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# Facile synthesis of primary amides and ketoamides via a palladium-catalysed carbonylation–deprotection reaction sequence

Eszter Takács,[a] Csilla Varga,[a] Rita Skoda-Földes[a,*] and László Kollár[b]

[a]*University of Pannonia, Institute of Chemistry, Department of Organic Chemistry, Egyetem u. 10, PO Box 158, H-8200 Veszprém, Hungary*
[b]*University of Pécs, Department of Inorganic Chemistry and Research Group for Chemical Sensors of the Hungarian Academy of Sciences, Ifjúság u. 6, PO Box 266, H-7624 Pécs, Hungary*

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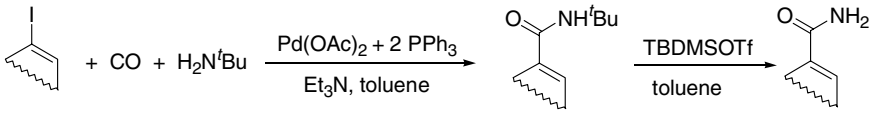
**Abstract**—Various primary amides and ketoamides have been obtained in good yields in a two-step reaction sequence. The first step involves the synthesis of aryl/alkenyl *N*-*tert*-butyl amides and aryl *N*-*tert*-butyl ketoamides from the corresponding iodides via palladium-catalysed carbonylation in the presence of *t*-BuNH$_2$ as the nucleophile. Carbonylation was followed by selective cleavage of the *t*-Bu group using TBDMSOTf as the reagent.


Palladium-catalysed aminocarbonylation of aryl halides or triflates is a powerful tool for the synthesis of aromatic secondary and tertiary amides.[1] However, the application of this method to produce primary amides is restricted to a few examples. Due to the low nucleophilicity of ammonia and the difficulties in handling this toxic reactant, various ammonia-synthons have been used in most reactions. Morera and Ortar[2] reacted aryl/alkenyl halides with hexamethyldisilazane and CO in the presence of a palladium catalyst. The primary amides were formed from the products after acidic workup. Indolese[3] reported on the aminocarbonylation of aryl halides with formamide under 5 bar CO pressure using imidazole as a base. Primary amides were also synthesised using a titanium–nitrogen compound[4] or hydroxylamine[5] as the ammonia source.

In the course of our ongoing interest in palladium-catalysed carbonylation reactions[6] we have found that primary amides can be synthesised from *N*-*t*-Bu amides, obtained by aminocarbonylation of aryl/alkenyl iodides, via deprotection of the *t*-Bu group using *tert*-butyldimethylsilyl triflate (TBDMSOTf) as the reagent (Scheme 1).

Removal of the *t*-Bu group from amides usually requires harsh reaction conditions, so it is rarely used for the protection of primary amides. Recently, Alterman reported a new method using scandium triflate in combination with both conventional and microwave heating for this purpose.[7]

Although TBDMSOTf was used effectively for the removal of *N*-Boc protecting groups of amino acids during peptide synthesis[8] and was shown to cleave the OCH$_3$ group of Weinreb amides[9] in the presence of 2,6-lutidine and Et$_3$N, respectively, to the best of our knowledge there is no precedent for its application for the deprotection of *N*-*t*-Bu amides.




**Scheme 1.** Synthesis of primary amides via a palladium-catalysed aminocarbonylation–deprotection sequence.

*Keywords*: Primary amide; Ketoamide; TBDMSOTf; Aminocarbonylation.
* Corresponding author. Tel.: +36 88 624719; fax: +36 88 624469; e-mail addresses: skodane@almos.uni-pannon.hu; skodane@almos.vein.hu

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Various alkenyl (Fig. 1, **1** and **2**) and aryl iodides (**3**–**6**) were reacted with *tert*-butylamine in the presence of the $Pd(OAc)_2 + 2\ PPh_3$ in situ catalyst and $Et_3N$ as the base under atmospheric CO pressure (Scheme 2). After separation of the resulting amides (**1a**–**6a**) and ketoamides (**3b**–**6b**) by column chromatography, the pure products were heated with 1 equiv of TBDMSOTf in toluene at 60 °C (**1a**, **2a**) or 100 °C (**3a**–**6a** and **3b**–**6b**).

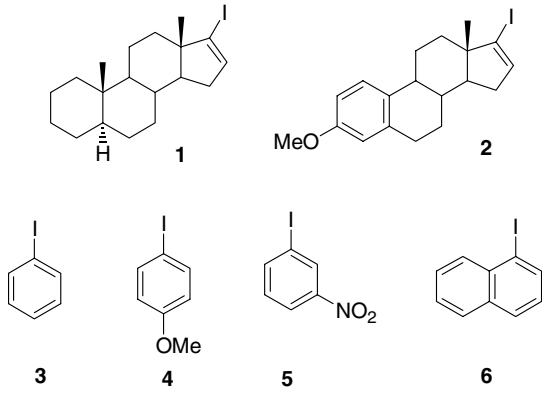
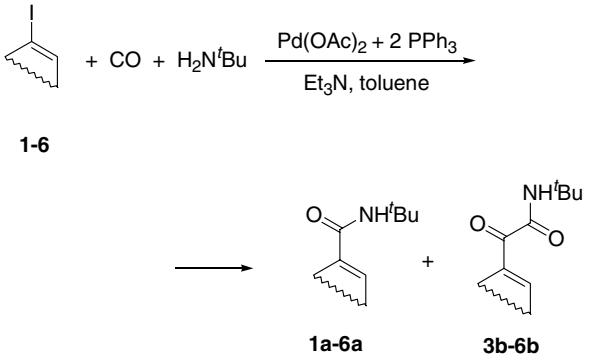



**Figure 1.** Alkenyl/aryl iodides used as substrates in the palladium-catalysed aminocarbonylation.




**Scheme 2.** Aminocarbonylation of alkenyl/aryl iodides **1**–**6**.

Under carbonylation conditions, alkenyl iodides **1** and **2** could selectively be converted to the corresponding amides **1a**[10] and **2a** at 60 °C and the products were obtained in 95% and 92% isolated yields, respectively.

Similar reactions of aryl iodides led to a mixture of amides (**3a**–**6a**) and ketoamides (**3b**–**6b**) even at atmospheric pressure.[11] As we had found before during the aminocarbonylation of iodoferrocene,[12] a change in the temperature had a marked effect on the selectivity of the reaction, except for substrate **6**. At 60 °C the ketoamides were the main products, while at 100 °C the formation of the amides was favoured (Table 1).

Accordingly, aromatic amides **3a**–**6a** were isolated in 52–85% yields and ketoamides **3b**–**6b** in 37–62% yields from the aminocarbonylation reactions carried out at 100 °C and 60 °C, respectively. All of the products were characterised by $^1H$ NMR and MS.

Amides **1a**–**6a** and ketoamides **3b**–**6b** were reacted with TBDMSOTf in toluene under an inert atmosphere. Amides **1a** and **2a** could selectively be converted to the primary amides **7**[13] and **8** at 60 °C, but a higher temperature (100 °C) had to be used for the removal of the *t*-Bu group from the aromatic derivatives.

TLC indicated complete conversion of amides **1a**–**6a** and ketoamides **3b**–**6b** into the primary derivatives **7**–**16** under the conditions mentioned above and most of the products could be isolated in good yields (Table 2). However, ketoamide **13** was obtained only in moderate yield due to the difficulties in the separation of the product and silicon containing by-products. It should be mentioned that the presence of a base ($Et_3N$ or 2,6-lutidine) had no effect on the cleavage.

In a typical experiment 1 mmol of alkenyl/aryl iodide was reacted with 5 mmol of *t*-$BuNH_2$, 0.05 mmol of $Pd(OAc)_2$, 0.1 mmol of $PPh_3$ and 3.5 mmol of $Et_3N$ in 10 ml of toluene under a CO atmosphere at 60 or 100 °C for 8 h. The reaction progress was followed by GC. After completion of the reaction, the solvent was

**Table 1.** Aminocarbonylation of aromatic iodides **3**–**6**[a]

| Entry | Substrate | Temperature (°C) | Product distribution[b,d] (%) | | Isolated yield (%) | |
|---|---|---|---|---|---|---|
| | | | **a** | **b** | **a** | **b** |
| 1 | **3** | 60 | 24 | 76 | | 62 |
| 2 | **3** | 100 | 92 | 8 | 85 | |
| 3[c] | **4** | 60 | 22 | 78 | | 59 |
| 4[c] | **4** | 100 | 74 | 26 | 58 | |
| 5 | **5** | 60 | 28 | 72 | | 51 |
| 6 | **5** | 100 | 83 | 17 | 72 | |
| 7[c] | **6** | 60 | 52 | 48 | | 37 |
| 8[c] | **6** | 100 | 64 | 36 | 52 | |

[a] Reaction conditions: 1 mmol aryl iodide (**3**–**6**), 5 mmol *t*-$BuNH_2$, 0.05 mmol $Pd(OAc)_2$, 0.1 mmol $PPh_3$, 3.5 mmol $Et_3N$, 10 ml toluene, 1 bar CO, 8 h.
[b] Determined by GC.
[c] Reaction time 10 h.
[d] Practically complete reactions (conversion >99%) were obtained in all cases.

**Table 2.** Primary amides and ketoamides produced by cleavage of *N*-*t*-Bu-derivatives[a]

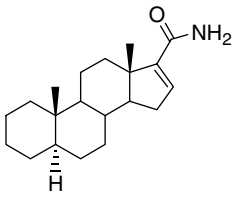
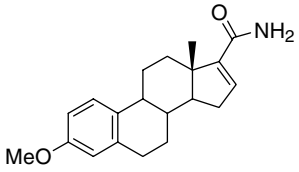
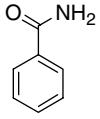
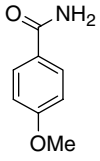
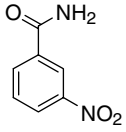
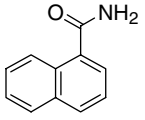
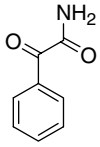
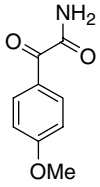
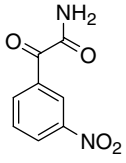
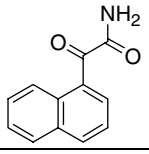
| Entry | Product | | Yield (%) |
|---|---|---|---|
| 1[b] |  | **7** | 98 |
| 2[b] |  | **8** | 75 |
| 3 |  | **9** | 91 |
| 4 |  | **10** | 74 |
| 5 |  | **11** | 83 |
| 6 |  | **12** | 90 |
| 7 |  | **13** | 52 |
| 8 |  | **14** | 86 |
| 9 |  | **15** | 86 |

**Table 2** (*continued*)

| Entry | Product | | Yield (%) |
|---|---|---|---|
| 10 |  | **16** | 84 |

[a] Reaction conditions: 0.5 mmol amide (**1a**–**6a**) or ketoamide (**3b**–**6b**), 0.5 mmol TBDMSOTf in 5 ml toluene, 100 °C, 8 h.
[b] The reaction was carried out at 60 °C.

removed in vacuo. The residue was dissolved in chloroform (20 ml) and washed twice with 5% HCl (20 ml), saturated $NaHCO_3$ (20 ml), brine (20 ml), dried over $Na_2SO_4$ and the solvent was removed by distillation. Chromatography (silica, toluene/ethanol = 15/1) yielded amides **1a**–**6a** and ketoamides **3b**–**6b**. Then 0.5 mmol of amide or ketoamide was heated with 0.5 mmol of TBDMSOTf in 5 ml of toluene at 60 or 100 °C for 8 h. After completion of the reaction, the solvent was removed in vacuo. Chromatography (silica, toluene/ethanol = 15/1) yielded the desired primary amides (**7**–**12**) or ketoamides (**13**–**16**).

In conclusion, TBDMSOTf can be used for cleavage of the *N*-*t*-Bu groups of *N*-*t*-Bu-amides and ketoamides. The palladium-catalysed carbonylation–deprotection reaction sequence proved to be an effective method for the synthesis of aromatic/alkenyl primary amides and aromatic primary ketoamides.

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10. *Selected spectroscopic data for* **1a**: $^{1}$H NMR ($\delta$): 6.31 (br s, 1H); 5.45 (br s, 1H); 2.2–0.7 (m, 22H, ring protons); 1.35 (s, 9H); 0.95 (s, 3H); 0.8 (s, 3H). MS (*m*/*z*/rel. int.): 357 ($M^{+}$)/20; 342/30; 285/49; 257/100; 191/53; 161/75; 147/85; 133/71; 119/45; 105/40; 95/44.
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13. *Selected spectroscopic data for* **7**: $^{1}$H NMR ($\delta$): 6.43 (br s, 1H); 5.60 (br s, 2H); 2.23–0.78 (m, 22H, ring protons); 0.98 (s, 3H); 0.80 (s, 3H). $^{13}$C NMR ($\delta$): 168.2 (CO); 138.5; 132.3; 57.0; 55.4; 47.5; 46.7; 38.7; 36.7; 35.2; 34.1; 32.2; 31.9; 29.2; 29.1; 27.0; 22.3; 20.9; 16.6; 12.4. MS (*m*/*z*/rel. int.): 301 ($M^{+}$)/18; 286/39; 257/100.