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Di-μ-hydroxy-bis(*N*,*N*,*N*′,*N*′-tetramethylenediamine)-copper(II) chloride $[Cu(OH)\cdot TMEDA]_2Cl_2$: an efficient, practical catalyst for benzylation and allylation of amides

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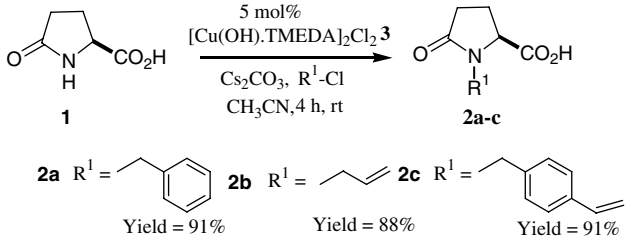
Abstract—An efficient protocol for the benzylation or allylation of amides using the corresponding benzyl or allyl chlorides as electrophiles under basic conditions with commercially available 5 mol % of $[Cu(OH)TMEDA]_2Cl_2$ as catalyst was developed. Under these conditions, unprotected amino acids were benzylated without any racemization.

Aryl amides are common moieties in many pharmaceuticals and their structural variations lead to a broad range of significant biological activities.[1] For amidation, in addition to Pd catalyzed reactions,[2] many traditional protocols have been developed using copper salts.[3] Most of these methods require large amounts of copper salts, high temperatures, and polar solvents. Recently, the most efficient approaches have been developed for C–N couplings using a catalytic amount of nitrogen ligand chelated copper salts with electron deficient halides as electrophiles.[4] In another variation, arylboronic acids as electrophiles with imidazoles have been developed using a catalytic soluble diamine–copper complex in the presence of oxygen.[5] Many of these reactions are restricted to bromo or iodoarenes as electrophiles and use high temperatures with strongly basic conditions. Moreover, these ligated-copper catalysts are poor activators of C–Cl bonds of arenes.

In continuation of our work on synthetic congeners of the antitumor, antibiotic Belactocin family, we needed to prepare various amide analogues.[6] Herein, we disclose an efficient protocol for the benzylation and allylation of amides using the corresponding benzyl or allyl chlorides as electrophiles under basic conditions with 5 mol % of $[Cu(OH)TMEDA]_2Cl_2$ **3** as catalyst[7] (Scheme 1). To our surprise, our initial screening employing many of the reported conditions[8] failed to give the product **2a** using benzyl chloride. Hence, the influence of bases and solvents on the amidation reaction was investigated. This reaction was found to be sensitive to the bases used in the reaction. The best choice was found to be Cs_2CO_3 in terms of reaction rate and yield of the product **2a**.

The reaction was much slower in the presence of weak bases such as K_2CO_3 (48%, 48 h), Na_2CO_3 (10%, 48 h), and $NaHCO_3$ (0%), whereas strong bases did not yield any product [K_3PO_4, NaOAc, $NaOBu^t$, and $KOBu^t$]. Various solvents were screened for the optimization of the yield of **2a**. Aprotic polar solvents like CH_3CN and DMF (89%) were found to be efficient for this transformation. 1,2-Dichloroethane (70%, 24 h) and toluene (30%, 24 h) also led to the product **2a** but in lower yields. With these optimum conditions



Scheme 1.

Keywords: Amidation; Benzylation; Allylation; Copper salts; $[Cu(OH)TMEDA]_2Cl_2$.
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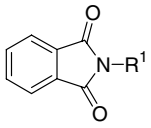
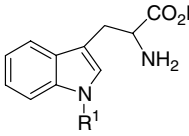
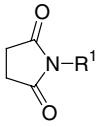
Table 1. Reaction times and yields of the $[Cu(OH)\cdot TMEDA]_2Cl_2$ catalyzed benzylation/allylation of amides[a–d]



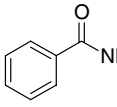
4a. R^1 = benzyl, (4 h), (83%)
4b. R^1 = allyl, (4 h), (75%)
4c. R^1 = 4-vinylbenzyl, (4 h), (80%)
4d. R^1 = *o*-nitrobenzyl, (4 h), (85%)
4e. R^1 = *p*-nitrobenzyl, (4 h), (85%)
4f. R^1= *o*-methoxybenzyl, (4 h), (80%)
4g. R^1 = *p*-methoxybenzyl, (4 h), (82%)



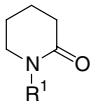
5a. R^1= benzyl, (6 h), (84%)
5b. R^1 = allyl, (6 h), (75%)
5c. R^1 = 4-vinylbenzyl, (6 h), (82%)



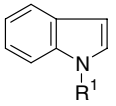
6a. R^1 = benzyl, (5 h), (74%)
6b. R^1 = allyl, (5 h), (70%)



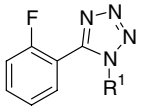
7a. R^1 = benzyl, (5 h), (72%)
7b. R^1 = allyl, (5 h), (75%)



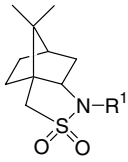
8a. R^1 = benzyl, (5 h), (76%)
8b. R^1 = allyl, (6 h), (75%)



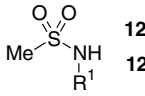
9a. R^1 = benzyl, (6 h), (70%)
9b. R^1 = allyl, (6 h), (68%)



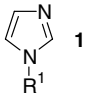
10a. R^1 = allyl, (2 h), (75%)[d]
10b. R^1 = 4-vinylbenzyl, (2 h), (65%)[d]



11a. R^1 = benzyl, (4 h), (72%)
11b. R^1 = allyl, (4 h), (70%)



12a. R^1 = benzyl, (4h), (72%)
12b. R^1 = allyl, (4h), (70%)



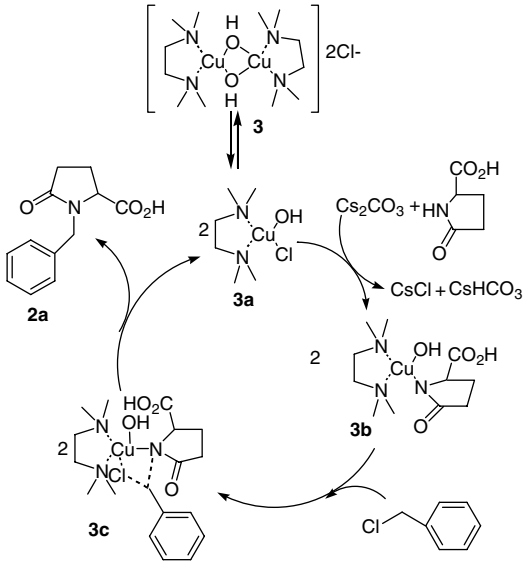
13. R^1 = benzyl, (6 h), (70%)

[a] All reactions were carried out on a 1 mmol scale.
[b] Isolated yields based on amides.
[c] All adducts gave satisfactory analytical data.
[d] All reactions were carried out at ambient temperatures except for **10a–b** and **13**, which were heated to 60 °C. In the case of **10a–b**, small amounts of regioisomers were isolated.

in hand, we subjected a number of structurally and electronically diverse substrates to the coupling reaction and our results are shown in Table 1.

Benzyl chlorides with electronically activated and deactivated rings were reacted with equal efficiency resulting in protected amides **4d–g** in good yields. The indole ring of L-tryptophan was not only protected with benzyl group but also with 4-vinylbenzyl and allyl groups without any loss of optical purity (**5a–c**).[9]

In order to understand the catalyst dependency on molecular oxygen or air,[5] we conducted the reaction under aerobic and strictly anaerobic conditions. In both cases, no significant changes were observed in the yield of product **2a** (91%). The reaction progress was clearly monitored by color indications. The reaction was initially bluish green in color followed by pink until amide consumption was complete upon which the blue color returned. A plausible mechanism for this reaction is via a four-centered transition state **3c** (Scheme 2) as



Scheme 2.

has been proposed for the Castro reaction.[3b] Further work is in progress to expand the scope of this reaction.

Acknowledgments

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7. *Typical experimental procedure for the benzylation of amides*: To a mixture of amide **1** (129 mg, 1 mmol), $CsCO_3$ (289.3 mg, 1.5 mmol), and $[Cu(OH)TMEDA]_2Cl_2$ **3** (5.1 mg, 5 mol %) was added CH_3CN under an N_2 atmosphere. The reaction mixture was stirred for 15 min at room temperature. To the resulting pink colored suspension, benzyl chloride was added dropwise and the reaction stirred for 4 h at rt. A blue color was observed indicating completion of the reaction. The solids were filtered off and washed twice with CH_3CN (2×10 mL). The combined filtrates were concentrated under reduced pressure. The residue was purified by column chromatography (silica gel 60–120 mesh; hexane/EtOAC, 8:2) to give **2a** (199 mg, 91%) as a colorless oil, $[\alpha]_D^{25}$ −13.5 (*c* 0.6, MeOH); ^{1}H NMR (200 MHz): δ 2.16–2.57 (m, 4H), 4.27 (t, $J = 6.68$ Hz, 1H), 4.95 (s, 2H), 7.06–7.35 (m, 5H). EIMS: 219 (M^+), 174 (62%), 141 (20%), 91 (100%). Compound **4a**. 196 mg (83%) colorless crystals, mp 128–129.5 °C ^{1}H NMR (200 MHz): δ 4.8 (s, 2H), 7.18–7.44 (m, 5H), 7.65–7.78 (dd, $J = 3.17$, 5.55 Hz, 2H), 7.80–7.88 (dd, $J = 3.17$, 5.55 Hz, 2H); EI MS: 237 (M^+), 219 (26%), 181 (10%), 104 (100%), 91 (28%), 77 (70%).
8. Several copper sources (CuOTf, CuCl, $CuCl_2$, CuI, CuBr, and CuOAc) were tested including Cu-diamine and Cu-phenanthroline[4] complexes at ambient temperature. No trace of product formation was observed.
9. Converting product **5a** into the corresponding methyl ester followed by debenzylation ($[\alpha]_D^{25}$ +35.8 (*c* 1, MeOH)) and comparing with an authentic sample ($[\alpha]_D^{25}$ +37 (*c* 1, MeOH)) prepared independently confirmed the optical purity. All other substrates optical purity for all the other substrates was assigned by analogy.