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Cross-coupling reactions of carbamoyl chlorides and Grignard reagents: a new rapid synthesis of tertiary amides†

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Abstract

Tributyl phosphine or nickel catalysts allow the cross-coupling reaction between *N*,*N*-dialkylcarbamoyl chlorides and alkyl or aryl Grignard reagents. This convenient and simple method affords tertiary amides with moderate to excellent yields in short reaction times.

Keywords: amide; coupling reaction; carbamoyl chloride; nickel catalyst; Grignard; trialkyl phosphine.

Amides are usually synthesized as a two-component reaction from amines and acids via their activated form.[1] Another strategy is based on the reaction of an amine, a carbonyl equivalent and a halogenated sp^2 and sp^3 carbon (electrophilic character). Carbon monoxide has been largely used as a carbonyl source and this three-component one-step reaction is catalyzed by transition metal complexes.[2] This procedure was shown to be valuable in the restricted field of radiochemistry.[3] Carbon dioxide,[4] carbamates,[5] and phosgene[6,7] are also used but more rarely. Recently our laboratory reported the successful application of this methodology for the preparation of radiolabeled amides using [^{11}C] carbon dioxide.[4] Due to the short half-life of this positron emitter (20 min), and the limited number of available sources of carbon-11 (CO_2, CO or CH_4) from a cyclotron, there is still a need for a rapid synthesis of amides, especially when the acid cannot be synthesized easily. Therefore we focussed our efforts on phosgene—easily prepared from methane in carbon-11 chemistry—to introduce the carbonyl part of the amide (Scheme 1).

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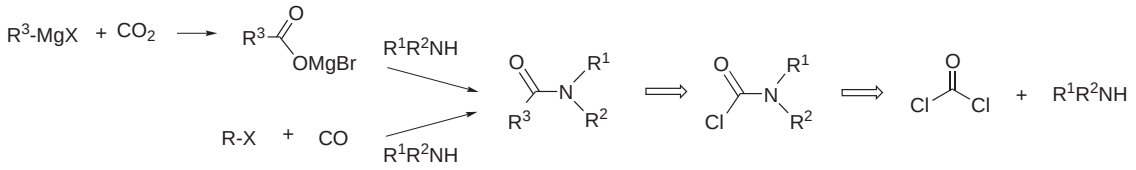


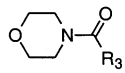
Scheme 1.

By analogy with the formation of ketones from acid chlorides,[8] we anticipated the possibility of synthesizing amides from carbamoyl chlorides. In stable isotope chemistry, these latter compounds are obtained in high yields by reaction of secondary amines in pyridine with triphosgene [bis(trichloromethyl)carbonate].[9] Their reactions with an organometallic reagent to yield amides is then the critical step. A few examples of amide formation using this strategy have been reported. Ivanov reagent $C_6H_4CH(MgCl)CO_2MgCl$ with diethyl- or diphenycarbamoyl chlorides was reported to afford the corresponding amides in 71 and 47% yields.[10] Carbamoyl chlorides (in large excess, dimethyl carbamoyl chloride, the most often) were used to trap lithiated species at low temperature[7] as amides. The reaction of organotin reagents with chlorocarbamates (1:1 ratio) in the presence of a palladium catalyst (5%) gave the corresponding amides in moderate to good yields.[6] However, the reaction was limited to aryl and vinylstannanes. Moreover, it required high temperature, then the removal of often toxic tin derivatives. We wish to describe herein our preliminary results on the rapid synthesis of amides from commercially available carbamoyl chlorides **1** or **2** (Table 1) and Grignard reagents **3** (Scheme 2).

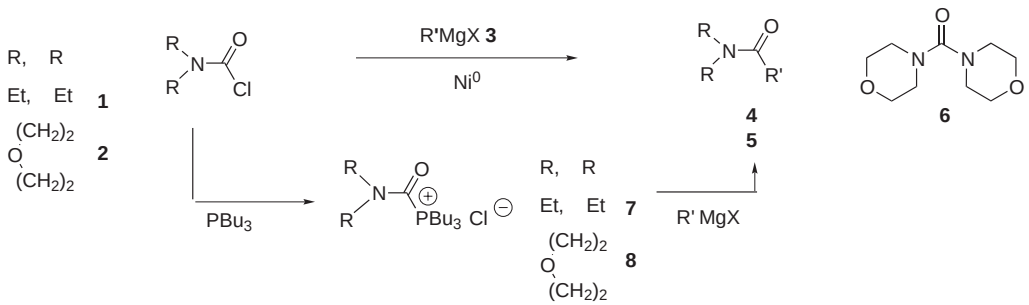
First, we examined the reaction of **1** with a stoichiometric amount of *n*-butylmagnesium bromide **3b** at rt. After 21 h, the ratio of the expected amide **4b** to the starting material **1** was 0.85/1. This ratio was not improved with a longer reaction time. Difficulties encountered to reproduce the reaction led us to envisage replacement of the C–Cl bond of the carbamoyl chloride. Tributyl phosphine, known to enhance the reactivity of acid chlorides in their transformation into ketones and esters[11] were allowed to react neat for 5 min with the carbamoyl chlorides **1** or **2**. Using a stoichiometric amount of reagents the corresponding acylphosphonium salts **7** or **8** were isolated in quantitative yields. To the best of our knowledge these salts have never been described.[12] Triphenylphosphine and triethylphosphite failed to give the phosphonium salt and the phosphonate, respectively, with **1** or **2**. The reaction of salts **7** and **8** with Grignard reagents **3a**–**f** in THF proceeded quickly (<30 min) to afford the desired amides in 38–96% yields (Table 1, method A). Amides **4c** or **5c** were not isolated when using trimethylsilylmethylmagnesium chloride.

As a promising alternative to this carbon–chloride bond replacement, we turned our attention to nickel catalysis, often used in cross-coupling reactions with Grignard reagents.[13] When diethylcarbamoyl chloride **1** was allowed to react with ethylmagnesium bromide **3a** in the presence of $NiCl_2$dppe [dppe: 1,2-bis(diphenylphosphino)ethane], under the conditions described to prepare thioamides from dialkylthiocarbamoyl chlorides and Grignard reagents,[14] we observed a complete conversion of **1** into the amide **4a** after 1 h. Therefore we compared the efficiency of a few nickel catalysts using the same reaction model. Using $NiCl_2$dppe, $NiCl_2$dppp [dppp: 1,3-bis(diphenylphosphino)propane] or $NiCl_2(PPh_3)_2$ similar conversions were obtained in 15 min (88, 83, and 84%, respectively). We then decided to employ $NiCl_2(PPh_3)_2$, a cheap and easily synthesized catalyst.[15] The results (method B) are presented in Table 1 and compared with those observed previously (method A).

Table 1
Reaction of carbamoyl chlorides **1** and **2** with Grignard reagents **3**

entry	R_3MgX	**3**	Method[a]	 **4**[b] Yields	 **5**[b] Yields
1	EtMgBr[c]	**a**	A	-	38
2		**a**	B	58	38[d]
3	nBuMgCl[e]	**b**	A	57	68
4		**b**	B	72	68[d]
5	$TMSCH_2MgCl$[f]	**c**	A	0[g]	0[g]
6		**c**	B	81	82
7	c-Hex-MgCl[e]	**d**	A	(87)[b]	79
8		**d**	B	25	20[d]
9	$Ph(CH_2)_3MgBr$[h]	**e**	B	74	51
10	PhMgBr[c]	**f**	A	34	72
11		**f**	B	95	73
12	$MeO\text{-}C_6H_4\text{-}MgBr$[i]	**g**	B	72	96
13	$H_2C{=}CH\text{-}MgBr$[c]	**h**	A or B	0	0

[a]Method A: via the carbamoyltributylphosphonium chloride **7** or **8**: 20 min, RT, THF. Method B: in the presence of $NiCl_2(PPh_3)_2$ (5 %), 2 h, THF. [b]Isolated yields (average of 3 runs) except for the number in parentheses: yield determined by GC using an internal reference. [c]1.0 M in THF. [d]The corresponding urea was formed in 5-15 % (proportion determined by GC analysis or ^{1}H- NMR). [e]2.0 M in THF. [f]1.0 M in Et_2O. [g]No starting material was recovered. [h]0.5 M in THF. [i]0.4 M in THF.



Scheme 2. Synthesis of amides from carbamoyl chlorides

Amides **4a**–**g** and **5a**–**g** were obtained in moderate to excellent yields, method B gave good results with aryl Grignard reagents (entries 10–12) and with $TMSCH_2MgCl$ (entries 5 and 6). When a branched Grignard reagent was used, the phosphonium method appeared superior (entries 7 and 8). Vinylmagnesium bromide gave no reaction in both methods and the starting

chlorocarbamates was almost recovered quantitatively (entry 13). In method B, the use of a limited excess of organomagnesium reagent was necessary to avoid the formation of the corresponding urea. This side product, not observed in method A, was formed in 5–15% yield when morpholine chlorocarbamate **2** was allowed to react with ethylmagnesium bromide **3a**, *n*-butylmagnesium chloride **3b** or with cyclohexylmagnesium chloride **3d** (entries 2, 4, and 8). We did not observe any decomposition of diethyl and morpholino chlorocarbamate under the reaction conditions. Palladium complexes showed either a lower [$Pd(PPh_3)_4$] or a similar [$PdCl_2(PPh_3)_2$] reactivity than nickel catalysts in reaction of **1** with **3b**.

General procedure: *Method A*: Under a nitrogen atmosphere, tri-*n*-butylphosphine (14.5 mmol, 1 equiv.) was added to the carbamoyl chloride (14.5 mmol). The reaction mixture was heated with a heat gun until crystallization occurred (5 min, quantitative yield). After cooling, the flask was charged with THF (10 mL) and a titrated solution of the Grignard reagent (15.95 mmol, 1.1 equiv.) was added dropwise at rt. The mixture turned yellow and was hydrolyzed with water (3 mL) after 20 min. The solution was then washed with HCl (6N, 10 mL) to remove most of the phosphine.[16] The solution was washed successively with a saturated solution of Na_2CO_3 and brine. Kugelrohr distillation or flash chromatography afforded the desired tertiary amide.

Method B: Under a nitrogen atmosphere, **1** (3.6 mmol) and $NiCl_2(PPh_3)_2$ (0.18 mmol, 0.05 equiv.) were mixed in THF (20 mL). The solution was stirred for a few minutes, and a titrated THF solution of *n*-BuMgCl (2 mL, 2 M, 4 mmol, 1.1 equiv.) was carefully added dropwise at rt. The solution turned dark brown and after 2 h it was quenched with a saturated NH_4Cl solution (10 mL) and extracted with CH_2Cl_2 (2×50 mL). The organic layers were dried over Na_2SO_4 and concentrated. Kugelrohr distillation afforded the amide **4b** (2.5 mmol) in 68% yield. The structures of amides **4a**–**f** and **5a**–**f** were assigned from their analytical and spectroscopic data.[17]

In summary, these two methods provide a useful tool for the preparation of tertiary amides in rapid and convenient processes. The yields are similar to those obtained in carbonylations of the corresponding amines.[18,19] Thus, carbamoyl chlorides afford a good carbonyl source usable on a large scale avoiding double carbonylation.[20] They also could be a good alternative to carbon monoxide in carbon-11 chemistry. Indeed, the low reactivity and solubility of this reagent require special equipment (recirculation flow or autoclave) in order for the reactions to occur. The cross-coupling reaction of carbamoyl chlorides was achieved with either alkyl or aryl Grignard complementing the procedure described with organotin compounds. Further studies are underway with other organometallics and polymer-supported phosphines to expand the scope of the reaction. Investigations for the synthesis of lactams as well as application to the synthesis of ^{11}C-amides will be reported in due course.

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12. **7**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.98 (t, $J=6.9$ Hz, 9H), 1.21 (t, $J=7.1$ Hz, 3H), 1.38 (t, $J=7.1$ Hz, 3H), 1.4–1.6 (m, 12H), 2.88 (m, 6H), 3.53 (q, $J=7.1$ Hz, 2H), 3.80 (q, $J=7.1$ Hz, 2H). ^{13}C NMR (62.8 MHz, $CDCl_3$): δ 11.9, 14.0, 13.3, 20.5 (d, $^{3}J_{CP}=41.4$ Hz), 23.6 (d, $^{2}J_{CP}=15.9$ Hz), 24.5 (d, $^{1}J_{CP}=4.8$ Hz), 40.9, 42.7, 159.1 (d, $^{1}J_{CP}=86.1$). ^{31}P NMR (101 MHz, $CDCl_3$, external H_3PO_4) δ 36.6. **8**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.98 (t, $J=7.0$ Hz, 9H), 1.3–1.7 (m, 12H), 3.0–3.3 (m, 6H), 3.7–4.2 (m, 8H). ^{13}C NMR (62.8 MHz, $CDCl_3$): δ 13.5, 20.6 (d, $^{3}J_{CP}=41.0$ Hz), 23.8 (d, $^{2}J_{CP}=16.0$ Hz), 24.8 (d, $^{1}J_{CP}=4.9$ Hz), 43.7, 46.9, 66.3, 67.5, 159.8 (d, $^{1}J_{CP}=86.5$ Hz). ^{31}P NMR (101 MHz, $CDCl_3$, external H_3PO_4) δ 38.7.
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17. **4c**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.13 (s, 9H), 1.10 (t, $J=7.1$ Hz, 2H), 1.16 (t, $J=7.1$ Hz, 2H), 1.95 (s, 2H), 3.26 (q, $J=7.1$ Hz, 2H), 3.37 (q, $J=7.1$ Hz, 2H).). ^{13}C NMR (62.8 MHz, $CDCl_3$): δ −1.1, 13.2, 14.1, 25.0, 39.6, 42.0, 171.6. IR (NaCl) ν (cm^{-1}) 1628 (CO).
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