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Convenient synthesis of α-amino amides using low-valent tantalum prepared from $TaCl_5$ and Zn

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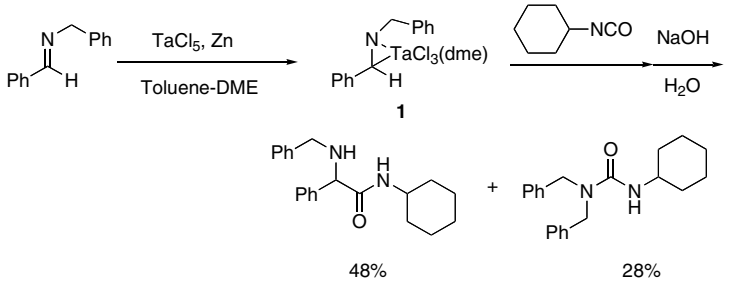
Abstract—We have developed a general preparation method of α-amino amides from imines and isocyanates using low-valent tantalum prepared from $TaCl_5$ and Zn in situ. This method was successfully applied to various imines derived from benzaldehyde derivatives with electron-withdrawing or electron-donating substituents, heteroaromatic aldehydes, and an aliphatic, α-branched aldehyde, giving the corresponding α-amino amides in high yields.

α-Amino acids and their analogues are among the most important, numerous and diverse families of natural products. They are not only used as building blocks for living things but also show biological activities by themselves. Therefore, many chemists have concentrated their efforts on the development of more efficient synthetic methods of natural and unnatural amino acid analogues.[1]

Whereas tantalum–imine complexes[2] have attracted much attention in the area of organometallic chemistry, their use in organic synthesis has been rather limited.[3] In 1998, Takai et al. reported the first example of direct synthesis of tantalum–imine complex (**1**) from an imine and low-valent tantalum prepared from $TaCl_5$ and Zn.[4] They also disclosed its characteristic structure and reactivity toward carbonyl compounds. On the other hand, it was reported that tantalum–imine complex **1** reacted with cyclohexyl isocyanate to afford a mixture of an α-amino amide and a urea in almost 2:1 selectivity (Scheme 1).[4] We thought that this type of reaction might provide an interesting synthetic method of α-amino amides, if the reactions proceeded regioselectively.

First, we used phenyl isocyanate instead of cyclohexyl isocyanate (Table 1). It was found that the use of an excess amount of the isocyanate decreased the yield of the desired product and led to an increase of unknown insoluble by-products (entries 1 and 2). We thought that the weakly basic work up using saturated aqueous



Scheme 1. The reaction of a Ta–imine complex with cyclohexyl isocyanate.

Keywords: α-Amino amides; Tantalum–imine complex; Isocyanate.
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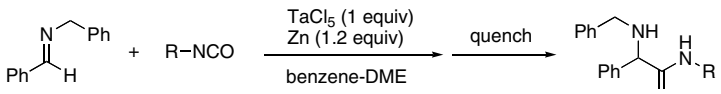
Table 1. Optimization of the reaction conditions

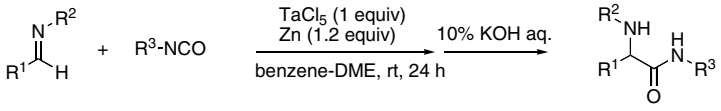


Entry	Imine (equiv)	R–NCO (equiv)	Time (h)	Quench	Yield (%)
1	1.0	PhNCO (1.2)	18	Satd $NaHCO_3$ aq	37
2	1.0	PhNCO (2.4)	18	Satd $NaHCO_3$ aq	Complex mixture
3	1.0	PhNCO (1.2)	18	10% KOH aq	78
4	1.2	PhNCO (1.0)	18	10% KOH aq	82
5	1.2	PhNCO (1.0)	24	10% KOH aq	90
6	1.2	PhNCO (1.0)	48	10% KOH aq	82
7	1.2	BnNCO (1.0)	24	10% KOH aq	90

$NaHCO_3$ resulted in by-product formation, because the unreacted isocyanate would remain after adding saturated aqueous $NaHCO_3$ and react with the desired product to give undesired compounds. We then decided to change the work up procedure by using aqueous 10% KOH. As expected, the yield was improved (entry 3) although a by-product, which was thought to be a urea derivative of the product was still obtained. Further optimization of the reaction conditions revealed that the use of a slight excess of the imine led to an increased yield, up to 90% in 24 h (entry 5). Benzyl isocyanate also gave a promising result (entry 7). In these cases, isocyanates inserted mainly into the Ta–C bond of cyclotantalacycle to give the α-amino amides in high yields.

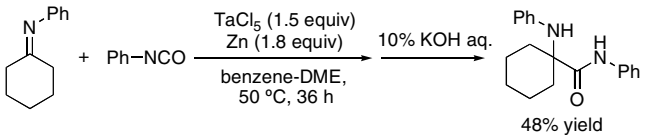
Encouraged by these results, we next investigated the substrate scope of this reaction (Table 2). In the cases of *N*-(4-substituted-benzylidene)benzylamine derivatives, the reactions proceeded smoothly to give the desired products in high yields (entries 1–3, 9–11), although longer reaction times were needed to form Ta–imine complexes when benzylamine derivatives with electron-withdrawing substituents were used. *N*-Benzylideneaniline and aldimines prepared from heteroaromatic aldehydes and benzylamine also required longer reaction times to form the corresponding Ta–imine complexes in good yields (entries 4 and 12). Even the aliphatic imine derived from cyclohexanecarboxyaldehyde afforded the corresponding product in

Table 2. Substrate scope



Entry	R^1	R^2	R^3	Yield (%)
1	4-$MeOC_6H_4$	Bn	Ph	85
2	4-MeC_6H_4	Bn	Ph	82
3[a]	4-ClC_6H_4	Bn	Ph	85
4[a,b]	4-Pyridyl	Bn	Ph	80
5[a]	Ph	Ph	Ph	84
6	Ph	(*R*)-1-Phenylethyl	Ph	78[c]
7	Ph	(*R*)-1-(α-Naphthyl)ethyl	Ph	72[d]
8	Ph	(*R*)-1-(β-Naphthyl)ethyl	Ph	74[e]
9	4-$MeOC_6H_4$	Bn	Bn	93
10	4-MeC_6H_4	Bn	Bn	86
11[a]	4-ClC_6H_4	Bn	Bn	86
12[a]	2-Furyl	Bn	Bn	74
13[a]	Ph	Ph	Bn	85
14[a]	Cyclohexyl	Ph	Bn	59
15[a]	Ph	(*R*)-1-Phenylethyl	Bn	83[f]
16[a]	Ph	(*R*)-1-(α-Naphthyl)ethyl	Bn	67[g]
17[a]	Ph	(*R*)-1-(β-Naphthyl)ethyl	Bn	88[h]

[a] Ta–imine complex formation time; 3 h.
[b] DCM–DME was used as a solvent.
[c] Major/minor = 68/32.
[d] Major/minor = 79/21.
[e] Major/minor = 66/34.
[f] Major/minor = 66/34.
[g] Major/minor = 75/25.
[h] Major/minor = 65/35.



Scheme 2. The reaction of a ketimine with an isocyanate.

good yield (entry 14), whereas an aliphatic imine without a branch at the α-position such as hydrocinnamaldehyde resulted in the formation of a complex mixture. In addition, it was found that aldimines derived from chiral amines moderately influenced the stereochemical outcome of subsequent additions of Ta–imine complexes to isocyanates (entries 6–8, 15–17). These preliminary results suggested that stereoselective synthesis of α-amino amides using low-valent tantalum–imine complexes might be possible. The ketimine derived from cyclohexanone and aniline reacted with low-valent tantalum followed by phenyl isocyanate to give the desired product in moderate yield (Scheme 2). This result suggests that this method is useful for the preparation of α-amino-α,α-disubstituted amide derivatives.[1,5,6]

In summary, we have shown that α-amino amides were readily prepared from imines and isocyanates using low-valent tantalum generated from $TaCl_5$ and Zn. A wide variety of imines and isocyanates were applicable, and various α-amino amides were synthesized in high yields. Further investigations to develop an asymmetric version of this reaction are now in progress.

Acknowledgements

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6. Typical experimental procedure (Table 1, entry 6): Under argon atmosphere, DME (0.25 mL) was added to a suspension of $TaCl_5$ (144 mg, 0.40 mmol) and Zn (32 mg, 0.49 mmol) in benzene (0.25 mL), and the mixture was stirred at room temperature for 1 h. *N*-Benzylidenebenzylamine (93 mg, 0.48 mmol) in benzene (0.50 mL) was added to the resulting green-brown suspension at the same temperature and the mixture was stirred for 1 h. The color of the suspension changed to dark red. Phenyl isocyanate (48 mg, 0.40 mmol) in benzene (0.50 mL) was then added and the mixture was stirred at room temperature for 24 h. The reaction was stopped by addition of aqueous 10% KOH (5 mL) and ether (5 mL), and the mixture was stirred vigorously for 30 min until the brown mixture became white suspension. The white solid was filtered off through Celite® and the residue was washed with ether (10 mL, three times). The filtrate and the washes were combined and extracted with ether (10 mL, two times). The organic layer was combined and washed with brine and dried over Na_2SO_4. The crude product was purified by P-TLC (CH_2Cl_2–EtOH, 30:1) to afford 2-(benzylamino)-*N*,2-diphenylacetamide (115 mg, 90%). Off-white solid; Mp: 80–82 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 3.85 (s, 2H), 4.33 (s, 1H), 7.01–7.60 (m, 15H), 9.47 (br s, 1H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 52.7, 67.5, 119.4, 124.1, 127.2, 127.5, 128.1, 128.7, 128.8, 128.9, 137.6, 138.8, 170.0; IR (KBr) 3303, 3261, 1672, 1603, 1533, 1495, 1443, 1119, 924, 739, 694 cm^{-1}; ESIMS *m/z* 317 ($[M+H]^+$). Anal. Calcd for $C_{21}H_{20}N_2O$: C, 79.44; H, 6.00; N, 9.26. Found: C, 79.50; H, 6.20; N, 9.22.