Iron porphyrins catalyze the synthesis of non-protected amino acid esters from ammonia and diazoacetates†

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Iron complexes of porphyrins (and corroles to a lesser extent) are the first catalysts to utilize ammonia for the synthesis of N-free amino acid esters.

The synthesis of *N*-substituted glycine ethyl esters from amines and ethyl diazoacetate (EDA) may be catalyzed by quite a variety of metal complexes.[1] Nevertheless, the iron complexes of triarylcorroles[2] and tetraarylporphyrins were found to display unique features. Full and very fast conversion was obtained by simultaneous addition of equimolar amounts of the substrates to the catalysts and the selectivity toward activation of the NH bonds was absolute.[3] These results contrast with those obtained with most other catalysts, which often suffer from metal-poisoning by excess amine, and which produce significant amounts of byproducts from EDA coupling. Even the recently developed copper-based catalysts operate at 4–10 mol%, require long reaction times and gradual addition of the diazo compound (1–6 h),[4] while reactions with the iron-based catalysts (0.1 mol%) are complete within seconds (Fig. 1b).[3]

Based on the superior results with amines, we now report success in a much more challenging reaction: the use of ammonia as the nitrogen atom source in the synthesis of the two smallest amino acids. To the best of our knowledge, there is no reported catalyst for the synthesis of N-free amino acid derivatives from diazoacetates. This approach is also significantly different from the biological processes, where ammonia is only utilized for transforming a larger amino acid (or the corresponding α-keto ester) into glycine or alanine.[5] The chemical reactions (condensation and reductive amination) employed for that purpose are quite trivial for ammonia and the same holds for the common laboratory and industrial procedures (alkylation by haloacetic esters).[6] The process described here is fundamentally different: ammonia (as solvated gas or ammonium salt) is reacted with the diazoacetates **1a** or **1b** (Scheme 1) in what is at least formally a NH activation process. This adds to the very rare cases where NH activation of ammonia was observed in a condensed phase and/or utilized for synthetic purposes.[7]

The initial research was concerned with discovering whether $Rh_2(OAc)_4$ or the iron complexes shown in Scheme 1 could catalyze the reaction of ammonia with EDA. Despite the extensive utilization of $Rh_2(OAc)_4$ as catalyst for the *seemingly* related reactions of amines (or amides) with EDA,[1f,8] solutions of ammonia and EDA were not affected by this complex (entry 1, Table 1). The iron corrole **6** was not inert under the same reaction conditions (entry 2), which led to diethylmaleate (**5a**) from EDA coupling as the main product and 3% of the trisubstituted amine (triethyl nitrilotriacetate **4a**).[10a] Much better selectivity to desired products was displayed by the iron porphyrins **7a** and **7b**: only **4a** and the glycine ester **2a**[9] (*i.e.*, no **5a** or **3a**) were formed and each of these compounds could be obtained as sole product by controlling the NH_3 : EDA ratio. The triple activation product (**4a**)[10] was exclusively obtained when ammonium acetate was used as the nitrogen source (entry 6). This result is indicative of insufficient amounts of free ammonia under these conditions and the same conclusion probably holds for the reactions performed in diethyl

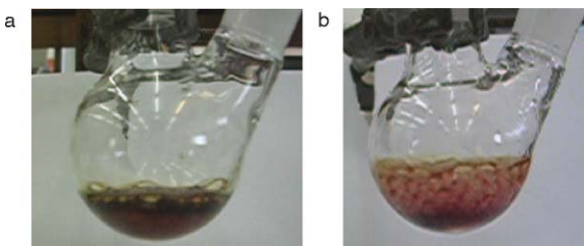

Fig. 1 Snapshots (full films available in ESI†) from the reactions of EDA with (a) ammonia (9 s after addition) and b) aniline (3 s after addition) in the presence of 1 mg **7b** (3 mL THF, 153 μL EDA, 133 μL aniline or 1 g NH_4OAc), demonstrating the very fast emission of $N_{2(g)}$.

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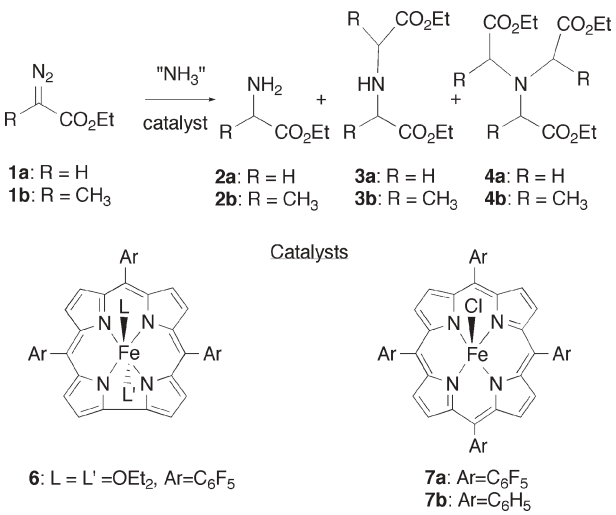
† Electronic supplementary information (ESI) available: NMR spectra and GC retention times of the products and the full films (in quicktime format) regarding the experiments described in Fig. 1. See DOI: 10.1039/b609265a



Scheme 1

Table 1 Products obtained from the reactions of ammonia with EDA (**1a**, Scheme 1)[a]

Entry	Catalyst	Solvent	"NH_3"	T/° C	Reaction time/h	Selectivity
1	$Rh_2(OAc)_4$	THF	Gas	25	24	No reaction
2	**6**	THF	Gas	25	5	**5a** (97%) **4a** (3%)
3	**7a**	Ether	Gas	25	5	**2a** (73%) **4a** (27%)
4	**7b**	Ether	Gas	25	3	**4a** (100%)
5	**7b**	THF	Gas	25	1	**2a** (100%)
6	**7b**	THF	NH_4OAc	25	10 min	**4a** (100%)

[a] The solutions (7 mL) containing all reagents and 1 mg catalyst were mixed until complete disappearance of EDA was assured by TLC. NMR spectroscopy, GC/MS, and GC were used for identification of the reaction products and their relative yields. Control reactions revealed that none of the products is obtained without catalyst. Specific amounts of reagents and mol% relative to catalyst were as follows. Entry 1: 118 μL EDA, 500 mol%. Entry 2: 50 μL EDA, 475 mol%. Entry 3: 100 μL EDA, 1000 mol%. Entry 4: 100 μL EDA, 651 mol%. Entry 5: 153 μL EDA 1000 mol% (0.2 M) and either saturated NH_3 solution (0.46 M) or under active NH_3 purging. Entry 6: 153 μL EDA, 1000 mol%, NH_4OAc (1 g, 12.9 mmol).

Table 2 Products obtained from the reactions of ammonia with the diazoester **1b** (Scheme 1)[a]

Entry	Catalyst	Solvent	"NH_3"	T/° C	Reaction time/min	Selectivity
1	**7b**	THF	Gas	65	3	**2b** (91%) **3b** (9%)
2	**7b**	THF	NH_4OAc	65	2	**2b** (68%) **3b** (32%)
3	**7b**	THF	**2b**	65	2	**3b** (100%)

[a] Reaction conditions as in Table 1, except of the temperature. Specific amounts of reagents and mol% relative to catalyst were as follows. **Entry 1**: 20 mg **1b**, 107 mol%, active NH_3 purging. **Entry 2**: 20 mg **1b**, 107 mol%, NH_4OAc (1 gr, 12.9 mmol). **Entry 3**: 20 mg **1b**, 107 mol%, **2b** (18.3 mg, 0.156 mmol).

ether (entries 3–4). Consistent with this assumption, only the product from single activation of ammonia (**2a**) was obtained when the reaction was performed in either saturated NH_3/THF solution (0.46 M by titration vs. 0.20 M EDA) or under NH_3 flow (entry 5). The glycine ester **2a** from these reactions was isolated as the trifuoroacetic acid salt in 81 and 87% yield,[11] respectively, corresponding to 810–870 catalytic turnovers.

The results presented so far clearly demonstrate that these catalysts can utilize ammonia as the nitrogen atom source of amino acid derivatives, that the reactivity of ammonia in this system is only slightly smaller than of the produced amines (**2a** and **3a**) and that the iron complex of the cheapest and most accessible porphyrin (**7b**) is an excellent catalyst for the transformation. A demonstration of these conclusions is provided in Fig. 1, which compares the **7b**-catalyzed reactions of EDA with ammonia (from ammonium acetate) and aniline. Bubbles due to the release of N_2 developed within seconds even in the reaction with ammonia, although with aniline this occurred more vigorously. No reaction took place under identical conditions within 24 h when $Rh_2(OAc)_4$ was used. Nitrogen evolution due to EDA decomposition started only after all ammonia was evaporated and **5a** and diethyl fumarate were the sole products in that case.

The iron porphyrin **7b** was further tested as a possible catalyst for the preparation of alanine esters as well (Scheme 1, R = CH_3). The methyl-substituted diazoester (ethyl diazopropionate, **1b**)[12] was less reactive than EDA and did not react with ammonia at room temperature, but reactions performed at 65 °C were nevertheless complete within minutes (Table 2, entries 1–2). The alanine ester **2b** and the doubly substituted ammonia derivative (diethyl 2, 2′-iminodipropionate **3b**) were the only products,[9,13] obtained in 10 : 1 and 2 : 1 ratios from dissolved ammonia and ammonium acetate, respectively. The fully substituted **4b** was not obtained in these reactions, even when **2b** was used as the starting material (entry 3, clean transformation into **3b**).

The iron complexes of porphyrins (and to a lesser extent corroles as well) are the first reported metal complexes to catalyze the formation of N-free glycine and alanine esters from ammonia and diazoesters. Mechanistic investigations of this catalytic process and advantageous extension of the unique features for synthetic purposes are currently carried out in our laboratories and will soon be reported.

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Notes and references

‡ Procedure for quantitative reactions of ammonia with EDA, leading to **2a** as exclusive product: THF (7 mL) was purged with ammonia gas for 15 minutes, leading a solution that is 0.46 M NH_3 (titration). Neat EDA (153 μL, 1.46 mmol, 0.2 M) was added to the solution, followed by solid catalyst (1 mg, 1.46 μmol, 0.1 mol% relative to EDA). This induced a color change from brown to red and nitrogen gas emission. The consumption of EDA was followed by TLC examinations. The solvent (and residual ammonia) was evaporated after 1 h, the oily residue was dissolved in diethyl ether (1 mL), and TFA (0.11 mL) was added. The TFA salt of glycine ethyl ester (mp = 138 °C)[9] separated from the solution, yielding 257 mg (81% yield relative to EDA) as white salt. Alternatively, the reaction was carried out under a slow stream of gaseous ammonia, yielding 275 mg (87% yield) after the same workup procedure.

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