Ammonia in Ugi Reactions – Four-Component versus Six-Component Couplings

Rigobert Pick, Michael Bauer, Uli Kazmaier,* Christina Hebach

Institut für Organische Chemie, Universität des Saarlandes, Postfach 151150, 66041 Saarbrücken, Germany
Fax +49(681)3022409; E-mail: u.kazmaier@mx.uni-saarland.de

Received 5 January 2005

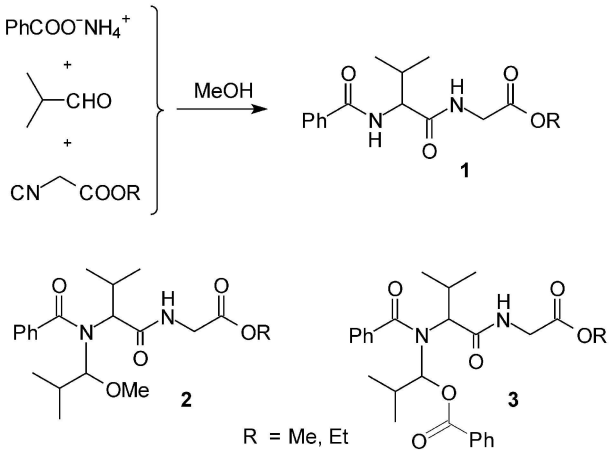
Abstract: If ammonia is used as amine component in Ugi reactions, the desired peptide sometimes is obtained only as the minor product or in traces. Side reactions such as six-component couplings are responsible for this observation. These side reactions can be suppressed or favoured depending on the reaction conditions used.

Key words: ammonia, peptide, Ugi reactions, six-component coupling

Non-proteinogenic amino acids are found in a wide range of peptides and cyclopeptides produced by marine organisms and microorganisms.[1] Many of these structures, especially the cyclic peptides, are highly interesting from a pharmaceutical point of view.[2] Unfortunately, the quantities isolated from natural resources are often very small, and therefore for therapeutic applications and/or for structure–activity investigations efficient synthetic concepts are necessary to provide enough material. Multicomponent reactions such as the Ugi reaction allow a straightforward approach towards peptide fragments containing unnatural amino acids.[3] In most cases good results are obtained with primary amines, giving rise to a wide range of N-alkylated peptides. In contrast, only a few examples are described where ammonia was used as a nitrogen source.[4] This is quite surprising, because the 'more natural' NH amide bonds are formed in this case. But in general the yields obtained with ammonia are significantly lower, compared to other amines.

Recently, we reported a straightforward approach towards the synthesis of cyclic peptides using the Ugi reaction in combination with a ring-closing metathesis (RCM).[5] As described by Grubbs and others, RCM is a very powerful tool for the synthesis of cyclic peptide structures.[6]

During these investigations we became interested in Ugi reactions with ammonia, and as a model reaction we investigated the reaction of isobutyraldehyde with the isonitrile obtained from glycine esters and the ammonium salt of various carboxylic acids in methanol.[7] No product was obtained with salts of strong acids such as trifluoroacetic acid, toluenesulfonic acid or pentafluorobenzoic acid, while benzoic acid gave the expected peptide **1**, albeit in moderate yield. Two major side products were formed depending on the reaction conditions (Scheme 1). When ammonium benzoate was treated with isobutyraldehyde (R = *i*-Pr) and the isonitrile in a 1:1:1 ratio, peptide **1** was obtained only in traces (5%) while the major product was **2**, which was isolated in 33% yield. Obviously a six-component coupling is more favoured under these conditions than the Ugi four-component reaction. To suppress this undesired side reaction we decided to use a less nucleophilic solvent. Indeed, in trifluoroethanol no such side product was observed, and the required Ugi product was obtained in 45% yield.



Scheme 1 Ugi reactions with ammonium salts

A similar effect was observed during replacing the isobutyraldehyde by the sterically more demanding pivaldehyde. In this case, the desired Ugi product could be obtained in excellent yield. Even in methanol as solvent the yield was higher than 50%.[7] Similar observations were described previously by Whittaker et al.[8]

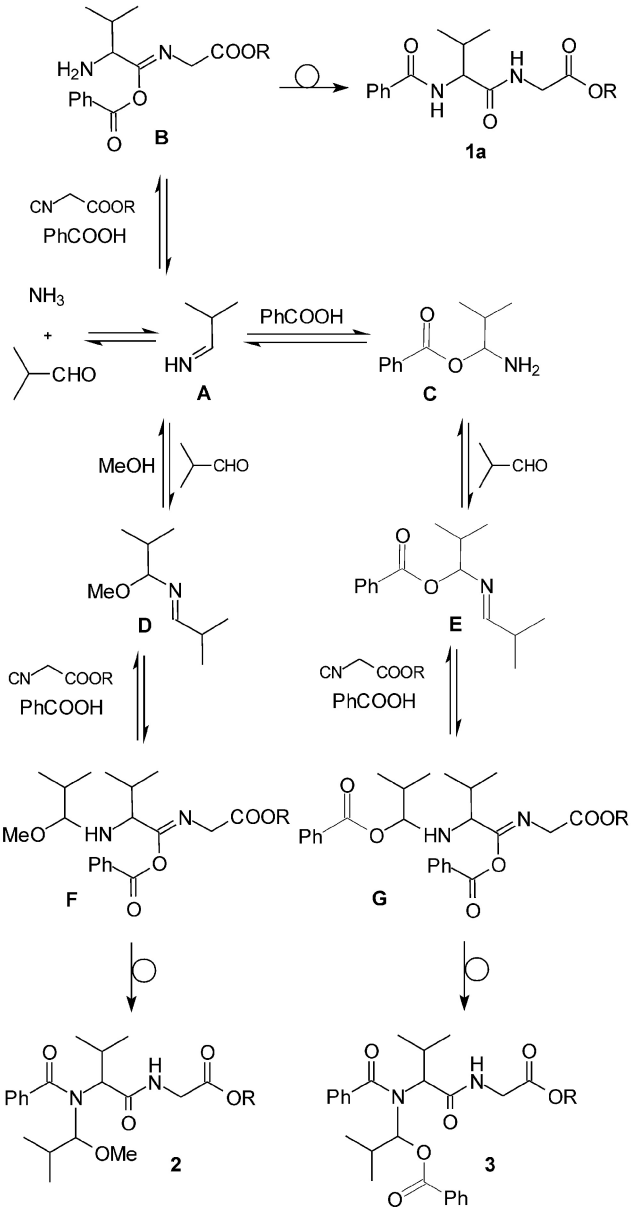
On the other hand, the six-component coupling provides fascinating structures of high molecular complexity. Therefore we were also interested to find reaction conditions giving mainly access to these products. The most obvious parameter for modifications is the relative ratio of the components used. A six-component product should be favoured if an excess of aldehyde is used, relatively to the isonitril. And indeed, continuously increasing the relative ratio of aldehyde raised the amount of the higher coupling product(s). Interestingly, besides **2** another six-component coupling product **3** was obtained, resulting from the incorporation of two molecules aldehyde and carboxylic acid as well. Under optimized conditions (ratio iso-

SYNLETT 2005, No. 5, pp 0757–0760
Advanced online publication: 09.03.2005
DOI: 10.1055/s-2005-863722; Art ID: G00305ST

nitrile–ammonium benzoate–aldehyde 1:2:4.4) **3** was the only six-component product besides the expected Ugi product **1**.[9]

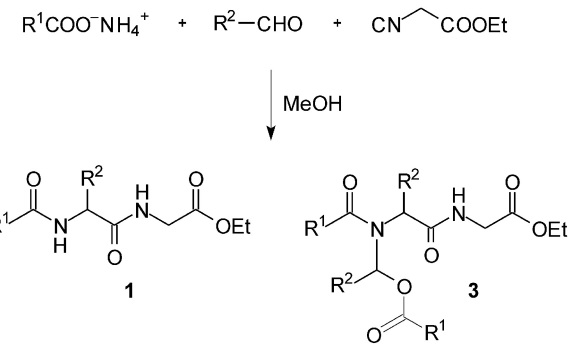
Obviously, the imine **A** formed in the first step does not react directly with the isonitrile as proposed for the Ugi reaction (**B**) but with another nucleophile, methanol or benzoate (Scheme 2). The resulting 'semiaminal'-type intermediates such as **C** now can react with a second equivalent aldehyde giving rise to intermediates **D** and **E**. Addition of the isonitrile and the carboxylate generates the highly reactive intermediates **F** and **G**, which subsequently undergo Mumm rearrangement to the amides **2** and **3**.

If the carboxylic acid (or the carboxylate, respectively) is directly involved in a product determining step (**A** → **C**) one might expect an relatively strong influence of the carboxylic acid used on the product distribution. Therefore, we varied the substituion pattern in the aromatic ring. Interestingly, with electron-donation groups (Table 1, entry 2) only the Ugi product **1** was obtained, while with electron-withdrawing groups (entry 3) the six-component product **3** was formed exclusively in rather good yield. To prove the generality of the reaction aliphatic acids, such as acetic acid, also were used. Here the six-component product was the major product (entry 5). Sterically less hindered aldehydes such as *n*-butyraldehyde are also tolerated (entry 4), but in this case a mixture of 4-fold and 6-fold coupling product was obtained albeit in moderate yield.



Scheme 2 Postulated mechanism for 6-fold couplings

Table 1 Four-Component vs. Six-Component Couplings



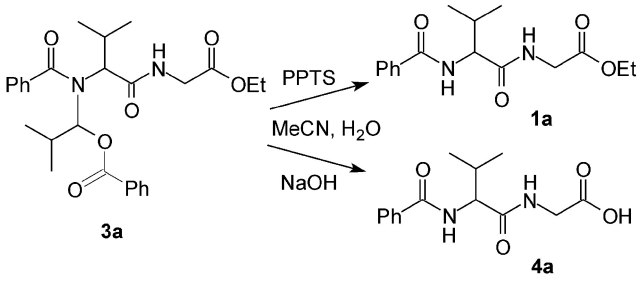
Entry	R^1	R^2	Products	Yield of **1** (%)	Yield of **3** (%)
1	Ph	*i*-Pr	**1a/3a**	41	28
2	4-MeO-Ph	*i*-Pr	**1b/3b**	21	0
3	4-NO_2-Ph	*i*-Pr	**1c/3c**	0	64
4	4-NO_2-Ph	*n*-Pr	**1d/3d**	6	17
5	Me	*i*-Pr	**1e/3e**	0	29
6	F_3C	*i*-Pr	**1f/3f**	42[a]	0

[a] MeCN was used as solvent.

Surprisingly in all reactions investigated so far mainly one diastereomer of **3** was formed, indicated by a single set of signals in the NMR spectra, in contrast to the spectra of **2**, which showed a second set of signals in the ^{13}C NMR.[10] The NMR spectra of **3** were very characteristic.[11] The newly formed aminoacylal centers showed sole doublets at δ = 5.8–6.1 ppm for R^2 = *i*-Pr and a double doublet at δ = 6.1 ppm for R^2 = *n*-Pr, while having a ^{13}C shift of δ = 87–89 ppm. In addition to that, there is a remarkable difference in the chemical shifts of the two *iso*-propylidene and *n*-propylidene signals, respectively (δ = 0.2–0.6 ppm in the ^1H spectra, δ = 3–7 ppm in the ^{13}C spectra). Compared to the Ugi four-component products **1** the α-^1H signals of the new generated amino acids are shifted upfield by 0.5 ppm.[12] The signals are cleanly separated and therefore there can be no doubt on the high stereoselectivity of the reaction.

All coupling products obtained were solids and we were able to obtain suitable crystals of **3a** to figure out the relative configuration of the stereogenic centers.[13] We found that the 'positive induced' products[14] (*S*/*S* or *R*/*R*, respectively) were formed preferentially.

With respect to the molecular structure of **3** one might expect that **3** should easily be convertible into **1** by simple hydrolysis of the aminoacylal subunit (Scheme 3). And indeed, stirring of **3a** under mild acidic conditions gave rise to the linear peptide **1a** in quantitative yield.[15] In a few cases such a cleavage was also observed during purification of some **3** via flash chromatography. Hydrolysis under basic conditions gave rise to the corresponding carboxylic acid **4a**,[16] which can be used directly for further peptide couplings.



Scheme 3 Cleavage of 6-fold coupling products

If the acidic hydrolysis was directly converted in one pot after the multi-component reactions, the required Ugi products were the only products formed, and the yields, e.g. of **1a** and **1e**, could be increased to 84% and 74%, respectively.[17]

In conclusion, we have shown that Ugi reactions with ammonia are less predictable than with other amines, because side reactions such as six-component couplings can occur. But under certain reaction conditions these products can be formed nearly exclusively, or the reactions can be directed towards the exclusive formation of the Ugi products. Further investigations concerning modifications at the aminoacylal substructure are currently under investigation.

Acknowledgment

This work was supported by the Fonds der Chemischen Industrie and the Deutsche Forschungsgemeinschaft. We also thank Prof. M. Veith and Dr. V. Huch from the Institute of Inorganic Chemistry for X-ray-structure analysis.

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(9) **4-Component vs. 6-Component Coupling.** Isobutyraldehyde (0.80 mL, 8.8 mmol) was added to a solution of ammonium benzoate (280 mg, 2.0 mmol) in methanol (6 mL) at 0 °C. After stirring for 30 min, ethyl isocyanoacetate (225 mg, 2.0 mmol) was added via syringe over a period of 5 min. The mixture was allowed to warm to 15 °C overnight. After stirring at r.t. for further 24 h, the solution was diluted with CH_2Cl_2 (30 mL) and washed with 1 N $KHSO_4$ and sat. $NaHCO_3$ solution. The organic layer was dried (Na_2SO_4) and the solvent was evaporated in vacuo. The crude product was purified by flash chromatography giving rise to **1a** and **3a**.

(10) Spectroscopic data of **2**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.72 (d, *J* = 6.7 Hz, 3 H), 0.75 (d, *J* = 6.7 Hz, 3 H), 1.01 (d, *J* = 6.6 Hz, 3 H), 1.03 (d, *J* = 6.6 Hz, 3 H), 2.08 (m, 1 H), 2.98 (m, 1 H), 3.31 (s, 3 H), 3.59 (d, *J* = 11.2 Hz, 1 H), 3.70 (s, 3 H), 3.94 (dd, *J* = 15.2, 2.5 Hz, 1 H), 4.01–4.16 (m, 2 H), 7.32–7.40 (m, 5 H), 8.95 (br s, 1 H). ^{13}C NMR (300 MHz, $CDCl_3$): δ = 18.2 (q), 18.6 (q), 19.2 (q), 19.8 (q), 27.2 (d), 32.1 (d), 40.6 (t), 51.8 (q), 57.5 (d), 67.4 (q), 97.4 (d), 126.4 (d), 128.4 (d), 129.3 (d), 136.5 (s), 169.9 (s), 172.6 (s), 173.3 (s). Selected signals of the minor diastereomer: ^{13}C NMR (300 MHz, $CDCl_3$): δ = 30.7 (d), 40.7 (t), 52.1 (q), 169.8 (s).

(11) Analytical and spectroscopic data of new 6-fold coupling products **3**.
Compound **3a**: mp 128 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.74 (d, *J* = 6.6 Hz, 3 H), 0.85 (d, *J* = 6.6 Hz, 3 H), 0.86 (d, *J* = 6.6 Hz, 3 H), 1.07 (d, *J* = 6.6 Hz, 3 H), 1.28 (t, *J* = 7.1 Hz, 3 H), 2.45 (m, 1 H), 3.06 (m, 1 H), 3.81 (d, *J* = 11.0 Hz, 1 H), 4.01 (dd, *J* = 17.9, 5.1 Hz, 1 H), 4.14 (dd, *J* = 17.9, 6.4 Hz, 1 H), 4.21 (q, *J* = 7.1 Hz, 2 H), 6.15 (d, *J* = 10.6 Hz, 1 H), 7.42–7.45 (m, 7 H), 7.61 (t, *J* = 7.6 Hz, 1 H), 8.07 (d, *J* = 7.6 Hz, 2 H), 9.04 (br s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.9 (s), 172.4 (s), 169.5 (s), 164.1 (s), 135.4 (s), 133.7 (d), 130.4 (d), 129.9 (2 d), 129.1 (s), 128.7 (2 d), 128.4 (2 d), 127.3 (2 d), 88.8 (d), 69.5 (d), 61.2 (t), 41.2 (t), 32.0 (d), 27.1 (d), 20.02 (q), 20.01 (q), 18.23 (q), 18.15 (q), 14.2 (q). Anal. Calcd for $C_{27}H_{34}N_2O_6$ (482.58): C, 67.20; H, 7.10; N, 5.81. Found: C, 67.18; H, 7.31; N, 5.74. HRMS (CI): *m*/*z* calcd for $C_{27}H_{35}N_2O_6$ [M + H]: 483.2495; found: 483.2490.
Compound **3c**: mp 176 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.76 (d, *J* = 6.6 Hz, 3 H), 0.78 (d, *J* = 6.7 Hz, 3 H), 0.91 (d, *J* = 6.7 Hz, 3 H), 1.04 (d, *J* = 6.6 Hz, 3 H), 1.28 (t, *J* = 7.1 Hz, 3 H), 2.54 (m, 1 H), 3.07 (m, 1 H), 3.74 (d, *J* = 11.3 Hz,

1 H), 3.91 (dd, *J* = 17.9, 4.5 Hz, 1 H), 4.21 (q, *J* = 7.1 Hz, 2 H), 4.25 (dd, *J* = 17.9, 7.0 Hz, 1 H), 5.89 (d, *J* = 10.5 Hz, 1 H), 7.68 (d, *J* = 8.8 Hz, 2 H), 8.23 (d, *J* = 8.8 Hz, 2 H), 8.33–8.35 (m, 4 H), 8.59 (dd, *J* = 7.0, 4.5 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.7 (s), 171.4 (s), 169.5 (s), 162.8 (s), 151.1 (s), 148.7 (s), 141.2 (s), 134.0 (s), 131.0 (2 d), 128.4 (2 d), 123.8 (2 d), 123.4 (2 d), 89.4 (d), 69.6 (d), 61.3 (t), 41.1 (t), 31.6 (d), 27.2 (d), 19.96 (q), 19.91 (q), 18.27 (q), 18.23 (q), 14.2 (q). Anal. Calcd for $C_{27}H_{32}N_4O_{10}$ (572.57): C, 56.64; H, 5.63; N, 9.79. Found: C, 56.41; H, 5.89; N, 9.65. HRMS (CI): *m*/*z* calcd for $C_{27}H_{31}N_4O_{10}$ [M – H]: 571.2040; found: 571.2086.

Compound **3d**: mp 123 °C (decomp.). Mixture of rotamers: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.805 (t, *J* = 7.4 Hz, 3 H), 0.811 (t, *J* = 7.3 Hz, 3 H), 1.21–1.33 (sh, 4 H), 1.28 (t, *J* = 7.2 Hz, 3 H), 1.98 (m, 1 H), 2.06 (m, 1 H), 2.13 (m, 1 H), 2.25 (m, 1 H), 3.87 (dd, *J* = 18.2, 4.8 Hz, 1 H), 4.18 (dd, *J* = 18.2, 6.8 Hz, 1 H), 4.19 (m, 1 H), 4.20 (q, *J* = 7.2 Hz, 2 H), 6.13 (dd, *J* = 7.3, 6.2 Hz, 1 H), 7.69 (d, *J* = 8.7 Hz, 2 H), 7.85 (br s, 1 H), 8.17 (d, *J* = 8.9 Hz, 2 H), 8.32 (d, *J* = 8.9 Hz, 2 H), 8.33 (d, *J* = 8.7 Hz, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.4 (s), 171.4 (s), 169.6 (s), 163.2 (s), 151.1 (s), 148.7 (s), 141.6 (s), 134.1 (s), 130.8 (2 d), 128.8 (2 d), 123.9 (2 d), 123.8 (2 d), 84.9 (d), 61.5 (d), 61.3 (t), 41.3 (t), 34.9 (t), 32.3 (t), 20.4 (t), 18.2 (t), 14.1 (q), 13.8 (q), 13.3 (q). Anal. Calcd for $C_{27}H_{32}N_4O_{10}$ (572.57): C, 56.64; H, 5.63; N, 9.79. Found: C, 56.64; H, 6.24; N, 9.63. HRMS (CI): *m*/*z* calcd for $C_{27}H_{32}N_4O_{10}$ [M]: 572.2118; found: 572.2120.

Compound **3e**: mp 89–90 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.69 (d, *J* = 6.6 Hz, 3 H), 0.83 (d, *J* = 6.6 Hz, 3 H), 0.88 (d, *J* = 6.6 Hz, 3 H), 0.95 (d, *J* = 6.6 Hz, 3 H), 1.22 (t, *J* = 7.1 Hz, 3 H), 2.06 (s, 3 H), 2.31 (m, 1 H), 2.35 (s, 3 H), 2.93 (m, 1 H), 3.35 (d, *J* = 11.1 Hz, 1 H), 3.93 (d, *J* = 5.8 Hz, 2 H), 4.14 (q, *J* = 7.1 Hz, 2 H), 5.27 (d, *J* = 10.2 Hz, 1 H), 8.62 (br s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.1 (d), 172.3 (d), 169.9 (d), 169.5 (d), 87.5 (d), 68.7 (d), 61.1 (t), 41.0 (t), 30.6 (d), 27.0 (d), 23.1 (q), 20.3 (q), 19.7 (q), 19.6 (q), 18.4 (q), 17.8 (q), 14.1 (q). Anal. Calcd for $C_{17}H_{30}N_2O_6$ (358.44): C, 56.97; H, 8.44; N, 7.82. Found: C, 56.85; H, 8.33; N, 7.85. HRMS (CI): *m*/*z* calcd for $C_{17}H_{31}N_2O_6$ [M + H]: 359.2182; found: 359.2183.

(12) ^{1}H NMR spectra of Ugi products **1**.

Compound **1a**: (400 MHz, DMSO-d_6): δ = 0.94 (d, *J* = 7.1 Hz, 3 H), 0.96 (d, *J* = 7.1 Hz, 3 H), 1.17 (t, *J* = 7.1 Hz, 3 H), 2.14 (m, 1 H), 3.79 (dd, *J* = 17.2, 5.8 Hz, 1 H), 3.90 (dd, *J* = 17.2, 6.2 Hz, 1 H), 4.07 (q, *J* = 7.1 Hz, 2 H), 4.34 (dd, *J* = 8.8, 7.1 Hz, 1 H), 7.46 (dd, *J* = 7.3, 7.0 Hz, 2 H), 7.53 (t, *J* = 7.3 Hz, 1 H), 7.89 (d, *J* = 7.0 Hz, 2 H), 8.30 (d, *J* = 8.8 Hz, 1 H) 8.48 (dd, *J* = 6.2, 5.8 Hz, 1 H).

Compound **1b**: (400 MHz, $CDCl_3$): δ = 0.99 (d, *J* = 6.8 Hz, 3 H), 1.00 (d, *J* = 6.7 Hz, 3 H), 1.23 (t, *J* = 7.1 Hz, 3 H), 2.19 (m, 1 H), 3.81 (s, 3 H), 3.88 (dd, *J* = 18.2, 5.1 Hz, 1 H), 4.11 (dd, *J* = 18.2, 5.7 Hz, 1 H), 4.16 (q, *J* = 7.1 Hz, 2 H), 4.56 (dd, *J* = 8.5, 7.2 Hz, 1 H), 6.87 (d, *J* = 8.8 Hz, 2 H), 6.94 (d, *J* = 8.5 Hz, 1 H), 7.16 (dd, *J* = 5.7, 5.1 Hz), 7.76 (d, *J* = 8.8 Hz, 2 H).

Compound **1d**: (400 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 7.3 Hz, 3 H), 1.24 (t, *J* = 7.1 Hz, 3 H), 1.39 (m, 2 H), 1.71 (m, 1 H), 1.87 (m, 1 H), 3.97 (dd, *J* = 18.2, 5.2 Hz, 1 H), 4.06 (dd, *J* = 18.2, 5.6 Hz, 1 H), 4.18 (q, *J* = 7.1 Hz, 2 H), 4.73 (ddd, *J* = 7.6, 6.6, 6.6 Hz, 1 H), 7.02 (dd, *J* = 5.6, 5.2 Hz), 7.49 (d, *J* = 7.6 Hz, 1 H), 7.95 (d, *J* = 8.8 Hz, 2 H), 8.22 (d, *J* = 8.8 Hz, 2 H).

Compound **1f**: (400 MHz, $CDCl_3$): δ = 0.95 (d, *J* = 7.0 Hz, 3 H), 0.97 (d, *J* = 6.9 Hz, 3 H), 1.26 (t, *J* = 7.2 Hz, 3 H), 2.12 (m, 1 H), 3.95 (dd, *J* = 18.2, 4.9 Hz, 1 H), 4.12 (dd, *J* = 18.2, 5.7 Hz, 1 H), 4.20 (q, *J* = 7.2 Hz, 2 H), 4.39 (dd, *J* = 8.5, 7.3 Hz, 1 H), 6.77 (dd, *J* = 5.7, 4.9 Hz, 1 H), 7.46 (d, *J* = 8.5 Hz, 1 H).

(13) Crystal data of **3a**: $C_{27}H_{34}N_2O_6$, M_r = 482.58, triclinic, space group P–1, *a* = 9.490 (2) Å, *b* = 15.015 (3) Å, *c* = 19.527 (4) Å, α = 83.69 (3)°, β = 78.94 (3)°, γ = 78.15 (3)°, *V* = 2665.4 (9) Å^3, *Z* = 4, ρ_{calcd} = 1.203 Mg/m^3, *F*(000) = 1032, λ = 0.71073 Å, *T* = 293 K, m(MoKa) = 0.085 mm^{-1}. Of the 16984 measured reflections 7822 were independent [*R*(int) = 0.0274]. The final refinement converged at *R*1 = 0.0404 for I > 2σ(I), *wR*2 = 0.1122 for all data. The data for structure **3a** were collected on a Stoe IPDS difractometer, the structure was solved by direct methods (SHELXS-97) and refined with all data by full matrix least squares on F^2.

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(15) A solution of pyridinium *p*-toluenesulfonate (PPTS, 503 mg, 2.00 mmol) in H_2O (2 mL) was added to a suspension of **3a** (483 mg, 1.00 mmol) in MeCN (2 mL) at r.t. After stirring overnight the suspension was diluted with H_2O (20 mL) and extracted with CH_2Cl_2 (20 mL). The organic layer was washed with sat. $NaHCO_3$ (20 mL) solution and dried (Na_2SO_4). Evaporation of the solvent leads to analytically pure **1a** (302 mg, 0.99 mmol, 99%) as a snow white powder.

(16) An aq NaOH solution (2 mL, 1 mol/L) was added to a suspension of **3a** (483 mg, 1.00 mmol) in MeCN (2 mL) at r.t. After stirring for 30 min the clear solution was diluted with H_2O (20 mL) and washed with Et_2O (20 mL). The aqueous layer was acidified by the addition of $KHSO_4$ solution (2.5 mL, 1 mol/L) and extracted with CH_2Cl_2 repeatedly. The organic layer was dried (Na_2SO_4) and the solvent was evaporated in vacuo. ^{1}H NMR analysis of the crude product indicates the formation of **4a** (0.67 mmol, 67%) and benzoic acid. Compound **4a**: ^{1}H NMR (500 MHz, $CDCl_3$ + 10% DMSO-d_6): δ = 0.72 (d, *J* = 6.8 Hz, 3 H), 0.73 (d, *J* = 6.8 Hz, 3 H), 1.95 (m, 1 H), 3.64 (dd, *J* = 17.9, 5.5 Hz, 1 H), 3.68 (dd, *J* = 17.9, 5.5 Hz, 1 H), 4.29 (dd, *J* = 8.8, 7.0 Hz, 1 H), 7.13 (dd, *J* = 7.5, 7.4 Hz, 2 H), 7.20 (tt, *J* = 7.4, 1.3 Hz, 1 H), 7.27 (d, *J* = 8.8 Hz, 1 H), 7.55 (sh, 3 H).

(17) Isobutyraldehyde (8.03 mL, 88 mmol) was added to a solution of ammonium benzoate (5.56 g, 40 mmol) in MeOH (40 mL) at 0 °C. After stirring for 30 min methyl isocyanoacetate (2.26 g, 20 mmol) was added. The mixture was allowed to warm to r.t. overnight. After evaporation of the solvent in vacuo the residue was suspended in a mixture of MeCN and H_2O (1:1), acidified to pH 2 by dropwise addition of concd HCl and stirred overnight. The MeCN was evaporated in vacuo and the resulting aqueous suspension was treated with H_2O and CH_2Cl_2 until two clear layers were formed. The organic layer was separated, washed with sat. $NaHCO_3$, dried (Na_2SO_4) and concentrated in vacuo. The solid residue was washed with Et_2O (50 mL) filtrated and dried, giving rise to analytically pure **1a** (5.2 g, 17 mmol) as a snow white powder.