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One-Pot, Three-Component Coupling Approach to the Synthesis of α−Iminocarboxamides

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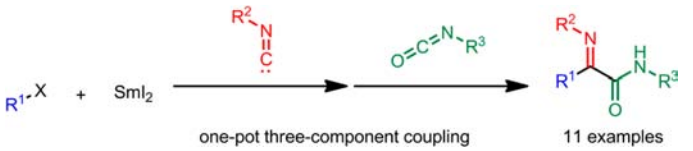
ABSTRACT



A one-pot, three-component coupling was accomplished via the nucleophilic addition of an alkylsamarium(III) species to isocyanides and the subsequent addition of the resultant imidoyl samarium(III) species to isocyanates under mild conditions for the formation of α-iminocarboxamides. The developed sequential C−C bond-forming procedure enabled the rapid synthesis of the α-iminocarboxamides in good to excellent yields from readily available starting materials.

α-Iminocarboxamides have garnered much attention in recent years because of their anti-HIV[1] and anticonvulsant[2] activities and their functions as dyes[3] and as ligands of polymerization catalysts and oxidation catalysts.[4] α-Iminocarboxamides are also useful as key intermediates for the synthesis of α-amino acids.[5]

The most conventional method for the synthesis of α-iminocarboxamides is the amidation of the α-keto acids and the subsequent imination of the obtained α-ketocarboxamides (Figure 1a).[6] Recently, we reported the construction of an 87-membered combinatorial library of α-iminocarboxamide ligands of alkene polymerization catalysts based on this procedure.[6d] The limitations of this procedure are as follows: (1) the imination usually requires heating conditions in the presence of acid, and thus, substrates with an acid-labile group cannot be employed, and (2) the availability of the starting material, α-keto acid, is somewhat limited. The convergent synthesis of α-iminocarboxamides by way of a C−C bond-forming reaction (Figure 1b) is an elegant methodology.[5e] However, imidoyl chlorides and carbamoyl silanes are not readily available materials. The development of a divergent, high-yielding, and mild synthetic method from readily available starting materials remains important. From this point of view, a sequential C−C bond-forming approach[7] (Figure 1c) is ideal because α-iminocarboxamides with various

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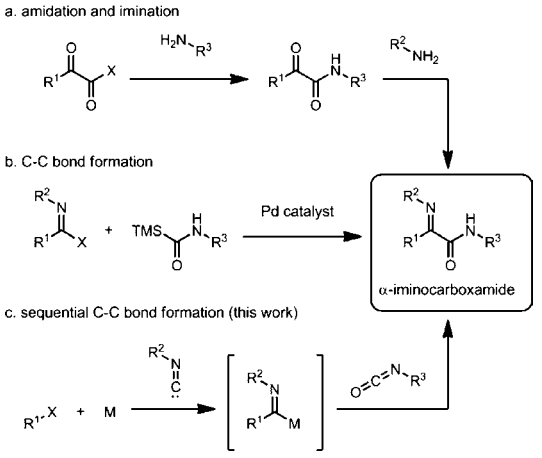


Figure 1. Strategies for the synthesis of α-iminocarboxamides.

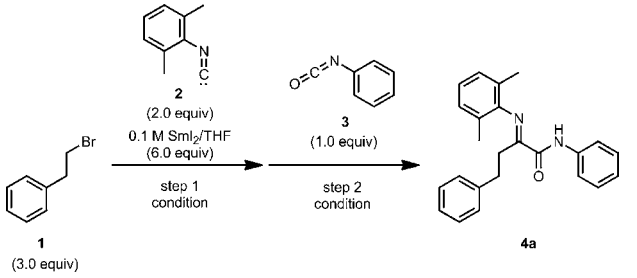
substituents, R^1, R^2, and R^3, can be rapidly synthesized from readily available starting materials.

One-pot, multicomponent reactions are powerful synthetic methodologies for the rapid synthesis of complex molecules from simple reactants. Such protocols require neither purification nor workup of reaction intermediates, and thus, they significantly improve synthetic efficiency. In particular, isocyanide-based multicomponent reactions, including Passerini and Ugi reactions,[8] are highly important because they are frequently used in organic synthesis. We have developed and reported a one-pot, multicomponent coupling approach to the synthesis of bioactive compounds for decades.[9]

Herein, we wish to report a one-pot synthesis of α-iminocarboxamides by the nucleophilic addition of an alkyl metal species to isocyanides and the subsequent addition of the resultant imidoyl metal species to isocyanates in good to excellent yields under mild conditions (Figure 1c). The developed sequential C−C bond-forming procedure enabled the rapid synthesis of α-iminocarboxamides with various substituents, R^1, R^2, and R^3, from readily available starting materials: alkyl halides, isocyanides, and isocyanates. In addition, we also report a novel one-pot synthesis of α,β-diiminocarboxamide and an α-amino acid.

For the development of a mild synthetic method for α-iminocarboxamides, we focused on the utilization of samarium(III) compounds (Figure 1c, M = Sm). Ito and Murakami et al. reported a beautiful procedure for the preparation of imidoyl samarium(III) species from the corresponding alkyl samarium(III) species and isocyanides.[10] However, the nucleophilic addition of an imidoyl samarium(III) species to isocyanates has not yet been reported. Therefore, we examined this coupling reaction as shown below.

Table 1. Optimization of the One-Pot, Three-Component Coupling Reaction



entry	step 1 conditions	step 2 conditions	yield (%)
1	HMPA, −15 °C, 3 h	−78 °C, 5 min	**4a**, quant
2	−15 °C, 3 h		no reaction
3	DMF, −15 °C to rt, 10 h		no reaction
4	DMPU, −15 °C to rt, 11 h	−15 °C, 1 h	**4a**, 20%

Phenethyl bromide (**1**), 2,6-xylyl isocyanide (**2**), and phenyl isocyanate (**3**) were selected as substrates for the ease of monitoring reactions (Table 1). Phenethyl bromide (**1**) (3.0 equiv) was added to a mixture of 2,6-xylyl isocyanide (**2**) (2.0 equiv) and SmI_2[11] (0.1 M in THF, 6.0 equiv) under conditions 1 (Table 1). After stirring, phenyl isocyanate (**3**) (1.0 equiv) was added, and the reaction mixture was stirred using conditions 2 (Table 1). To our delight, a one-pot, sequential C−C bond-forming reaction afforded the desired product **4a** in a quantitative yield under mild conditions (entry 1). The addition of HMPA was crucial to a good yield. The desired intermediate, imidoylsamarium(III) species, was not generated in the absence of HMPA (entry 2) or by the addition of DMF instead of HMPA (entry 3). When DMPU was added instead of HMPA, the yield of the desired product was decreased to 20% (entry 4).

The substrate scope of the developed one-pot procedure was explored using various alternatives (Table 2).[12] In the

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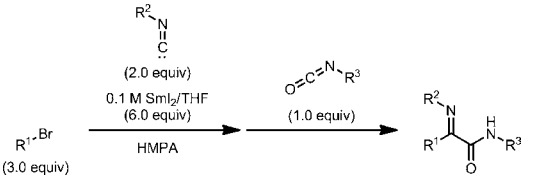
(11) SmI_2 solution was prepared according to a literature procedure: Girard, P.; Namy, J. L.; Kagan, H. B. *J. Am. Chem. Soc.* **1980**, *102*, 2693. The concentration of SmI_2 was determined by titration according to literature procedure: Iwamoto, T.; Ono, M. *Chem. Lett.* **1987**, 501.

(12) It was reported that the use of hexyl isocyanide or 4-tolyl isocyanide caused undesired reductive deisocyanation (ref 10b). Therefore, aryl isocyanides with *ortho* substituents were employed as substrates.

Table 2. Synthesis of α-Iminocarboxamides



entry	R^1Br	R^2NC	$OCNR^3$	yield
1	**1**	**2**	**3**	**4a** quant
2	**1**	**2**	**5**	**4b** quant
3	**1**	**2**	**6**	**4c** 86%
4	**1**	**2**	**7**	**4d** quant
5	**1**	**8**	**3**	**4e** 79%
6	EtBr **9**	**2**	**3**	**4f** 80%
7	EtBr **9**	**2**	**5**	**4g** 99%
8	EtBr **9**	**2**	**6**	**4h** 66%
9	EtBr **9**	**2**	**7**	**4i** quant
10	EtBr **9**	**10**	**3**	**4j** 57%
11	**11**	**2**	**3**	**4k** 82%

case of R^1 = phenethyl or ethyl (R^1Br = **1** or **9**), the desired products **4a**–**j** were obtained in good to excellent yields (entries 1–10). The coupling reaction with isocyanides **8** or **10**, or isocyanate **7**, which have either a bulky 2,6-diisopropyl phenyl group or a 2,4,6-tri-*tert*-butylphenyl group, provided the corresponding α-iminocarboxamides in satisfactory to excellent yields (entries 4, 5, and 10, respectively). An acid-labile THP group was tolerated under the coupling conditions (entry 11). The structures of all α-iminocarboxamides were confirmed by ^1H NMR, ^{13}C NMR, IR, and HRMS.

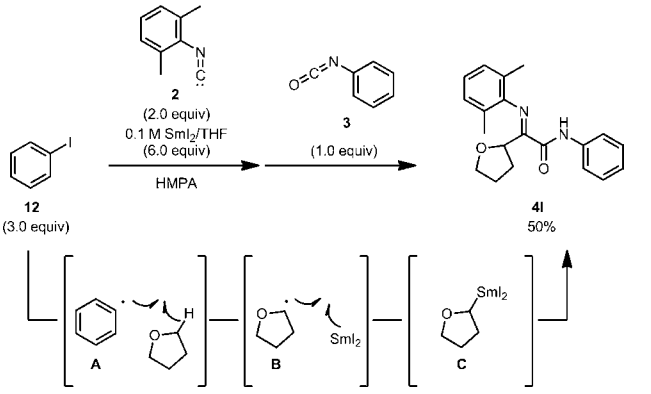


Figure 2. Plausible mechanism for the formation of tetrahydrofuranyl iminocarboxamide.

When iodobenzene (**12**) was employed as an alkyl halide, tetrahydrofuranyl iminocarboxamide **4l** was obtained in a 50% yield (Figure 2). This observation is consistent with a previous report.[10b] It is conceivable that phenyl radical intermediate **A** was generated from iodobenzene (**12**) and SmI_2 abstracted hydrogen from the solvent THF. The resultant tetrahydrofuranyl radical **B** was converted into tetrahydrofuranyl samarium(III) species **C**, resulting in a sequential coupling reaction with isocyanide **2** and isocyanate **3**.

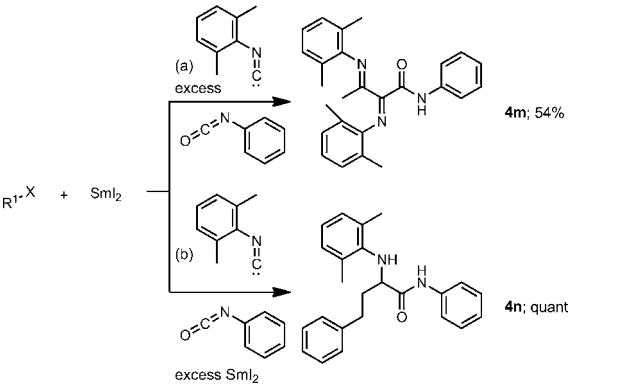


Figure 3. Synthesis of (a) α,β-diiminocarboxamides and (b) α-amino acid by changing the amount of substrate or reagent.

It is interesting that the product of the one-pot coupling reaction could be switched by changing the amount of reagent or substrate. When an excess amount (8.0 equiv

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against isocyanate) of isocyanide was used, α,β-diiminocarboxamide was obtained by double insertion[13,14] of the isocyanide. α,β-Diiminocarboxamide **4m** was obtained in a 54% yield (Figure 3a). This coupling reaction is useful for the synthesis of structurally interesting vicinal tricarbonyl compounds. When an excess amount (8.0 equiv against isocyanate) of SmI_2 was used in the one-pot reaction, the resultant α-iminocarboxamide was reduced with SmI_2 in situ, and the corresponding α-amino acid **4n** was obtained in a quantitative yield (Figure 3b).[15] This is a novel approach for the rapid synthesis of α-amino acids.

In conclusion, we successfully demonstrated a rapid one-pot synthesis of various α-iminocarboxamides via the nucleophilic addition of an alkyl samarium(III) species to isocyanides and the subsequent nucleophilic addition of the resultant imidoyl samarium(III) species to isocyanates. The developed sequential C−C bond-forming approach allowed us to obtain α-iminocarboxamides with various substituents, R^1, R^2, and R^3, from readily available starting materials: alkyl halides, isocyanides, and isocyanates in good to excellent yields under mild conditions. In addition, structurally diverse products, i.e., α,β-diiminocarboxamides and an α-amino acid, were successfully synthesized by changing only the amount of either the reagent or the substrate in a one-pot reaction. The developed procedure should be very useful for the rapid synthesis of various iminocarboxamide-based compounds.

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Supporting Information Available. Detailed experimental procedures and characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(14) When phenethyl bromide was employed as R^1-X, the corresponding α,β-diiminocarboxamide was obtained as a mixture of diastereomers with respect to the direction of the 2,6-xylyl groups in a 59% combined yield.

(15) Reduction by $NaBH_4$ after similar three-component reaction: (a) Murakami, M.; Ito, H.; Ito, Y. *J. Org. Chem.* **1993**, *58*, 6766. (b) Murakami, M.; Ito, H.; Ito, Y. *Chem. Lett.* **1996**, 185.

The authors declare no competing financial interest.