and C–H functionalizations using the *N*-nitroso moiety as a removable directing group [12,13c], herein we report the solvent-free synthesis of 2-aminoanilides by rhodium(III)-catalyzed *N*-nitroso-directed *ortho*-amidation of *N*-nitrosoanilines with 1,4,2-dioxazol-5-ones under ball-milling conditions [17].

2. Results and discussion

Initially, we chose *N*-nitrosoaniline **1a** and methyl-1,4,2-dioxazol-5-one **2a** as the model substrates to screen the optimal

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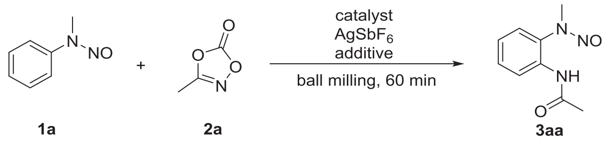
Table 1
Optimization of reaction conditions[a].



Entry	Catalyst (mol%)	Additive	Yield (%)[b]
1	[{Ru(*p*-cymene)Cl_2}$_2$] (2.5)	–	–
2	[{Cp*$IrCl_2$}$_2$] (2.5)	–	–
3	Cp*Co(CO)I_2 (2.5)	–	–
4	Pd$(OAc)_2$ (2.5)	–	–
5	Pd$(PPh_3)_2Cl_2$ (2.5)	–	–
6	[{Cp*$RhCl_2$}$_2$] (2.5)	–	51
7	[{Cp*$RhCl_2$}$_2$] (2.5)	AgOAc	78
8	[{Cp*$RhCl_2$}$_2$] (2.5)	Cu$(OAc)_2$	43
9	[{Cp*$RhCl_2$}$_2$] (2.5)	KOAc	71
10	[{Cp*$RhCl_2$}$_2$] (2.5)	NaOAc	76
11[c]	[{Cp*$RhCl_2$}$_2$] (2.5)	NaOAc	95
12[c,d]	[{Cp*$RhCl_2$}$_2$] (2.5)	NaOAc	88
13[c]	[{Cp*$RhCl_2$}$_2$] (1)	NaOAc	94
14[c]	[{Cp*$RhCl_2$}$_2$] (0.5)	NaOAc	72
15[c,e]	[{Cp*$RhCl_2$}$_2$] (0.5)	NaOAc	76
16[c,f]	**[{Cp*$RhCl_2$}$_2$] (1)**	**NaOAc**	**95**
17[c,g]	[{Cp*$RhCl_2$}$_2$] (1)	NaOAc	77
18[c,f,h]	[{Cp*$RhCl_2$}$_2$] (1)	NaOAc	92

[a] Unless otherwise noted, the reaction was carried out in a Retsch MM 400 mixer mill at 30 Hz with 0.5 mmol of **1a**, 0.55 mmol of **2a**, 2.5 mol% of catalyst, 10 mol% of $AgSbF_6$, 10 mol% of additive under an air atmosphere at room temperature for 60 min.

[b] Isolated yield based on **1a**.

[c] 15 mol% of $AgSbF_6$ and 15 mol% of NaOAc were used.

[d] 0.5 mmol **2a** was used.

[e] The reaction time was 120 min.

[f] The reaction time was 30 min.

[g] The reaction time was 20 min.

[h] A polytetrafluoroethylene jar (5 mL) and a zirconium dioxide ball (10 mm in diameter) were used.

reaction conditions, and selected results are summarized in Table 1. At first, a mixture of **1a** (0.5 mmol), **2a** (0.55 mmol), [{Ru(*p*-cymene)Cl_2}$_2$] (2.5 mol%) and $AgSbF_6$ (10 mol%) together with a stainless steel ball (10 mm in diameter) was introduced into a stainless steel jar (5 mL) and milled vigorously (30 Hz) in a Retsch MM 400 mixer mill at room temperature for 60 min. Unfortunately, the expected amidated product **3aa** was not detected (Table 1, entry 1). Replacing [{Ru(*p*-cymene)Cl_2}$_2$] with [{Cp*$IrCl_2$}$_2$], Cp*Co(CO)I_2, Pd$(OAc)_2$ or Pd$(PPh_3)_2Cl_2$ failed to provide the desired product either (entries 2–5). To our delight, the expected product **3aa** was obtained in 51% yield when [{Cp*$RhCl_2$}$_2$] was employed as the catalyst (entry 6). In order to increase the reaction efficiency, we tried to add an additive to the reaction system. After the addition of 10 mol% AgOAc, the yield of **3aa** could be increased to 78% (entry 7). In contrast, the use of Cu$(OAc)_2$ led to product **3aa** in a reduced yield of 43% (entry 8). KOAc was less effective than AgOAc (entry 9), while NaOAc gave nearly the same product yield as that with AgOAc (entry 10 *vs*. entry 7). Considering that NaOAc is cheaper than AgOAc, so NaOAc was chosen as the optimal additive. We were pleased to find that the reaction efficiency was significantly improved by increasing the amounts of $AgSbF_6$ and NaOAc to 15 mol%, and **3aa** was isolated in 95% yield (entry 11). Encouraged by these results, we further optimized the reaction conditions for a more practical synthesis of **3aa** by screening the amounts of **2a** and [{Cp*$RhCl_2$}$_2$] as well as the reaction time (entries 12–17). When the amount of **2a** was lowered from 0.55 mmol to 0.5 mmol, **3aa** was isolated in a lower yield of 88% (entry 12). Gratifyingly, reducing the amount of [{Cp*$RhCl_2$}$_2$] from 2.5 mol% to 1 mol%, nearly the same product yield was obtained (entry 13 *vs*. entry 11). Further decreasing the amount of catalyst to 0.5 mol% led to an obviously lower yield even with a prolonged reaction time (120 min) (entries 14 and 15). Meanwhile, shortening the reaction time from 60 min to 30 min, a slightly higher product yield of 95% could be achieved (entry 16 *vs*. entry 13), while further shortening the reaction time to 20 min would reduce the product yield to 77% (entry 17). When the stainless steel jar and milling ball were replaced with a polytetrafluoroethylene jar and a zirconium dioxide ball with the same size, a slightly lower product yield of 92% was obtained (entry 18). Thus, the optimal reaction conditions were as follows: **1a** (0.5 mmol), **2a** (0.55 mmol), [{Cp*$RhCl_2$}$_2$] (1 mol%), $AgSbF_6$ (15 mol%) and NaOAc (15 mol%) under solvent-free ball-milling conditions for 30 min (entry 16).

With the optimized reaction conditions in hand, we then investigated the scope and generality of this reaction for the synthesis of a variety of 2-aminoanilide derivatives. First, a series of differently substituted *N*-nitrosoanilines were allowed to react with **2a** under the optimal conditions. As seen from Table 2, the *N*-nitrosoanilines bearing both electron-rich and electron-deficient groups at the *para*-position of the aromatic ring reacted smoothly with **2a**, generating the corresponding aminated products **3ba**–**3ga** in good to excellent yields of 61–96%. Substrate **1c** with the strong electron-donating methoxy group at the *para*-position provided **3ca** in a high yield of 94%. To our delight, substrates **1d** and **1e** containing fluorine and chlorine at the *para*-position of the aromatic ring proceeded well under our optimal reaction, affording the corresponding products **3da** and **3ea** in 90% and 83% yields, respectively. Strong electron-withdrawing groups such as the ester and nitro groups located at the *para*-position were inferior in this transformation. When both of the amounts of $AgSbF_6$ and NaOAc were increased to 30 mol% and the time was prolonged to 60 min, the desired products **3fa** and **3ga** could be isolated in 80% and 61% yields, respectively. In addition, the influence on the reactivity by substituents at other positions of the aromatic ring were also examined. Notably, *meta*-methyl- (**1h**) and chloro- (**1j**) substituted *N*-nitrosoanilines exhibited high regioselectivities and efficiencies under the optimal conditions to give products **3ha** and **3ja** in 95% and 89% yields, respectively. In contrast, the reaction of *meta*-methoxy-substituted substrate **1i** with **2a** exhibited low regioselectivity, and **3ia** was obtained in 29% yield, along with another regioisomer **3ia'** in 24% yield. An obvious steric hindrance effect was observed when the reaction was applied to *ortho*-substituted substrates. With a prolonged ball-milling time (60 min) and an increased loadings of $AgSbF_6$ (30 mol%) and NaOAc (30 mol%), *ortho*-fluoro-substituted *N*-nitrosoanilines (**1l**) gave a higher yield (81%) than that (39%) of *ortho*-methyl-substituted *N*-nitrosoanilines (**1k**), perhaps due to the small atomic radius of the fluorine atom. As anticipated, *N*-methyl-*N*-(naphthalen-2-yl)nitrous amide **1m** gave the desired product **3ma** at the less sterically hindered position in 76% yield. Furthermore, we also examined the reaction of other *N*-alkyl substituted substrates with **2a**. Gratifyingly, when the methyl group on the amide nitrogen atom was replaced by an ethyl, *n*-butyl or isopropyl group, all of them were successfully transformed to the desired amidated products **3na**, **3oa** and **3pa** in comparable high yields (93%, 92% and 92%, respectively), indicating that a steric hindrance on the amide nitrogen atom did not affect the efficiency of our reaction. Moreover, *N*-nitrosoanilines **1q** with a cyclic scaffold could also undergo facile C–H amidation (91%). Next, to expand the substrate scope of the reaction, the amidating reagent was varied. Replacement of the methyl substituent on 1,4,2-dioxozol-5-one **2a** with a *tert*-butyl, cyclohexyl or phenyl group gave the expected amidated products **3ab**–**3ad** in yields varying from 61% to 93%. It is worth pointing out that the 3-phenyl-1,4,2-