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View Article Online
DOI: 10.1039/D0CC06468H

COMMUNICATION

Nickel-Catalyzed *C*-Alkylation of Thioamide, Amides and Esters by Primary Alcohols through Hydrogen Autotransfer Strategy

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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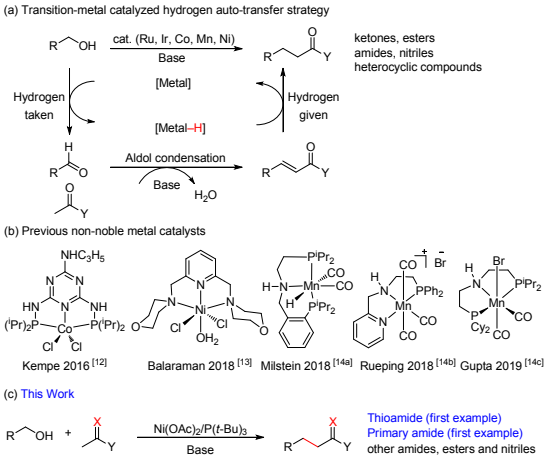
A simple catalyst of $Ni(OAc)_2$ and $P(t\text{-}Bu)_3$ enables selective *C*-alkylation of thioacetamides and primary acetamide with alcohols for the first time. Monoalkylation of thioamides, amides and *t*-butyl esters occurs in excellent yields (>95%). Mechanistic studies reveal that the reaction proceeds via a hydrogen autotransfer pathway.

α-Alkylation of carbonyl compounds, such as ketones, esters and amides, is widely used in organic synthesis.[1] In recent years, using cheap and readily available alcohols, instead of alkyl halides,[2] as alkylating reagents in hydrogen autotransfer reactions has attracted great attention (Scheme 1a).[3] The hydrogen autotransfer reaction involves dehydrogenation of an alcohol to form an aldehyde, in situ aldol condensation to form an α,β-unsaturated compound, and finally hydrogenation of α,β-unsaturated compound by metal hydride species to afford the product. Water is the only by-product and alcohols are consumed directly without pre-activation, so this reaction is a green alternative to alkylation of carbonyl compounds using alkyl halides.

Thioamides have many biological and pharmaceutically activities.[4] Thioamides are also introduced as isosters of amides at desired positions of modified peptides to enhance therapeutics effect.[5] Moreover, thioamides are important building blocks for the construction of many sulfur-containing heterocycles.[6] Although Lawesson's reagent[7] is commonly used to synthesize thioamides, its strong odour makes this reagent unpleasant to use in experiments and workup. Since thioamides have more acidic α-hydrogens than common amides (pKa 25.7 vs 35 in DMSO),[8] α-alkylation of thioacetamides with primary alcohols will provide a convenient route to value-added thioamides. But such a reaction has never been reported, probably owing to poisoning of noble metal catalysts by thioamides. Additionally, treatment of thioamides by Raney nickel was known to result in reduction product alkylamines in moderate yields in the presence of ethanol.[9]



Scheme 1 Strategies for α-C alkylation with alcohols.

Compared with ketones, amides and esters are more challenging in α-alkylation reaction with alcohols, because amides have less acidified α-hydrogens, while esters readily undergo base-catalysed transesterification with alcohols as side reaction. Previously, efficient catalysts for α-alkylation of secondary and tertiary amides and esters were mainly based on noble metals, especially Ir[10] and Ru.[11] Although earth-abundant base catalysts, such as Co,[12] Ni,[13] and Mn[14] have been developed in recent years, drawbacks of these catalytic methods include high catalyst loading, harsh reaction condition (>110 °C) and moderate yields. Furthermore, in all reported examples, these base metal complexes required relatively complex chelators (Scheme 1b). Until now, *C*-selective alkylation of *primary acetamide* with alcohols has not been reported. Recently, Madsen *et al*. reported that

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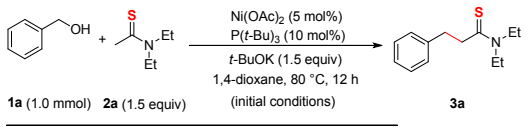
Electronic Supplementary Information (ESI) available. See
DOI: 10.1039/x0xx00000x

potassium *t*-butoxide alone promoted radical *C*-alkylation of secondary and tertiary acetamides with benzylic alcohols at 164 °C, in which no transition metal catalyst was needed.[15]

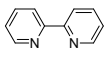
In continuation with our studies on nickel-catalyzed *N*-alkylation of amines through hydrogen autotransfer,[16] herein we describe for the first time, α-alkylation of thioacetamides and primary acetamides with alcohols using a nickel catalysis (Scheme 1c). The active catalyst was generated in situ from cheap $Ni(OAc)_2$ and $P(t\text{-}Bu)_3$. The reaction was conducted at 80 °C for 12 h which gave excellent yields for most substrates.

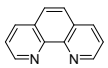
Table 1 Optimization of the reaction conditions

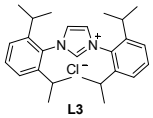


1a (1.0 mmol) **2a** (1.5 equiv) **3a**

Entry	Change from initial conditions	Yield (%)[b]
1	none	95
2	PCy_3 as ligand	84
3	**L1** as ligand	41
4	**L2** as ligand	35
5	**L3** as ligand	76
6	$NiBr_2$ as catalyst	86
7	$Ni(acac)_2$ as catalyst	72
8	Toluene as solvent	81
9	*t*-BuOH as solvent	63
10	$CsCO_3$ as base	0
11	2% $Ni(OAc)_2$, 4% $P(t\text{-}Bu)_3$, 1.0 equiv *t*-BuOK (optimized conditions)	95
12	no Ni and ligand	0


L1

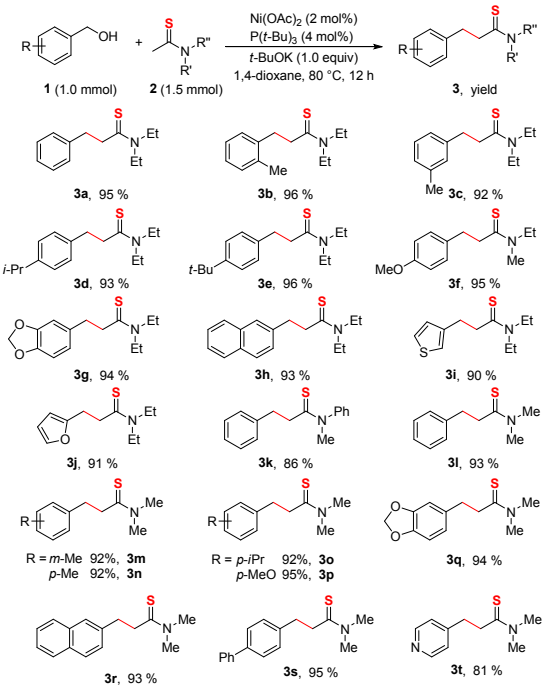

L2


L3

[a]Optimized reaction conditions: $Ni(OAc)_2$ (2 mol%), $P(t\text{-}Bu)_3$ (4 mol%), benzyl alcohol **1a** (1 mmol), N,N-diethylthioacetamide **2a** (1.5 mmol) and *t*-BuOK (1.0 mmol) in 1 mL of solvent at 80 °C for 12 h. [b]Yields shown are of isolated products.

Our initial reaction between *N,N*-diethyl thioacetamide **2a** and benzyl alcohol **1a** was carried out in the presence of $Ni(OAc)_2$ (5 mol%), $P(t\text{-}Bu)_3$ (10 mol%) and *t*-BuOK (1.5 equiv) in 1,4-dioxane at 80 °C for 12 h (Table 1). We were pleased to isolate product **3a** in 95% yield (Table 1, entry 1). We next tested the ligand effect and found that PCy_3 also give 84% yield of **3a**, bipy **L1** and phenanthroline **L2** have low activity, while *N*-heterocyclic carbene IPr **L3** afford 76% of **3a** (Table 1, entry 2-5). The reactivity of other nickel salts was also examined. $NiBr_2$ and $Ni(acac)_2$ gave **3a** in 86% and 72% yield (Table 1, entry 6-7). In toluene and *t*-butanol solvents 81% and 63% yields of **3a** were formed, respectively (Table 1, entry 8-9). When Cs_2CO_3 was used, no desired alkylation occurred at all (Table 1, entry 10). We were pleased to find that the yield of **3a** did not decrease even with 2% nickel catalyst and 1 equiv *t*-BuOK (Table 1, entry 11). Notably, when the reaction was performed in the absence of $Ni(OAc)_2$ and $P(t\text{-}Bu)_3$, only a trace amount of an α,β-unsaturated thioamide was isolated (5%).

With the optimized conditions, we explored the substrate scope using 2 mol% nickel catalyst (Scheme 2). Benzylic alcohols bearing alkyl and alkoxy substituents at *o*-, *m*- and *p*-positions and 2-naphthyl methanol gave *C*-alkylated thioamide products **3a-h** in 92-95% yields. Heteroaromatic thiophene and furan were well tolerated, giving **3i-j** in 90-91% yields. Reactions of other tertiary thioacetamide resulted in **3k-s** in excellent yields. 4-Pyridyl methanol also furnished product **3t** 81% yield. Unfortunately, secondary thioacetamide did not react, while the reaction of primary thioacetamide with benzyl alcohol afforded benzyl thiol as one of side products. Aliphatic alcohols often gave low yields of desired products, owing to competitive self-aldol condensations of aldehyde derived from aliphatic alcohols, alcoholysis of thioamides and etherification with secondary alcohols.

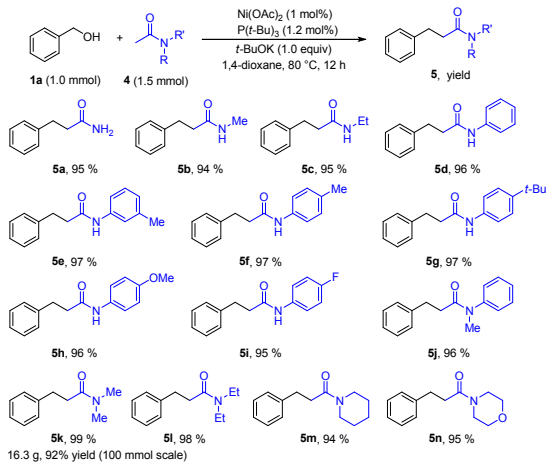


Scheme 2. The α-alkylation of thioamides with alcohols

We next examined α-alkylation of amides (Scheme 3). Reaction of *primary* acetamide **4a** with benzyl alcohol **1a** in the presence of 1 mol% nickel catalyst and *t*-BuOK gave C-alkylated amide **5a** in 95% yield, while no trace amount of *N*-alkylation was detected. The pKa values of primary and secondary amide N–H bonds (25 for acetamide and 21 for MeC(O)NHPh in DMSO) are 10 orders of magnitude lower than C(α)–H bonds of amides (35 in DMSO).[8] When we carried out the model reaction of **4a** at 140 °C for 24 hours, both 48% *N*-alkylation[17] and 52% *C*-alkylation products were isolated. Thus, relatively low temperature (80 °C) was the main reason of the observed *C*-selectivity. When we tested weaker bases, K_3PO_4 and K_2CO_3, the model *C*-alkylation reactions did not occur; neither *N*-alkylation was observed. This is the first example that selective *C*-alkylation of primary amides with an alcohol was achieved. Traditional *C*-alkylation methods using alkyl halides and strong bases were also accompanied with *N*-alkylation.[1-2]

The *C*-alkylation of secondary amides also proceeded smoothly (Scheme 3), and the reaction tolerated methoxy- and fluorine-substituents on *N*-aryl rings, giving alkylated amides **5b-i** in 94-97% yields. Tertiary amides gave products **5j–n** in very high yields, 94–98%, respectively. The reaction of **1a** and *N,N*-dimethylacetamide **4k** using 1 mol% of $Ni(OAc)_2$ was easily scale-up to 100 mmol, producing 16.3 g of **5k** in 92% yield (see

the Supporting Information). Notably, *N*-morpholinyl amide **5n** can be readily transformed to ketones or aldehydes after treatment with Grignard reagents or hydride reductants, in a way similar to Weinreb amides.[12] α-Alkylation of amides bearing longer chains didn't occur and only starting materials were recovered.

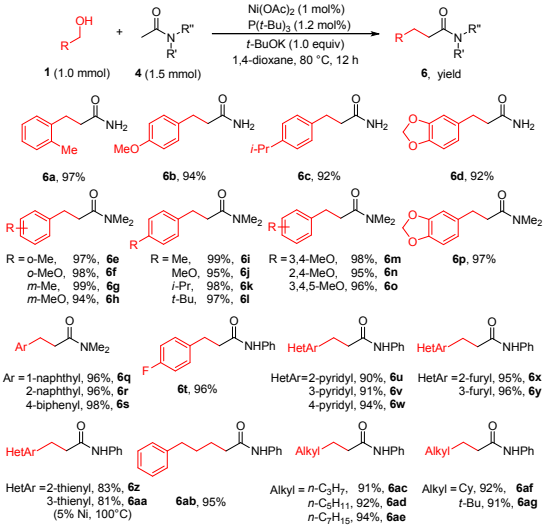


Scheme 3. The α-alkylation of various acetamide with benzyl alcohol **1a**

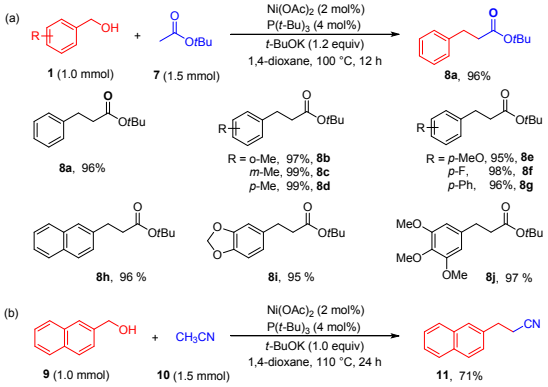
We next explored the substrate scope of alcohols (Scheme 4). Reactions of acetamide **4a** with various primary alcohols occurred efficiently, affording *C*-alkylated product **6a-d** in 92-97% yields. Benzyl alcohols bearing alkyl and alkoxy substituents at *o*-, *m*- and *p*-positions of the phenyl ring reacted with *N*,*N*-dimethylacetamide to furnish products **6e–p** in very high yields (94-99%). Reactions of naphthyl and biphenyl methanols gave **6q-s** in 96-98% yields. Aryl fluoride was also tolerated (**6t**), but aryl chloride and bromide led to side products of dehalogenated α,β-unsaturated amides in 84% and 89% yields. It is noteworthy that heteroaryl alcohols, including pyridinyl and furyl methanols, smoothly reacted with acetanilide, leading to products **6u-y** in excellent yields (90-96%). Reactions of 2- and 3-thienyl alcohols with acetanilide, however, needed to be conducted at 100 °C with 5 mol% of $Ni(OAc)_2$, which produced amides **6z** and **6aa** in 83% and 81% yields, respectively. Furthermore, both linear and *β*-branched aliphatic alcohols reacted smoothly to offer amides **6ab-ag** in 91-95% isolated yields. When secondary alcohols were used, no desired products were isolated. Instead, a small amount of α,β-unsaturated ketones were generated from self-aldol condensation of the corresponding ketones. Sometimes etherification with secondary alcohols also occurred.

The nickel catalyst was also suitable for α-alkylation of *t*-butyl esters and acetonitrile (Scheme 5). Under the same reaction conditions of amides, coupling of *t*-butyl acetate **7** and benzyl alcohol **1a** gave rise to *C*-alkylated ester **8a** in 86% yield. Besides incomplete conversion of **1a**, main byproducts included α,β-unsaturated esters and benzyl esters from transesterification. After condition modification, a higher yield (96%) was achieved in the presence of 2 mol% nickel catalyst at 100 °C (Scheme 4a), and the transesterification was suppressed. Various benzylic alcohols reacted to afford *C*-alkylated *t*-butyl acetates **8a–j** in very high yields (Scheme 5a).

However, ethyl acetate only yielded 40% *C*-alkylated product, because of competing base-mediated transesterification. The method was also applicable to monoalkylation of acetonitrile with 2-naphthyl methanol, which afforded product **11** in 71% yield (Scheme 5b).



Scheme 4. α-Alkylation of amides with various primary alcohols.



Scheme 5. The α-alkylation of esters and acetonitrile with primary alcohol

To probe the reaction mechanism, deuterium labeling experiment was carried out with thioamide **2a** (2.0 equiv) and deuterated benzyl alcohol **1a-D_2** (1.0 equiv, > 99% deuterium content) under standard reaction conditions (Scheme 6a). Deuterated product **3a** was obtained in 63% yield. ^{1}H NMR revealed that 72% deuterium was incorporated at β position and 5% deuterium at α position. The ratio of **3a**, **3a-D_1** and **3a-D_2** was 10%, 34% and 56% determined by HRMS analysis. About 15% deuteration was detected at the α-CH_3 in the recovered thioamide **2a**. When 2 equivalent of benzylic alcohol **1a-D_2** reacted with thioamide **2a**, 67% of alkylated thioamide **3a-D** was obtained with 71% deuterium incorporation at β-position and 5% deuteration at α-position (Scheme 6b). The deuterium content of recovered **1a-D_2** decreased to 93%. These deuterium experiments indicate that the reaction takes place via a hydrogen autotransfer mechanism with a nickel monohydride species. The partial loss of deuterium at β-position of **3a-D** (>99%D under ideal conditions) is attributed to reversible H/D exchange of nickel deuteride with *t*-BuOH or water. A small amount of deuteration at α-position of **3a-D**

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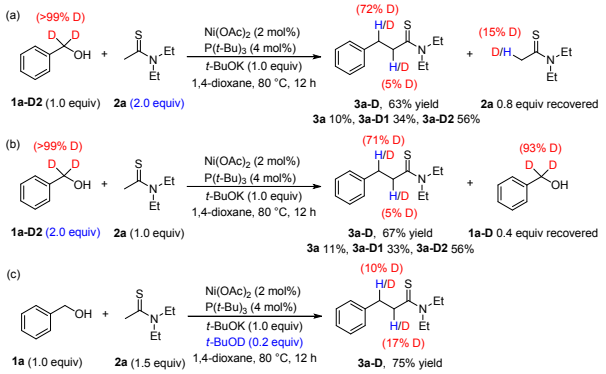
may be generated via reversible protonation by *t*-BuOK and *t*-BuOD. These conclusions were further supported by the model reaction with 0.2 equivalent of added *t*-BuOD, which gave the alkylation product **3a** contained deuterium at both α- and β-positions (Scheme 6c).



Scheme 6. The deuterium labeling experiments

In summary, we have developed a nickel-catalyzed α-alkylation of thioamides, unactivated acetamides and *t*-butyl esters with primary alcohols. Notably, this method enables *C*-selective monoalkylation of *both primary acetamides and tertiary thioacetamide* with alcohols for the first time. The simple $Ni(OAc)_2/P(t\text{-}Bu)_3$ is also applicable to other amides and *t*-butyl esters.

PY and BT thank the National Natural Science Foundation of China (21602126, 91753111, 21675103, and 21804081), the Key Research and Development Program of Shandong Province (2018YFJH0502), the Higher Educational Science and Technology Program of Shandong Province (J18KA077) for financial support. JSZ acknowledges financial supports from Peking University Shenzhen Graduate School and Shenzhen Bay Laboratory Institute of Chemical Biology.

Conflicts of interest

There are no conflicts to declare.

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Table of Contents

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