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SHORT COMMUNICATION

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Synthesis of α-Amino Acids through Samarium(II) Iodide Promoted Reductive Coupling of Nitrones with CO_2

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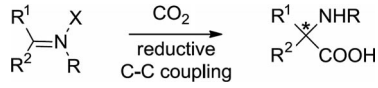
Several *N*-benzylnitrones reacted with carbon dioxide in the presence of samarium(II) iodide leading to α-amino acids as the products of reductive C–C coupling. The best selectivities were observed at a carbon dioxide pressure of 50 bar at ambient temperature. The influences of different functional groups in the nitrone backbone and of the coordinating additives to samarium(II) iodide on the product distribution were investigated. The racemic α-amino acids were obtained in up to 70 % yield based on HPLC data.

Introduction

The use of carbon dioxide (CO_2) as a carbon synthon in organic synthesis[1] (for instance, as a C_1 building block to obtain carboxylic acids) often requires activation of this rather inert molecule, which can be achieved through coordination to an electronically rich metal center.[2] Among recent advances in this field are the nickel-catalyzed carboxylation of styrenes[3] or ethylene,[4] the reaction of carbon dioxide with organozinc reagents,[5] and the palladium-catalyzed carboxylation of aryl bromides.[6] Carboxylic acids themselves are considered valuable synthons in organic chemistry and exhibit a high potential as medicinally important compounds.[7] In this view, special attention is paid to non-proteinogenic α-amino acids,[8] which are extensively explored as promising pharmaceutics.[9]

However, synthetic approaches to α-amino acids by using CO_2 as a C_1 building block are still scarce. Until recently, these methods were mostly represented by reactions of CO_2 with lithium organics,[10] with electrochemically generated free radicals,[11] and with in situ generated stannylated imines.[12] Formally, the umpolung of imines followed by the reaction with CO_2 would represent an ideal approach for α-amino acid synthesis (Scheme 1). It would be the most straightforward and atom-economic alternative to the Strecker synthesis,[8,13] which involves nucleophilic addition of cyanide followed by hydrolysis of the cyano group into a carboxylic acid (the latter proceeds usually under drastic acidic conditions).



Scheme 1. Reductive C–C coupling of imine derivatives with CO_2 (imine: X = electron pair; nitrone: X = O).

Among the reagents used in organic synthesis to mediate umpolung of imines and nitrones[14] in reductive C–C bond formation, samarium diiodide[15] (Kagan's reagent, SmI_2) has emerged as one of the most versatile ones.[16] In particular, it proved to be a reagent of choice to mediate reductive cross-coupling reactions involving nitrones and various electrophiles.[17] Moreover, the reaction of organosamarium intermediates derived from carbonyl compounds with CO_2 was reported to yield carboxylic acids.[18] Besides this, the reaction of bis(pentamethylcyclopentadienyl)samarium(II) complexes with CO_2 can produce oxalates[19] or N–CO_2 coupled products[20] showing that electron transfer can be also achieved from Sm^{II} to carbon dioxide.[21] With these precedents, the work presented herein led to the first successful SmI_2-mediated reductive C–C coupling between nitrones or aldimines and carbon dioxide to produce α-amino acids.

Results and Discussion

For these studies, solutions of SmI_2 (0.1 M in THF) were freshly prepared by using a fast and convenient reaction

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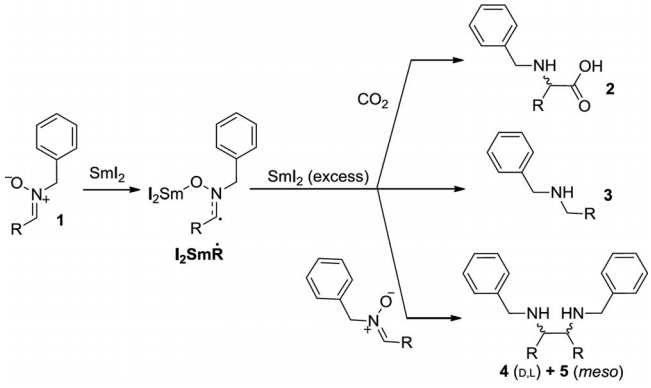
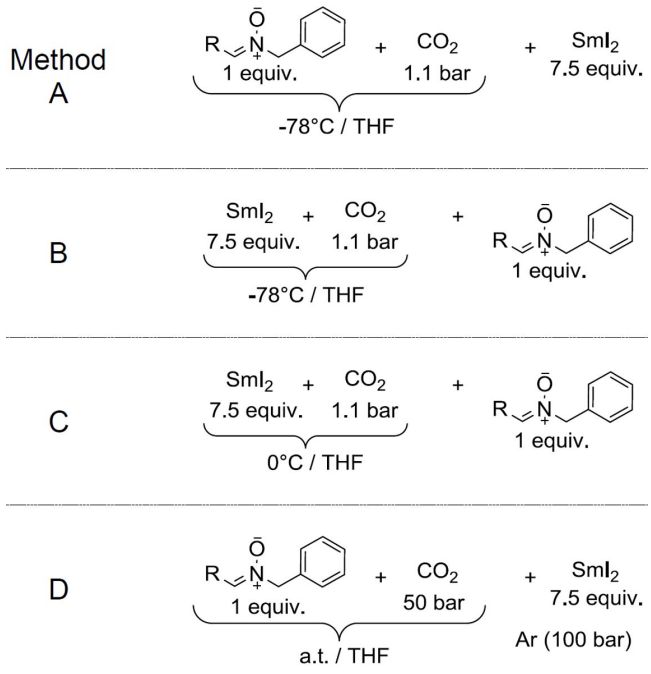
between metallic Sm and I_2 in THF under ultrasonic irradiation.[22] The starting SmI_2 solution was found to be unreactive towards CO_2: it could be saturated with gaseous carbon dioxide at room temperature or treated with CO_2 at –78 °C without any noticeable changes in the initial dark-blue color. As a consequence, the first species to be reduced with SmI_2 has to be the organic substrate – the nitrone – leading initially to the samarium-coordinated organic anion–radical $I_2SmR^{\cdot}$ (see Scheme 2).[23] Attempts to react nitrones with CO_2 "step by step" (i.e., in the presence of 1 or 2 equiv. of SmI_2 under various conditions) did not result in the isolation of intermediate C–C coupled products. However, it was possible to obtain *N*-benzyl-substituted α-amino acids by employing an excess amount of the reducing agent (up to 10 equiv. of SmI_2), which suggests three possible reaction pathways after the preliminary formation of the $I_2SmR^{\cdot}$ intermediate (Scheme 2): (1) A C–C coupling with CO_2 followed by reduction with deoxygenation of nitrogen atom[24] leading to α-amino acid **2**. (2) Further reduction by reaction with additional SmI_2 plus proton abstraction from the solvent leading to amine **3**. (3) Dimerization of the radical intermediate ($I_2SmR^{\cdot}$) by C–C coupling followed by further SmI_2 reduction and protonation to yield diamines **4** and **5**.



Scheme 2. Possible pathways for the reaction of nitrones with SmI_2 in presence of CO_2.

The reaction was then carried out under different conditions (Scheme 3), which were optimized by using the reaction of (*Z*)-*N*-(4-isopropylbenzylidene)-1-phenylmethanamine oxide (**1a**) with SmI_2 and CO_2 as the model reaction (Table 1, Entries 1–4).

In the first experiment, a sample of nitrone **1a** was dissolved in THF, the solution was cooled down to –78 °C, and argon was replaced by gaseous CO_2; the reaction Schlenk vessel was connected to a CO_2 bottle at 1.1 bar (Table 1, Entry 1; method A in Scheme 3). The SmI_2 solution (7.5 equiv.) was added drop by drop to the nitrone solution at –78 °C under a CO_2 atmosphere with vigorous stirring. After 30 min, the blue reaction mixture was slowly brought to room temperature and left to stir overnight. It was then exposed to air to oxidize the excess amount of SmI_2 and subjected to HPLC analysis. Under these conditions, only trace amounts of *N*-benzyl-substituted α-amino



Scheme 3. Reaction conditions and successions of the reagent mixing tested in experiments with nitrones, CO_2, and SmI_2.

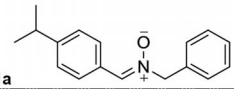
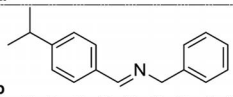
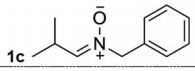
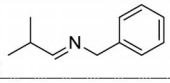
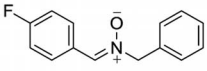
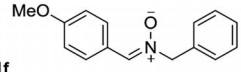
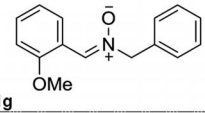
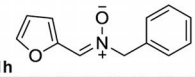
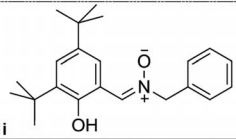
acid **2a** were detected, and most of the starting nitrone was converted into reductive homocoupling product (D,L)-1,2-diamine **4a**. Isomeric *meso*-1,2-diamine **5a** and amine **3a** were also formed.[25]

A similar distribution of the products was found when the sequences of mixing was changed, that is, when the solution of nitrone **1a** was added dropwise to the stirred SmI_2 solution at –78 °C under CO_2 (Table 1, Entry 2; method B in Scheme 3). These results are similar to those obtained by treatment of imines with SmI_2[26] and show that at –78 °C single-electron transfer from SmI_2 to nitrone **1a** is likely to occur, and the resulting Sm^{III}-coordinated radical anion dimerizes producing diamines **4a** and **5a** as the major products (after reduction of the N–O bond of the intermediate vicinal bishydroxylamines[24]), but the reaction with CO_2 does not proceed. Concurrently, the formation of *N*-benzyl-1-(4-isopropylphenyl)methanamine (**3a**) results from simple reduction of **1a** by the excess amount of SmI_2.

The distribution of the products changed considerably when the reagents were mixed at 0 °C (Table 1, Entry 3; a solution of nitrone **1a** was added drop by drop to the stirred SmI_2 solution under CO_2, method C in Scheme 3). In this case, the main products were 1,2-diamines **4a** and **5a** (≈55%) and α-amino acid **2a** (≈30%). Thus, upon increasing the temperature, the reactivity of the systems becomes high enough to enable the C–C coupling reaction between the organosamarium radical ($I_2SmR^{\cdot}$) and CO_2 (see Scheme 2). As a consequence, ≈30% of α-amino acid **2a** was formed and correspondingly ≈30% less of diamines **4a** and **5a**.

The yield of α-amino acid **2a** was further increased up to 70% when the reaction was carried out at ambient temperature (≈20 °C) and at elevated CO_2 pressure of 50 bar

Table 1. Synthesis of amino acids by SmI_2 reduction of nitrones or imines in the presence of CO_2.

Entry	Substrate	Method	Yield [%] [a] 2	3	4+5 (D,L: *meso*)
1	 1a	A	0.5	16	82 (70:12)
2		B	1	11	86 (69:17)
3		C	33	7	56 (39:17)
4		D	70	20	8 (6:2)
5	 1b	D	65	21	12 (7:5)
6	 1c	A	25	66	7 (5:2)
7		B	46	48	4 (only D,L)
8		D	43	42	13 (9:4)
9	 1d	D	22	67	7 (4:3)
10	 1e	D	57	24	17 (13:4)
11	 1f	D	43	50	5 (3:2)
12	 1g	D	54	20	24 (11:13)
13	 1h	D	73	18	*7 (4:3)*
14	 1i	D	7	91	-
15 [b]		D	13	85	-

[a] Yields were determined by HPLC and NMR techniques by using *N*-benzylglycine as an internal standard, see the Supporting Information for specifics. [b] The sodium salt of nitrone **1i** was used as a starting material (see text for explanation).

(Table 1, Entry 4; method D in Scheme 3). To a solution of nitrone **1a** pressurized with 50 bar CO_2 in a stainless steel autoclave (see the Supporting Information, Figure S1) the SmI_2 solution (7.5 equiv.) was added by an argon overpressure (100 bar). Simultaneous to an increase in the yield of the α-amino acid, the yields of 1,2-diamines **4a** and **5a** decreased to below 10% in total, and the formation of **3a** as the simple reduction product was limited to 20% (Table 1). Reaction of aldimine **1b** under the same conditions (Table 1, Entry 5, method D) led to a product distribution similar to that obtained for nitrone **1a**. Although the deoxygenation of nitrones to imines by SmI_2 has not yet been reported, this could be explained by assuming the reaction of nitrone **1a** as well as its corresponding aldimine **1b** passes through formation of the same intermediate.

The reactivity of aliphatic nitrone **1c**[14b] in the presence of SmI_2 (Table 1, Entries 6–8) seems to be higher than the reactivities of the aromatic nitrones (Table 1, Entries 1–5, 10–15). This could be correlated to a shorter lifetime of the $I_2SmR^{\cdot}$ radical intermediate compared to the lifetimes of the intermediates resulting from the SmI_2-mediated reduction of aromatic nitrones. Accordingly, even at –78 °C the C–C coupling reaction of nitrone **1c** with CO_2 yields (±)-*N*-benzylvaline in yields up to 45% (Table 1, Entry 7). In further accordance, the formation of amine **3c** in the reaction of **1c** or **1d** with SmI_2 becomes competitive, whereas C–C coupling side products **4c** and **5c** are only formed in very small amounts (Table 1, Entries 6–9). Again, this can be taken as a sign of enhanced reactivity, as reduction can be considered to proceed faster than C–C bond formation. This could also explain why in the case of nitrone **1c** compared to its corresponding aldimine **1d** the selectivity towards α-amino acid **2c** [(±)-*N*-benzylvaline] decreases, because for aldimine **1d** even fewer reduction steps are needed for the formation of amine **3c**. Noteworthy, the yields of (±)-*N*-benzylvaline (Table 1, Entry 7, method B; Entry 8, method D) are comparable, which indicates that the positive effect of the CO_2 pressure on the formation of the α-amino acid is compensated by the increased temperature.

To test the influence of various heteroatoms in the starting materials on the product distribution, nitrones **1e**–**i** (Table 1, Entries 10–15) were treated with CO_2 in the presence of SmI_2 by employing method D (vide supra). It was found that 4-fluoro- (i.e., **1e**), 4-methoxy- (i.e., **1f**), and 2-methoxy-substituted aromatic nitrones (i.e., **1g**) yielded the corresponding α-amino acids as the major products in reasonable yields (Table 1, Entries 10–12), and the amounts of the corresponding byproducts varied (Table 1). An excellent yield of α-amino acid **2h** (73%) was detected from the reaction involving (*Z*)-*N*-(furan-2-ylmethylene)-1-phenylmethanamine oxide (**1h**; Table 1, Entry 13). Dimerization products **4h** and **5h** were detected in only 7% yield, in agreement with the observation that the SmI_2-mediated dimerization of the corresponding imine is ineffective.[26d] This effect could originate from the coordination of SmI_2 to the oxygen atom of the furanyl group, enhancing the reducing power of the reagent.

In contrast, the yield of the carboxylated product dropped considerably starting from nitrone **1i** containing an unprotected phenol functionality (Table 1, Entry 14). This suggests that the OH group in the proximity of the C=N bond leads the reaction towards **3i**, probably by intramolecular proton transfer. Accordingly, a marginal increase in the yield of α-amino acid **2i** was found by using the sodium salt of nitrone **1i** (Table 1, Entry 15). In addition, trace amounts of 1,2-diamines **4i** and **5i** or other coupling products were not detected, pointing out that the reduction of the intermediate anion–radical is favored over a dimerization due to steric reasons and/or delocalization of the negative charge over the phenolate anion. To investigate further the influence of coordination to the samarium reagent, samples of (*Z*)-1-phenyl-*N*-(pyridin-2-ylmethylene)methanamine oxide[27] and (*Z*)-1-phenyl-*N*-(pyridin-4-ylmethylene)methanamine oxide[28] were treated under conditions of method D. Surprisingly, the reduction products *N*-benzyl-1-(pyridin-2-yl)methanamine and *N*-benzyl-1-(pyridin-4-yl)methan-

amine were detected together with considerable amounts of phenylmethanamine indicating partial decomposition. This may be related to the nature of the pyridyl substituent leading to a stronger delocalization of the electron density in the $I_2SmR^{\cdot}$ intermediate leading to a complete suppression of any C–C coupling reaction.

Conclusions

A novel, one-pot synthesis of α-amino acids is disclosed. The method is based on the coupling of nitrones or imines with CO_2 in the presence of SmI_2. Aliphatic, aromatic, and heteroaromatic *N*-benzyl α-amino acids were obtained in moderate to synthetically useful yields (up to 70% yield) under mild conditions (r.t., 50 bar pressure of CO_2) without the use of toxic metals. Mechanistic investigations provided evidence that the reaction of SmI_2 with nitrones firstly forms an intermediate that then undergoes C–C bond formation or reduction. Further optimization of the reaction conditions and development of preparative procedures also with respect to an asymmetric version to obtain enantioenriched α-amino acids are the objectives of future work.

Experimental Section

General Description of Method D: A sample of the nitrone (0.276 mmol) was dissolved in freshly distilled THF (15 mL) under an atmosphere of argon and transferred into an autoclave (total volume 170 mL). The solution was pressurized with CO_2 to 50 bar whilst stirring (about 40 mL of liquid CO_2 under pressure of 200 bar). Then, a solution of SmI_2 (0.1 M in THF, 20 mL, 7.5 equiv.) was injected into the autoclave under overpressure of argon at ambient temperature (final pressure in the autoclave was 100 bar). The reaction mixture was stirred overnight (16 h), and the pressure was then gradually decreased to atmospheric. The blue reaction mixture was exposed to air, which resulted in a color change to yellow. The mixture was diluted with 0.1 M CF_3COOH (30 mL), an HPLC reference was added to the clear yellow solution [*N*-benzylglycine hydrochloride (Aldrich), 0.0557 g, 0.276 mmol, 1 equiv. considering the starting nitrone], and the solution was evaporated. The residue was dried in vacuo and then dissolved in 0.1% trifluoroacetic acid (10 mL; water/acetonitrile, 1:9). The solution was then subjected to HPLC.

Supporting Information (see footnote on the first page of this article): Detailed experimental procedures, copies of the ^1H NMR and ^{13}C NMR spectra, ESI mass spectra and HPLC traces, notes concerning mechanistic investigations under influence of various additives and analytical data for *N*-benzyl-1-(1,2,3,4,5-pentamethylcyclopenta-2,4-dienyl)propan-1-amine, which was isolated when $(\eta\text{-}C_5Me_5)_2Sm$ was used as a reducing agent.

Acknowledgments

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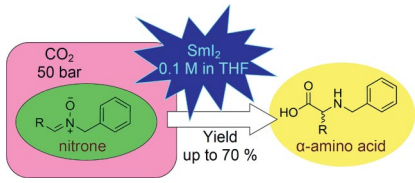
Carbon Dioxide Chemistry

A novel approach to the synthesis of α-amino acids is disclosed, involving *C*-carboxylation of nitrones by gaseous CO_2 under reductive coupling reaction conditions (SmI_2, 0.1 M in THF) at ambient temperature and 50 bar of CO_2 pressure.



Keywords: Amino acids / Nitrones / Carbon dioxide / Samarium / High-pressure chemistry

