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N-Alkylation of poor nucleophilic amine and sulfonamide derivatives with alcohols by a hydrogen autotransfer process catalyzed by copper(II) acetate

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ABSTRACT

Copper(II) acetate is a versatile, cheap, and simple catalyst for the selective N-monoalkylation of amino derivatives with poor nucleophilic character, such as aromatic and heteroaromatic amines as well as sulfonamides, using in all cases primary alcohols as initial source of the electrophiles, through a hydrogen autotransfer process. In the case of sulfonamides, the monoalkylation process followed by a naphthalene-catalyzed reductive deprotection gives primary amines, which is an indirect alternative to the direct monoalkylation of ammonia.

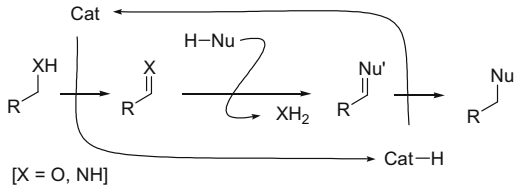
The hydrogen autotransfer,[1] also called borrowing-hydrogen, is an old reaction[2] with a great interest nowadays in C–C bond formation processes (Scheme 1).[3] This interest leans now toward the use of amines, and other nitrogenated compounds, as nucleophiles to yield the corresponding N-alkylated products. The reason for this change takes root in the great variety of amines present in nature, as well as their relevant importance in the pharmaceutical and agrochemical industries as usual building blocks. The extremely high advantage of this N-alkylation process, compared with classical protocols,[4] is based, on the one hand, in the simplicity of the protocol and, on the other hand, in the avoidance of using either mutagenic alkyl halides, sulfates, etc., or difficult storable carbonyl compounds, as well as the reduction of wastes.

Many different complexes have been proposed as catalysts for this thrifty process.[5] However, only a few examples of copper-containing catalysts have been proposed for this reaction and all of them are used in heterogeneous phase. Thus, a copper–chromite catalyst ($CuCr_2O_4$–$BaCr_2O_4$) has been used in the N-alkylation of high nucleophilic aliphatic amines with alcohols in the presence of hydrogen (125 atm) at 180–250 °C with modest results (lower than 70% yield).[6] Other catalysts such as CuO–Cr_2O_3 on silica[7] and CuO on alumina[8] have been also tested in similar conditions giving better results, in all cases with the temperature being higher than 220 °C.

The obtained results using copper(II) carboxylates were more interesting. For instance, the reaction of dimethylamine with dodecylalcohol at 210 °C using copper stearate gave the expected tertiary amine in 40% yield, while the same reaction failed using copper acetylacetonate.[9] A further improvement of the system was the use of mixtures from 5:1 to 8:1 of $Cu(C_{17}H_{35}CO_2)_2$ and $Ni(C_{17}H_{35}CO_2)_2$, which increased the above-mentioned yield up to 72%.[9,10] It should be pointed out that the presence of other stearate salts, such as barium and calcium derivatives, permitted to increase the results up to 99%.[11] This colloidal catalytic system, presenting Cu–Ni nanoparticles of about 125 nm, could be recovered by a complicated distillation of all reagents and products.[12]

Notwithstanding these partially successful examples, there are no studies on the synthetic possibilities of other most simple and cheap copper salts, with the reaction with less nucleophilic aromatic and heteroaromatic amine[13] or amide derivatives having been unexplored.[14] With this Letter, we would like to fill this lack, presenting copper(II) acetate as a simple, selective, and economical catalyst for the N-alkylation of poor nucleophilic amines and amide derivatives using alcohols as a source of electrophiles.

Initially, the reaction outlined in Table 1 was used as the standard one for the reaction–condition optimization. Firstly, we proceed to perform the reaction using nearly equimolecular amount of aniline and benzyl alcohol catalyzed by 10 mol % of copper(II) acetate in the presence of 1 equiv of base in dioxane. After one day the expected secondary amine **3a** was obtained with a good result (Table 1, entry 1). The reduction of the catalyst amount to 1 mol % only produces an increase in the reaction time, obtaining the compound **3a** in practically quantitative yield (entry 2). Then,



Scheme 1. General scheme for a hydrogen autotransfer process.

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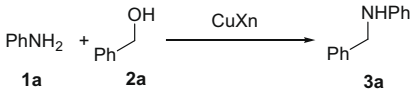
Table 1
Reaction–condition optimization



1a **2a** **3a**

Entry	CuX_n (mol %)	Base	Solvent	T (°C)	t (d)	Yield **3a**[a] (%)
1	$Cu(AcO)_2$ (10)	*t*BuOK	Dioxane	130	1	92
2	$Cu(AcO)_2$ (1)	*t*BuOK	Dioxane	130	2	>99
3	$CuCl_2$ (1)	*t*BuOK	Dioxane	130	2	40
4	$Cu(TfO)_2$ (1)	*t*BuOK	Dioxane	130	2	60
5	CuCl (1)	*t*BuOK	Dioxane	130	2	50
6	CuI (1)	*t*BuOK	Dioxane	130	4	60
7	$Cu(AcO)_2$ (1)	KOH	Dioxane	130	2	95
8	$Cu(AcO)_2$ (1)	K_2CO_3	Dioxane	130	2	15
9	$Cu(AcO)_2$ (1)	*t*BuOK[b]	Dioxane	130	2	40[c]
10	$Cu(AcO)_2$ (1)	*t*BuOK	PhMe	130	2	84
11	$Cu(AcO)_2$ (1)	*t*BuOK	DMSO	130	2	15
12	$Cu(AcO)_2$ (1)	*t*BuOK	Dioxane	170	1	95
13	$Cu(AcO)_2$ (1)	*t*BuOK	Dioxane	90	2	48

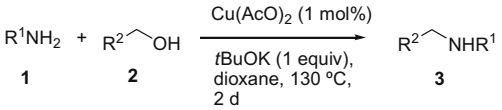
[a] Isolated yields after column chromatography (silica gel: hexane/ethyl acetate.
[b] Reaction performed using 10 mol %.
[c] 35% of the relate imine was detected.

we focused on the copper salt effect, and it was clear that copper(II) acetate is a better catalyst than other tested salts (compare results of entries 2–6). The yield using KOH as a base was similar to that using *t*BuOK, but superior to either using less basic K_2CO_3 or substoichiometric amounts of *t*BuOK (entries 7–9). Other solvents or temperatures did not improve the aforementioned result (compare entries 2 and 10–13), with the increase of the amount of alcohol (400 mol %) decreasing only the reaction time to one day (96% of **3a**).

Once the reaction conditions were optimized, we faced the problem of the reaction scope using poor electrophilic amines (Table 2), starting by changing the electronic nature of substituent on the benzylic alcohol **2**. The reaction using different 4-substituted benzylic alcohols gave nearly the same results (Table 2, entries 1–3), independent of the electron-donating or electron-withdrawing character of the substituent. However, it should be pointed out that in the case of the chlorinated alcohol (entry 3) the dehalogenation process occurred as a by-reaction, decreasing the yield of the expected compound **3c**.

As in the previous cases, when different substituted anilines were used as nucleophiles the results were practically the same independent of the electronic nature of substituent (entries 4–6

Table 2
Copper(II) acetate catalyzes the N-alkylation process



1 **2** **3**

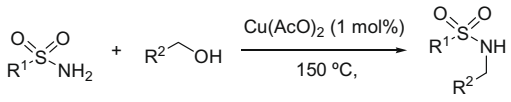
Entry	R^1	R^2	Product	Yield[a] (%)
1	Ph	Ph	**3a**	>99
2	Ph	4-$MeOC_6H_4$	**3b**	85
3	Ph	4-ClC_6H_4	**3c**	60[b]
4	4-$MeOC_6H_4$	Ph	**3d**	>99
5	2-$MeOC_6H_4$	Ph	**3e**	90[c]
6	3-ClC_6H_4	Ph	**3f**	99
7	2-Pyridyl	Ph	**3g**	>99[d]
8	2-Pyridyl	4-$MeOC_6H_4$	**3h**	>99[d]
9	2-Pyridyl	4-MeC_6H_4	**3i**	>99
10	2-Pyridyl	4-ClC_6H_4	**3j**	90[e]
11	2-Pyridyl	2-$MeOC_6H_4$	**3k**	>99
12	4-Pyridyl	Ph	**3l**	>99
13	2-Pyrimidyl	Ph	**3m**	>99
14	5-Methylthiazol-2-yl	Ph	**3n**	0[f]
15	*t*Bu	Ph	**3o**	0[f]
16	2-Pyridyl	$Me(CH_2)_5$	**3p**	69[f]

[a] Isolated yields after column chromatography (silica gel: hexane/ethyl acetate).
[b] 30% of **3a** was isolated.
[c] After 5 days.
[d] After 1 day.
[e] After 1 day, and 8% of **3g** detected.
[f] After 6 days.

in Table 2). It should be pointed out, however, that the reaction with more hindered 2-substituted anilines took place in longer reaction time and the dehalogenation by-reaction did not occur here. The reaction can also be performed using electron-poor heteroaromatic amines: For instance, the reaction with the 2-pyridyl derivative gave quantitative yield, practically independent of the benzylic alcohol **2** used (entries 7–11). A small amount of the by-product **3g** was detected by GC–MS in the case of using 4-chlorobenzyl alcohol as an electrophile (entry 10). The position of this extra-nitrogen atom, as well as the existence of two nitrogen atoms on the six-membered ring of the amine, seems to have no influence on these unbeatable results (entries 12 and 13).

On the contrary, the reaction with electron-rich heteroaromatic amines, such as thiazolamine and high nucleophilic *tert*-butylamine failed after 6 reaction days (entries 14 and 15). The reaction

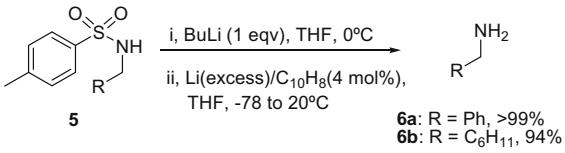
Table 3
N-Alkylation of amides



4 **2** **5**

Entry	R^1	R^2	Solvent	Base	t (d)	Yield 5 (%)[a]
1	4-MeC_6H_4	Ph	Dioxane	*t*BuOK	6	40
2	4-MeC_6H_4	Ph	PhMe	*t*BuOK	5	92
3	4-MeC_6H_4	Ph	PhMe	K_2CO_3	5	71
4	4-MeC_6H_4	Ph	—	K_2CO_3	5	85
5	4-MeC_6H_4	3-ClC_6H_4	PhMe	*t*BuOK	5	>99
6	4-MeC_6H_4	2,3-$(OCH_2O)C_6H_3$	PhMe	*t*BuOK	5	>99
7	4-MeC_6H_4	1-$C_{10}H_7$	PhMe	*t*BuOK	5	94
8	4-MeC_6H_4	$(CH_2)_5CH$	PhMe	*t*BuOK	5	84
9	4-$MeOC_6H_4$	Ph	PhMe	K_2CO_3	5	81
10	Me	Ph	PhMe	*t*BuOK	5	93

[a] Isolated yields after column chromatography (silica gel: hexane/ethyl acetate).



Scheme 2. Deprotection of sulfonamides **5**.

can also be carried out with aliphatic alcohols such as 1-heptanol, although in this case the reaction time should be increased up to 6 days. Finally, the reaction of secondary *N*-methylaniline with benzyl alcohol failed after 6 days under standard conditions, showing the selectivity of the process.

Once the catalytic activity and scope of the copper(II) acetate were demonstrated, we faced the problem of using other less nucleophilic amino derivatives such as sulfonamides[14,15] (Table 3). The best conditions were obtained when a strong base in toluene was used (compare entries 1–4). Under these conditions other amides and alcohols were submitted to the alkylation process, obtaining similar results independently on the use of either aliphatic or aromatic sulfonamide or alcohol (entries 5–10).

Finally, the above-mentioned sulfonamides **5** were deprotected to give the corresponding primary amines **6** with excellent results,[16] by a protocol which implied the initial deprotonation of amide followed by a reductive cleavage of N–S bond through a naphthalene-catalyzed lithiation[17] reaction (Scheme 2). The whole process, N-alkylation of sulfonamide and deprotective reduction, is an interesting alternative to the direct monoalkylation of ammonia, which is a difficult task.

In conclusion, cheap and commercially available copper(II) acetate has been shown to be an active, stable, versatile, and highly selective catalyst for the selective monoalkylation of aromatic amines and amides through a hydrogen autotransfer process. The simplicity of the protocol and the wide scope of substrates, which could be used, permitted us to anticipate a good future for the process shown in this Letter not only in the academia but also in industries. The combined alkylation–deprotection process is an alternative to the direct monoalkylation of ammonia.

Acknowledgments

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