Nucleophilic Carbenes and Pseudo-Cross-Conjugated Mesomeric Betaines of Indazole Starting from Analogues of the Alkaloid-Betaine Nigellicine

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The alkaloid Nigellicine possesses the indazolium-3-carboxylate ring system as electronically relevant partial structure which represents a member of the class of pseudo-cross-conjugated mesomeric betaines. Indazolium-3-carboxylate, prepared starting from indazole-3-carboxylic acid by an esterification–methylation–saponification sequence, can be converted into the isoconjugated phenyl- and 4-(nitrophenyl)-amidates and the thiocarboxylate as additional examples of pseudo-cross-conjugated systems. In accordance with results of ab initio calculations decarboxylation of indazolium-3-carboxylate with formation of the nucleophilic carbene indazol-3-ylidene begins at approximately 40 °C as evidenced by temperature-dependent NMR spectroscopy. The carbene can be trapped with protons as indazolium salts, and carbon dioxide which reconstitutes the pseudo-cross-conjugated mesomeric betaine. According to the calculations, the carbene adopts a singlet ground state.

Introduction

The class of alkaloids contains a surprisingly large number of heterocyclic mesomeric betaines which recently have been surveyed and classified in a first review article.[1] Mesomeric betaines are neutral aromatic compounds which can exclusively be represented by an even number of positive and negative charges within a common π-electron system.[2] This feature obviously contradicts one of the most fundamental rules for the formulation of canonical formulae, i.e. "stability is decreased by an increase in charge separation". In the history of heterocyclic mesomeric betaines this fact induced controversal discussions about the correct structures and their adequate representation.[1] Mesoions such as sydnones and münchnones are five-membered mesomeric betaines[3] and have been used in numerous elegant syntheses of alkaloids.[4] According to a classification first proposed by Ollis, Stanforth, and Ramsden in 1985, all mesomeric betaines can be divided into four major classes, conjugated (CMB), cross-conjugated (CCMB), and pseudo-cross-conjugated heterocyclic mesomeric betaines (PCCMB) as well as *N*-ylides which are related to CMBs.[2] The type of conjugation considerably influences the chemistry and properties of those systems so that its recognition enables the prediction of physical and chemical properties of a given betaine.[5] However, whereas CMB are well documented and widely applied in 1,3-dipolar cycloaddition reactions,[4] less is known about CCMB, and information about chemical, physical, and biological properties of pseudo-cross-conjugated mesomeric betaines (PCCMB) are very scarce.[1,5] It is apparent, however, that nature produces a relatively broad variety of representatives of this class of compounds.[1] Homarine (found in numerous marine organisms such as *Arca noae*, *Arbatia, Cnidaria*, *Porifera*, *Arthropoda*, *Echinodermata*),[6] 1-methylisoquinolinium 2-carboxylate (*Photuris versicolor*),[7] Shihunine (*Dendrobium sp.*),[8] Flavocarpine (*Pleiocarpa mutica*),[9] Aeroginosine A and B (*Pseudomonas aeruginosa*),[10] as well as Vincarpine and its dihydro derivative (*Vinca major elegantissima*)[11] are examples for PCCMB isolated from natural sources. Some scattered reports provide evidence for the assumption that pseudo-cross-conjugated mesomeric betaines can be converted into nucleophilic carbenes by decarboxylation.[12] Interestingly, the reverse process was also realized by trapping experiments of imidazol-2-ylidenes with carbon dioxide.[13]

We focussed our interest on analogues of the betaine-alkaloid Nigellicine (**1**)[14] which was isolated from the widely distributed herbaceous plant *Nigella sativa* L. (black cummin) (Scheme 1). The seeds of this plant have been used for thousands of years as a spice and for the treatment of various diseases.[15] The pseudo-cross-conjugated mesomeric betaine Nigellicine and the closely related zwitterion Nigellidine (**2**)[16] belong to the seldom class of indazole alkaloids.

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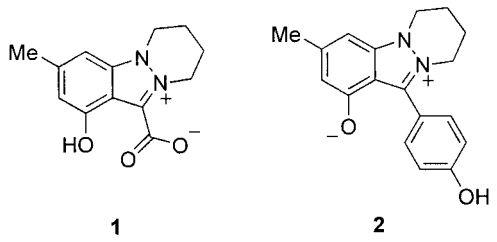


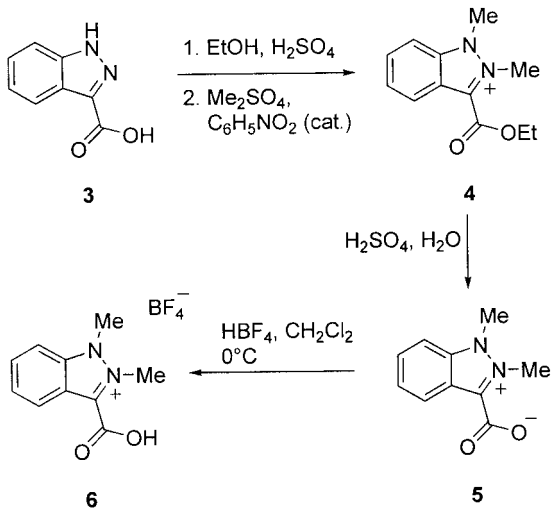
Scheme 1. Nigellicine **1** and Nigellidine **2** from *Nigella sativa* L.

In continuation of our interest in heterocyclic mesomeric betaines[17] including alkaloids,[18] nucleobases,[19] and betaines of pyrazole[20] we report here the syntheses of Nigellicine analogues possessing the indazole nucleus and their conversion into amidates and thiocarboxylates as additional new representatives of the class of pseudo-cross-conjugated mesomeric betaines. We examined the decarboxylation of indazolium-3-carboxylate to indazol-3-ylidene, and report trapping experiments of this new nucleophilic carbene, as well as results of spectroscopic examinations and ab initio calculations.

Results and Discussion

The synthesis of the target 1,2-dimethyl-1*H*-indazolium-3-carboxylate (**5**) starts with the esterification of indazole-3-carboxylic acid (**3**) which proved to be insensitive towards the conditions necessary for the subsequent alkylation. Two-fold methylation of the nitrogen atoms of **3** to the salt **4** was accomplished in one step by reaction with dimethyl sulfate in the presence of catalytic amounts of nitrobenzene (Scheme 2). Without this catalyst, no reaction took place, regardless of the methylating agent applied. Saponification of **4** was best achieved with aqueous sulfuric acid and subsequent neutralization, which resulted in the straightforward formation of the target pseudo-cross-conjugated mesomeric betaine, the indazolium-3-carboxylate **5**, in good yields.

1,2-Dimethyl-1*H*-indazolium-3-carboxylate (**5**) was isolated as a slightly yellow solid which decomposed at temperatures above 120 °C in the solid state with loss of carbon dioxide (vide infra). It is stable in water and acids and can be recovered quantitatively even after prolonged heating times in these solvents. As described below, in non-polar solvents decomposition of the betaine **5** occurs. Evidenced by (^{1}H,^{13}C)-HSQC- and (^{1}H,^{13}C)-HMBC-measurements, the methyl groups appear at δ = 4.21 ppm (N^2–Me) and 3.90 ppm (N^1–Me) in ^{1}H NMR spectroscopy. The nitrogen atoms show two resonance frequencies at δ = –180.2 ppm (N2) and –211.1 ppm (N1) which were assigned by means of (^{1}H,^{15}N)-HMBC spectra. Protonation of the betaine **5** to the indazolium salt **6** was accomplished by HBF_4 in dichloromethane at low temperatures in quantitative yield. On protonation, the resonance frequency of the carbonyl atom shifts from δ = 157.1 ppm to 160.4 ppm in ^{13}C NMR spectroscopy; the corresponding absorption band shifts

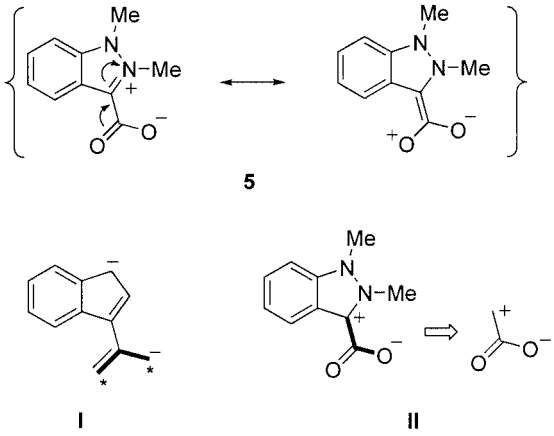


Scheme 2. Synthesis of indazolium-3-carboxylate **5** as model compound for the pseudo-cross-conjugated mesomeric betaine alkaloid Nigellicine.

from $\tilde{\nu}$ = 1657 cm^{-1} to $\tilde{\nu}$ = 1740 cm^{-1} in the IR spectra in the solid state.

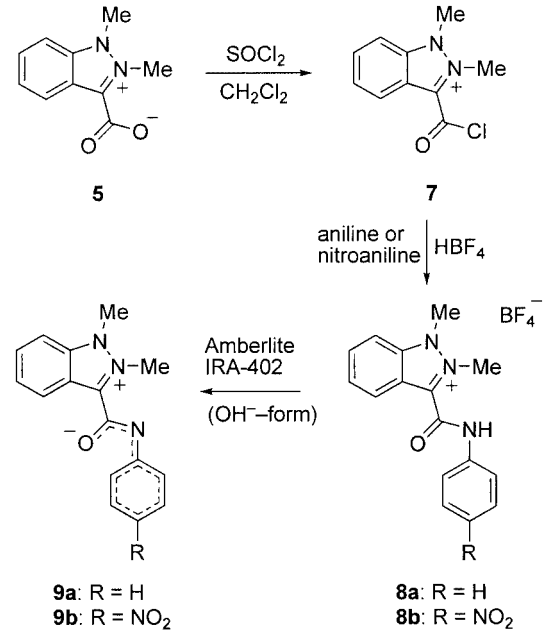
Several canonical formulae of the mesomeric betaine **5** can be drawn. Two of them possess electron-sextet structures without internal octet stabilisation (one of which is shown in Scheme 3) which are characteristic for pseudo-cross-conjugated mesomeric betaines.[1,2,5] Although these formulae have only a small contribution, if at all, to the overall-electronic structure of the molecule, the charges are *effectively*, but obviously not *exclusively* delocalised in separated parts of the common π-electron system. The second characteristic feature of PCCMB is the masked 2-oxyallyl 1,3-dipole **II** which can be dissected from the canonical formulae. As **5** is isoconjugate to the 3-isopropenyl-1*H*-indene dianion **I** it represents at the same time a member of class 16 of heterocyclic mesomeric betaines[2] which was unknown before Nigellicine was isolated.[1] As an additional characteristic feature of PCCMB[1,2,5] the negative partial structure of the pyrazolium-carboxylate is isoconjugate with an odd alternant hydrocarbon anion, the propenyl anion (cf. **I**). It is joined by a union bond through an unstarred, i.e. even-numbered atom, to the cationic structure element. The results of our ab initio calculations are discussed below.

Before we focussed our interest on decarboxylation reactions to nucleophilic carbenes, we studied the properties of the carboxylate group of **5** and intended to prepare additional representatives of the class of pseudo-cross-conjugated mesomeric betaines. Thus, the acid chloride **7** is available as a stable compound starting from the betaine **5** on reaction with thionyl chloride in dichloromethane in the presence of pyridine. When the hot solution is treated with aniline and 4-nitroaniline, respectively, followed by the addition of HBF_4, the amides **8a** and **8b** were isolated in good yields (Scheme 4). The corresponding pseudo-cross-conjugated mesomeric betaines, the indazolium-3-amidates **9a** and **9b**, were prepared by deprotonation with Amberlite



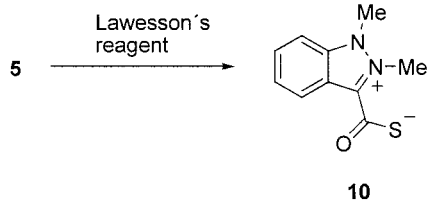
Scheme 3. Characteristic features of pseudo-cross-conjugation.

IRA-402 in its hydroxy form. These betaines were isolated as stable solids which are greenish in color. On deprotonation, the absorption band of the NH band at $\tilde{\nu}$ = 3338–3278 cm^{-1} disappears in parallel to the resonance frequency at δ = 12.00–11.40 ppm in the ^{1}H NMR spectra. The amidates **9a** and **9b** are formal isocyanate adducts of the nucleophilic carbene indazol-3-ylidene.



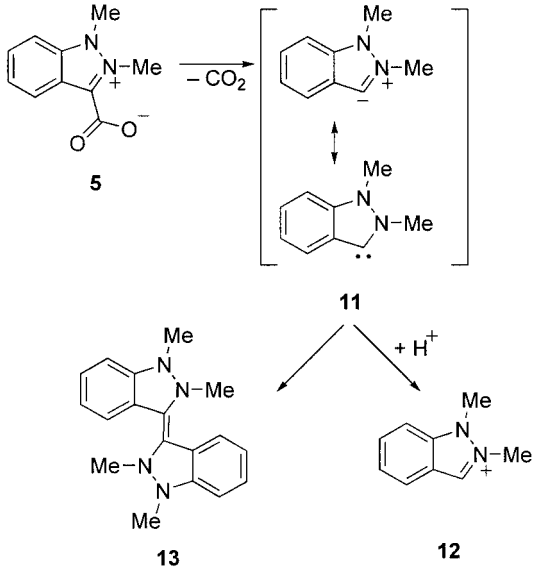
Scheme 4. Synthesis of new PCCMBs: amidates.

Lawesson's reagent, 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane 2,4-disulfide, converted the betaine **5** into the corresponding thiocarboxylate **10** (Scheme 5) which is an additional stable representative of the class of pseudo-cross-conjugated mesomeric betaines, albeit this reaction proceeds in low yields (Scheme 5). On thionation, the carboxylate carbon atom shifts from 161.7 ppm (D_2O) to 194.7 ppm ([D_6]DMSO) in the ^{13}C NMR spectra.



Scheme 5. Synthesis of new PCCMBs: thiocarboxylates.

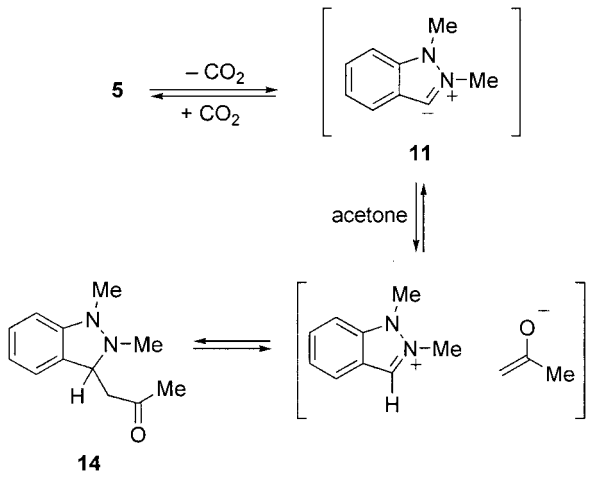
Decarboxylation of the indazolium-3-carboxylate **5**, which appears as a peak at *m*/*z* = 213 [**5**·Na]$^+$ in electrospray ionization mass spectrometry (ESI-MS), results in the formation of the nucleophilic carbene **11** which can be detected mass spectroscopically, whereas the extrusion of phenyl isocyanate or 4-(nitrophenyl) isocyanate from **9a**,**b**, respectively, was not observed under the applied reaction or measurement conditions. The carbene sodium adduct [**11**·Na], the mass of which was calculated to be 169.07417 [$C_9H_{10}N_2Na_1$], causes a prominent peak at *m*/*z* = 169.07376. In addition, characteristic peaks of the indazolium cation **12** and a dimerized species such as **13** are observable at *m*/*z* = 147.09117 and *m*/*z* = 293.17669, respectively [calculated masses: 147.09167 for $C_9H_{11}N_2$ and 293.17662 for $C_{18}H_{21}N_4$] (Scheme 6).



Scheme 6. Decarboxylation produces a nucleophilic carbene **11** and characteristic trapping products.

Heating of the betaine **5** at reflux temperature in acetone results in the formation of the (2,3-dihydroindazol-3-yl)propan-2-one **14** by deprotonation of the solvent by the nucleophilic carbene **11**, and subsequent addition of the resulting acetone enolate to the iminium moiety of the indazolium cation. This reaction is reversible at room temperature on exposure to carbon dioxide. Thus, indazolidine **14**, the structure of which was unambiguously elucidated by HSQC, HMBC, and H,H-COSY experiments, reacts reproducibly within a couple of days at room temperature in the presence of carbon dioxide to form the mesomeric betaine

5 and acetone in addition to approximately 10% of yet unidentified by-products (Scheme 7).



Scheme 7. Formal CH-insertion into the methyl group of acetone by the nucleophilic carbene.

We examined the decarboxylation of **5** by temperature dependent ^{1}H NMR spectroscopy, taking advantage of the equimolar amounts of water of crystallization present in the crystals of **5**. The temperature between 20 °C and 60 °C was adjusted in the NMR spectrometer before a freshly dissolved sample of 10 mg of **5** in 0.6 mL of anhydrous [D_6]-DMSO was inserted. After 10 minutes, the ^{1}H NMR spectra were measured. The resonance frequency of 4-H of **5** at δ = 8.41 ppm was taken as the reference signal to determine the concentration of the iminium salt by integration of the signal of 3-H of **12** which appears at δ = 9.23 ppm. The imininium salts formed by protonation of the *in-situ* generated nucleophilic carbene **11** by the water of crystallization. Our results are presented in Figure 1 and Table 1. At 20 °C and 30 °C, the concentration of the indazolium salt is less than 5%. The decarboxylation accelerates on warming to approximately 40 °C. Prolonged heating at 60 °C does not cause considerable changes, as the concentration of **12** increases from 57.6% to only 62.4% within 50 minutes. Under analoguous reaction conditions, the amidates **9a**,**b** as well as the thiocarboxylate **10** are stable up to 90 °C.

A mixture of indazolium salt **12**, the dimeric species **13**, and unchanged starting material is formed in 10 mg samples of **5** in 0.6 mL of [D_6]DMSO solution after ultrasound irradiation for 30 seconds. The dimeric species **13**, which is red in color, can be assigned to the resonance frequencies at δ = 2.75, 2.95, 6.80, 6.89, and 7.13 ppm in the ^{1}H NMR spectra, which correspond well to calculated values, and, as already mentioned, the high resolution ESI-MS measurements. We were not able, however, to separate this species from the crude reaction mixture as it decomposes rapidly on trying to chromatograph the crude mixture.

Density functional theory (DFT) calculations at the B3LYP/6-31G(d) level were carried out for compounds **5** and **11**.[21,22] The Gibbs free energy difference for the decarboxylation of **5** under standard conditions (25 °C, 1 atm) is found to be 3.4 kcal/mol. A threshold temperature of 38 °C

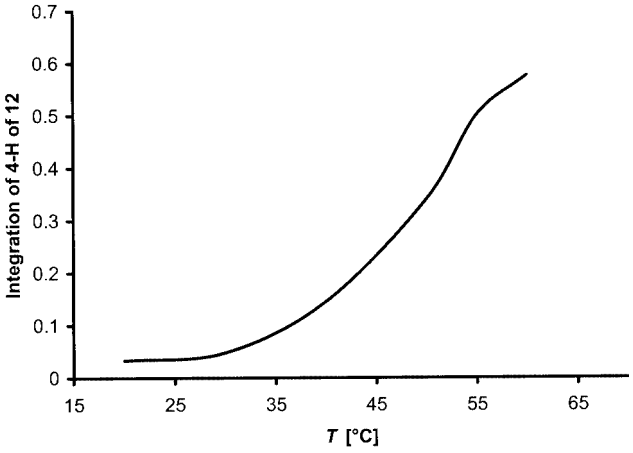


Figure 1. Decarboxylation of the mesomeric betaine **5** in [D_6]-DMSO with temperature: Integration of the signal of 4-H of the resulting indazolium salt **12**.

Table 1. Integration of the ^{1}H NMR signal of indazolium salt **12** in a [D_6]DMSO solution of PCCMB **5** dependent on the temperature. Spectra were taken after 10 minutes at the temperature indicated in the table.

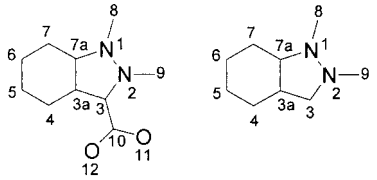
T [°C]	Integration of the signal at δ = 9.23 ppm [%]
20	3.3
30	4.8
40	14.5
50	34.0
55	50.0
60	57.6
60 (1 h)	62.4

was calculated, necessary for the decarboxylation of **5** to start under a pressure of 1 atm. This is in excellent agreement with the results of the temperature-dependent ^{1}H-NMR measurements. The singlet ground state of the resulting nucleophilic carbene was calculated to be 45.2 kcal/mol more stable than the triplet state. The N1–N2 bond length increases from 138.8 to 144.6 pm on decarboxylation, which reflects a conversion of a N–N bond with partial double bond character to a N–N bond. The N2–C3 bond length is a shortened C–N single bond in the betaine **5** (133.9 pm) as well as in the carbene (132.9 pm). The dihedral angle C8–N1–N2–C9 is 20.6° in the betaine **5**. On decarboxylation to the singlet carbene, this angle is widened to 43.4°, whereas the triplet carbene adopts an angle of 97.5° (Table 2).

The charge distribution is also obtained by the DFT calculations. Table 3 lists the partial Mulliken charges of groups and atoms for the betaine **5** and the carbenes **11**.

It is evident that the CO_2 fragment of **5** carries a significant negative charge (–0.52 a.u.). Within the CO_2 moiety the negative charge is evenly distributed over both O atoms and thus completely delocalized. The adjacent carbon atom (C3) compensates this charge only partially, corresponding to structure **II** in Scheme 3. Comparison with the carbenes **11** shows that the positive charge of C3 is increased in **5**, indeed. It is also observed that the negative charge of the N1–CH_3 group of **5** increases on decarboxylation while the

Table 2. Results of DFT B3LYP/6-31G(d) calculations of the PCCMB **5** and the nucleophilic carbene **11** in the singlet and triplet ground state. Bond lengths [pm], bond angles [°], and dihedral angles [°]. Numberings.



	Betaine **5**	Carbene **11** (singlet)	Carbene **11** (triplet)
N1–N2	138.8	144.6	146.1
N2–C3	133.9	132.9	138.9
C3–C3a	142.4	145.8	139.5
C3a–C7a	141.5	141.6	143.3
C3a–C4	141.0	140.2	141.1
C4–C5	138.2	139.0	139.4
C5–C6	141.6	140.9	140.1
C6–C7	138.6	139.2	140.9
C7–C7a	140.4	140.0	138.3
C7a–N1	137.3	138.3	141.8
N1–C8	145.1	145.5	146.2
N2–C9	146.2	145.3	146.8
C3–C10	157.8	–	–
C10–O11	124.7	–	–
C10–O12	124.0	–	–
O11–C10–O12	133.1	–	–
C8–N1–N2–C9	20.6	43.4	97.5

Table 3. Mulliken charges [a.u.] of groups and atoms from B3LYP/6-31G(d) calculations.

Group/atom	**5**	**11** (singlet)	**11** (triplet)
CO_2	–0.520	–	–
C3–CO_2	–0.230	–	–
C3	0.290	0.009	0.062
phenyl	0.389	0.187	0.218
C7a	0.384	0.340	0.302
N1–CH_3	–0.125	–0.201	–0.198
N2–CH_3	–0.034	0.009	–0.082

charge of the N2–CH_3 fragment remains essentially unchanged. The compensation of the negative partial charge is achieved not only by C3 but also by the phenyl ring which shows an increased positive charge in comparison to **11**. Within the six membered ring C7a plays a particular role as the main carrier of positive partial charge, not only in the betaine but in the carbenes as well. In fact, the change in the group charge of the phenyl system is due to small increases on all carbon atoms of the ring. Thus, apparently the positive partial charge of **5** is strongly delocalized.

Experimental Section

General Remarks: The ^{1}H and ^{13}C NMR spectra were recorded on Bruker ARX-400 and DPX-200 spectrometers and were taken in [D$_6$]DMSO and D$_2$O at 200 and 400 MHz. The chemical shifts are reported in ppm relative to internal tetramethylsilane (δ = 0.00 ppm) or HDO (δ = 4.65 ppm). Multiplicities are described by using the following abbreviations: s = singlet, d = doublet, t = triplet, m = multiplet, br = broad. Peak assignments were accomplished by results of HMBC-, HSQC-NMR and HH-COSY measurements. FT-IR spectra were obtained on a Bruker Vektor 22 in the range of 400 to 4000 cm^{-1} (2.5% pellets in KBr). The GC-MS spectra (EI) were recorded either on a GC Hewlett–Packard 5980, Serie II / MS Hewlett–Packard 5989 B, or on a Varian GC3900 with SAT2100T. The ESI mass spectra were measured with an Agilent LCMSD Series HP1100 with APIES. Samples were sprayed from methanol at 0 V fragmentor voltage unless otherwise noted. Melting points are not corrected.

Ethyl Indazole-3-carboxylate: Indazole-3-carboxylic acid (10 g, 123 mmol) in 350 mL of ethanol and 40 mL of concentrated sulfuric acid was heated at reflux temperature over a period of 5 h. After cooling to room temp., the solution was neutralised with 2 N NaOH, and extracted seven times with 100 mL of diethyl ether, respectively. The combined organic extracts were dried over Na_2SO_4 and the solvents evaporated in vacuo to give 21.7 g (114 mmol) of the ester as a yellowish solid, m.p. 130 °C. ^{1}H NMR ([D$_6$]DMSO): δ = 13.94 (s, 1 H), 8.10 (d, J = 8.08 Hz, 1 H), 7.69 (d, J = 8.34 Hz, 1 H), 7.47 (m, 1 H), 7.33 (m, 1 H), 4.41 (q, J = 7.13 Hz, 2 H), 1.39 (t, J = 7.13 Hz, 3 H) ppm. ^{13}C NMR ([D$_6$]-DMSO): δ = 163.6, 142.2, 136.5, 127.9, 124.1, 123.4, 122.3, 112.4, 61.6, 15.6 ppm. IR (KBr): $\tilde{\nu}$ = 3297, 1718, 1480, 1233 cm^{-1}. ESI-MS: m/z = 191.1 (6%) [M + H]$^+$, 213.1 (100%) [M + Na]$^+$. $C_{10}H_{10}N_2O_2$ (190.1): calcd. C 63.15, N 14.73, H 5.30; found: C 62.95, N 14.65, H 5.33.

Ethyl 1,2-Dimethyl-1*H*-indazolium-3-carboxylate Hydrogen Sulfate (4): Ethyl indazol-3-carboxylate (3.8 g, 20 mmol) was suspended in a mixture of 50 mL of xylene and 0.21 mL (2 mmol) of nitrobenzene and heated for 30 min to 140 °C. The hot solution was then treated with dimethyl sulfate (2.28 mL; 24 mmol) and heated for an additional hour at that temperature whereupon a brown oil developed. After cooling the solution was concentrated in vacuo and treated with 100 mL of acetone. After several days at 8 °C, 3.62 g (12.4 mmol, 62%) of **4** precipitated which was filtered off and washed with cold acetone, m.p. 203 °C. ^{1}H NMR ([D$_6$]DMSO): δ = 8.28 (d, J = 8.46 Hz, 1 H), 8.20 (d, J = 8.97 Hz, 1 H), 7.97 (m, 1 H), 7.70 (m, 1 H), 4.63 (s, 3 H), 4.58 (q, J = 7.13 Hz, 2 H), 4.44 (s, 3 H), 1.48 (t, J = 7.13, 3 H) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 158.8, 140.5, 134.6, 130.9, 128.7, 124.1, 120.5, 113.2, 64.7, 38.5, 35.6, 15.2 ppm. IR (KBr): $\tilde{\nu}$ = 3092, 2875, 1736. ESI-MS: m/z = 219.1 (100%) [M – HSO$_4$]$^+$. $C_{12}H_{16}N_2O_6S$ (316.1): calcd. C 45.56, N 8.86, H 5.10, S 10.14; found: C 45.04, N 8.85, H 5.04, S 10.09.

1,2-Dimethyl-1*H*-indazolium-3-carboxylate (5): A sample of the ester **4** (10 g, 32 mmol) was dissolved in 20 mL of 50% sulfuric acid and heated at reflux temperature for six hours. The solution was then neutralized with dilute NaOH and the solvents evaporated to dryness. The resulting precipitate was extracted with ethanol, the solvent evaporated, and the residue subjected to column chromatography (silica gel, methanol). The betaine **5** was isolated as yellowish solid, dec. >145 °C, yield 4.6 g (24 mmol; 76%). ^{1}H NMR (D$_2$O): δ = 7.64 (d, J = 8.31 Hz, 1 H, C4-*H*), 7.43 (m, 1 H, C6-*H*), 7.27 (d, J = 8.80 Hz, 1 H, C7-*H*), 7.11 (m, 1 H, C5-*H*), 4.21 (s, 3 H, N2-CH_3), 3.90 (s, 3 H, N1-CH_3) ppm. ^{1}H NMR ([D$_6$] DMSO): δ = 8.41 (d, J = 8.29 Hz, 1 H, C4-*H*), 7.92 (d, J = 7.78 Hz, 1 H, C6-*H*), 7.78 (d, J = 8.45 Hz, 1 H, C7-*H*), 7.44 (dd, J = 8.32 Hz, 1 H, C5-*H*), 4.65 (s, 3 H, N2-CH_3), 4.22 (s, 3 H, N1-CH_3) ppm. ^{13}C NMR (D$_2$O): δ = 161.7 (C10), 139.2 (C7a), 137.4 (C3), 133.1 (C6), 125.7 (C5), 123.1 (C4), 119.0 (C3a), 110.4 (C7), 35.8 (C9), 33.0 (C8) ppm. ^{15}N NMR (D$_2$O): –211.1 (N1), –180.2 (N2) ppm. IR (KBr): $\tilde{\nu}$ = 1657, 1320, 760 cm^{-1}. ESI-MS (25 V):

m/*z* = 147.1 (16%) [M – CO_2 + H]$^+$, 213.0 (26%) [M + Na]$^+$. $C_{10}H_{10}N_2O_2{\cdot}H_2O$ (190.1): calcd. C 57.68, N 13.45, H 5.81; found: C 56.81, N 13.26, H 5.75.

1,2-Dimethyl-1*H*-indazolium-3-carboxylic Acid Tetrafluoroborate (6): A sample of **5** (100 mg, 0.53 mmol) was suspended in 5 mL of dichloromethane and treated whilst stirring with 50% HBF_4 (0.2 mL; 2.8 mmol) at 0 °C. Stirring was continued for additional 30 min. The precipitate was then filtered off and dried in vacuo to give 147 mg (0.53 mmol) of the salt **6** (100%), m.p. 168–172 °C. ^{1}H NMR ([D$_6$]DMSO): δ = 8.31 (d, *J* = 8.59 Hz, 1 H), 8.14 (d, *J* = 8.84 Hz, 1 H), 7.95 (m, 1 H), 7.65 (m, 1 H), 4.62 (s, 3 H), 4.38 (s, 3 H) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 160.4, 140.6, 134.5, 132.7, 128.3, 124.5, 120.9, 113.0, 38.2, 35.3 ppm. IR (KBr): $\tilde{\nu}$ = 3575, 3574, 1740, 1625, 1432, 1286 cm^{-1}. ESI-MS: *m*/*z* = 191 (55%) [M – BF_4]$^+$, 381 (100%) [M + (M – H)]$^+$. HR-ESI-MS calcd. for $C_{10}H_{11}N_2O_2$: 191.0821; found: 191.0827.

3-Chlorocarbonyl-1,2-dimethyl-1*H*-indazolium Chloride (7): Under an inert atmosphere, a sample of 570 mg (3 mmol) of **5** was suspended in freshly distilled $SOCl_2$ (20 mL, 275 mmol) and stirred for 30 min at room temp. Then the $SOCl_2$ was distilled off in vacuo. The resulting residue was dissolved in 5 mL of diethyl ether, the solvent evaporated and the dry residue treated with 10 mL of petroleum ether. The suspension was stirred at room temp. for 30 min and then evaporated to dryness to give 628 mg (3 mmol, 100%) of the chloride **7** as a colorless solid, m.p. 159 °C (dec.). ^{1}H NMR ([D$_6$]DMSO): δ = 8.31 (d, *J* = 8.46 Hz, 1 H), 8.17 (d, *J* = 8.97 Hz, 1 H), 7.94 (m, 1 H), 7.64 (m, 1 H), 4.64 (s, 3 H), 4.41 (s, 3 H) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 160.1, 140.5, 134.3, 133.0, 128.1, 124.5, 120.8, 112.9, 38.1, 35.3 ppm. IR (KBr): $\tilde{\nu}$ = 3169, 1707, 1623, 1231 cm^{-1}. $C_{10}H_{10}Cl_2N_2O$ (244.0): calcd. C 49.00; H 4.11, N 11.43; found: C 48.90, H 5.46, N 11.24.

1,2-Dimethyl-3-(*N*-phenylcarbamoyl)-1*H*-indazolium Tetrafluoroborate (8a) and 1,2-Dimethyl-3-[*N*-(4-nitrophenyl)carbamoyl]-1*H*-indazolium Tetrafluoroborate (8b): Samples of 570 mg (3 mmol) of **5** in 15 mL of dichloromethane were suspended under nitrogen atmospheres with 1.3 mL of freshly distilled $SOCl_2$ (9 mmol) and pyridine (0.16 mL; 2 mmol). The mixtures were then heated at reflux temperature for 15 min. Freshly distilled aniline (0.82 mL; 9 mmol) or 4-nitroaniline (414 mg; 9 mmol) were then added to the hot solutions which were heated for additional 2 h at that temperature. Evaporation to dryness in vacuo gave residues which were treated with water and evaporated again. The resulting brown oils were dissolved in 15 mL of methanol and treated with 2 mL of 50% HBF_4 at 0 °C. After stirring for 30 min the amides were isolated as colorless solids. 540 mg of **8a** (1.53 mmol; 51%) and 884 mg (2.2 mmol; 74%) of **8b** were obtained, respectively.

1,2-Dimethyl-3-(*N*-phenylcarbamoyl)-1*H*-indazolium Tetrafluoroborate (8a): M.p. 159 °C, ^{1}H NMR ([D$_6$]DMSO): δ = 11.40 (s, 1 H), 8.15 (m, 2 H), 7.98 (m, 1 H), 7.81 (d, *J* = 7.71 Hz, 2 H), 7.65 (m, 1 H), 7.47 (m, 2 H), 7.26 (m, 1 H), 4.50 (s, 3 H), 4.42 (s, 3 H) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 156.0, 140.5, 138.8, 136.6, 134.8, 130.4, 127.3, 126.8, 123.9, 122.2, 118.7, 112.7, 38.2, 35.2 ppm. IR (KBr): $\tilde{\nu}$ = 3278, 1661, 1552 cm^{-1}. ESI-MS: *m*/*z* = 266 (100%) [M – BF_4]$^+$. HR-ESI-MS: calcd. for $C_{16}H_{16}N_3O$ 266.1293; found: 266.1284. $C_{16}H_{16}N_3OBF_4$ (353.1): calcd. C 54.42, N 11.90, H 4.57, B 3.06; found: C 53.91, N 11.73, H 4.46, B 2.97.

1,2-Dimethyl-3-[*N*-(4-nitrophenyl)carbamoyl]-1*H*-indazolium Tetrafluoroborate (8b): M.p. 189 °C, ^{1}H NMR ([D$_6$]DMSO): δ = 12.00 (s, 1 H), 8.37 (d, *J* = 9.22 Hz, 2 H), 8.19 (m, 2 H), 8.08 (d, *J* = 9.22 Hz, 2 H), 8.00 (m, 1 H), 7.66 (m, 1 H), 4.52 (s, 3 H), 4.44 (s, 3 H) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 156.7, 145.0 (2 C), 140.5, 135.9, 134.8, 127.4, 126.3, 123.9, 122.2, 118.8, 112.8, 38.4, 35.3 ppm. IR (KBr): $\tilde{\nu}$ = 3338, 1691, 1513, 1348 cm^{-1}. ESI-MS: *m*/*z* = 311.08 (100%) [M – BF_4^-]$^+$. HR-ESI-MS calcd. for $C_{16}H_{15}N_4O_3$ 311.1144; found: 311.1154.

1,2-Dimethyl-*N*-phenyl-1*H*-indazolium-3-amidate (9a): Amberlite IRA-402 (100 mL) was filled into a small column and was subsequently treated with 400 mL of water and 50 mL of 4% NaOH. After 1 h the resin was first washed with water until the elute was neutral, and then with ethanol/water (1:1). A sample of **8a** (200 mg, 0.57 mmol) was dissolved in the same solvent mixture and was given on the resin and eluted. Evaporation of the elute gave **9a** as a greenish solid in almost quantitative yield (99%, 148 mg, 0.56 mmol), dec. 128 °C. ^{1}H NMR ([D$_6$]DMSO): δ = 8.33 (d, *J* = 8.41 Hz, 1 H, C4-*H*), 8.06 (d, *J* = 8.80 Hz, 1 H, C7-*H*), 7.88 (m, 1 H, C6-*H*), 7.76 (d, *J* = 7.43 Hz, 2 H, C14-*H* and C18-*H*), 7.53 (m, 1 H, C5-*H*), 7.33 (m, 2 H, C15-*H* and C17-*H*), 7.07 (m, 1 H, C16-*H*), 4.61 (s, 3 H, C9-H_3), 4.34 (s, 3 H, C8-H_3) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 156.9 (C10), 140.4 (C7a), 139.8 (C3), 134.1 (C6), 129.8 (C15/C17), 126.4 (C5), 125.1 (C4), 124.6 (C16), 123.4 (C14/C18), 119.4 (C3a), 112.3 (C7), 37.8 (C9), 34.7 (C8) ppm, C13 was not detectable. ^{15}N NMR ([D$_6$]DMSO): δ = –210.4 (N1), –176.8 (N2) ppm, N12 was not detectable. IR (KBr): $\tilde{\nu}$ = 3487, 3410, 1682, 1555, 758 cm^{-1}. ESI-MS (0V): *m*/*z* = 266.1 (100%) [M + H$^+$]. HR-ESI-MS: calcd. for $C_{16}H_{15}N_3O$ 266.1293; found: 266.1288. $C_{16}H_{15}N_3O{\cdot}3H_2O$ (265.03): calcd. C 60.23, H 6.63, N 13.17; found: C 59.87, H 5.52, N 12.50.

1,2-Dimethyl-*N*-(4-nitrophenyl)-1*H*-indazolium-3-amidate (9b): Amberlite IRA-402 (100 mL) was filled into a small column and was subsequently treated with 400 mL of water and 50 mL of 4% NaOH. After 1 h the resin was first washed with water until the elute was neutral, and then with ethanol/water (1:1). A sample of **8b** (200 mg, 0.50 mmol) was dissolved in the same solvent mixture and was given on the resin and eluted. Evaporation of the elute gave **9b** as a yellow solid in almost quantitative yield (99%, 199 mg, 0.50 mmol), m.p. 110–111 °C. ^{1}H NMR ([D$_6$]DMSO): δ = 8.64 (d, *J* = 8.33 Hz, 1 H), 8.11 (d, *J* = 8.87, 2 H), 7.99 (m, 1 H), 7.85 (m, 1 H), 7.79 (d, *J* = 8.57 Hz, 2 H), 7.51 (m, 1 H), 4.74 (s, 3 H), 4.29 (s, 3 H) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 132.2, 125.1, 124.5, 124.2, 123.2, 110.4, 35.6, 32.8 ppm, C_q not detectable due to insufficient solubility. IR (KBr): $\tilde{\nu}$ = 1599.2, 1583.3, 1541.9, 1511.8, 1493.3, 1103.8 cm^{-1}. ESI-MS (0V): *m*/*z* = 311.08 (100%) [M + H]$^+$. HR-ESI-MS: calcd. for $C_{16}H_{15}N_4O_3$ 311.1144; found: 311.1154.

1,2-Dimethyl-1*H*-indazolium-3-thiocarboxylate (10): Compound **5** (950 mg, 5 mmol) was suspended in toluene (100 mL) and treated with Lawesson′s reagent (2 g, 5 mmol). Then, the mixture was heated at 90 °C and stirred at that temperature over a period of 2 h. The solvent was then distilled off in vacuo and purified by column chromatography (silica gel; petroleum ether ether/ethyl acetate, 2:1). The thiocarboxylate was isolated in low yield (77 mg; 0.37 mmol, 7%), dec. 130 °C. ^{1}H NMR ([D$_6$]DMSO): δ = 8.34 (d, *J* = 8.34 Hz, 1 H), 7.90 (d, *J* = 8.72 Hz, 1 H), 7.78 (m, 1 H), 7.44 (m, 1 H), 4.35 (s, 3 H), 4.20 (s, 3 H) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 194.7, 145.0, 140.4, 133.6, 125.7, 125.6, 118.4, 111.8, 36.5, 34.1 ppm. IR (KBr): $\tilde{\nu}$ = 1530, 1250, 1018 cm^{-1}. ESI-MS: *m*/*z* = 229 (75%) [M + Na]$^+$, 435 (100%) [2 M + Na]$^+$. $C_{10}H_{10}N_2OS{\cdot}H_2O$ (206.05): calcd. C 53.60, H 5.39, N 10.50; found: C 53.42, H 4.79, N 10.55.

1-(2,3-Dihydro-1,2-dimethyl-1*H*-indazol-3-yl)propan-2-one (14): Compound **5** (570 mg; 3 mmol) was suspended in 40 mL of acetone and the mixture was refluxed for 1 h during which time the betaine was dissolved. After cooling, the solvent was distilled off and the resulting residue was chromatographed (silica gel; ethyl acetate) to

give **14** as a yellow oil in 80% yield (489 mg, 2.4 mmol). ^{1}H NMR (D_2O): δ = 7.11 (t, J = 7.63 Hz, 1 H, C5-*H*), 6.91 (d, J = 7.43 Hz, 1 H, C4-*H*), 6.84 (t, J = 7.43 Hz, 1 H, C6-*H*), 6.67 (d, J = 8.02 Hz, 1 H, C7-*H*), 4.19 (t, J = 5.97 Hz, 1 H, C3-*H*), 2.88 (d, J = 6.06 Hz, 2 H, C10-H_2), 2.69 (s, 3 H, C8-H_3), 2.47 (s, 3 H, C9-H_3), 2.07 (s, 3 H, C12-H_3) ppm. ^{13}C NMR (D_2O): δ = 212.5 (C11), 149.3 (C7a), 130.7 (C3a), 129.2 (C5), 123.4 (C6)*, 123.2 (C7)*, 112.2 (C4), 65.7 (C3), 49.4 (C10), 42.5 (C9), 41.5 (C8), 30.3 (C12) ppm (* peak assignments exchangeable). ^{15}N NMR (40.5 MHz, D_2O): δ = –259.8 (N2), –255.9 (N1) ppm. ESI-MS: *m/z* = 147 (43%) $[M - CH_2COCH_3]^+$, 203 (100%) $[M - H]^+$.

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[1] A. Schmidt, *Adv. Heterocycl. Chem.* **2003**, *85*, 67.
[2] W. D. Ollis, S. P. Stanforth, C. A. Ramsden, *Tetrahedron* **1985**, *41*, 2239.
[3] G. W. Gribble, in: The Chemistry of Heterocyclic Compounds, vol. 59: Synthetic Applications of 1,3-dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products (Eds.: A. Padwa, W. H. Pearson), Wiley, New York, **2002**, p. 681; C. G. Newton, C. A. Ramsden, *Tetrahedron* **1982**, *38*, 2965; C. A. Ramsden, in: Comprehensive Organic Chemistry (Eds.: D. H. R. Barton, W. D. Ollis), Pergamon Press, Oxford, **1979**, vol. 4, p. 1171; W. D. Ollis, C. A. Ramsden, *Adv. Heterocycl. Chem.* **1976**, *19*, 1.
[4] A. Padwa, L. S. Beal, T. M. Heidelbaugh, B. Liu, S. M. Sheehan, *J. Org. Chem.* **2000**, *65*, 2684; A. Padwa, T. M. Heidelbaugh, J. T. Kuethe, *J. Org. Chem.* **2000**, *65*, 2368; A. Padwa, S. M. Sheehan, C. S. Straub, *J. Org. Chem.* **1999**, *64*, 8648; C. S. Straub, A. Padwa, *Org. Lett.* **1999**, *1*, 83; S. M. Sheehan, A. Padwa, *J. Org. Chem.* **1997**, *62*, 438.
[5] A. Schmidt, *Curr. Org. Chem.* **2004**, *8*, 653.
[6] P. Polychronopoulos, P. Magiatis, A.-L. Skaltsounis, F. Tillequin, E. Vardala-Theodorou, A. Tsarbopoulos, *Nat. Prod. Lett.* **2001**, *15*, 411; H. Nishitani, S. Kikushi, K. Okumura, H. Taguchi, *Arch. Biochem. Biophys.* **1995**, *322*, 327; A. R. Davies, N. M. Targett, O. J. McConell, C. M. Young, *Bioorg. Marine Chem.* **1989**, *3*, 85; J. C. Netherton, S. Gurin, *J. Biol. Chem.* **1982**, *257*, 11971.
[7] A. Gonzáles, F. Schroeder, J. Meinwald, T. Eisner, *J. Nat. Prod.* **1999**, *62*, 378.
[8] Y. Inubishi, Y. Tsuda, T. Konita, S. Matsumoto, *Chem. Pharm. Bull.* **1964**, *12*, 749; M. Elander, L. Gawell, K. Lander, *Acta Chem. Scand.* **1971**, *25*, 721; E. Breuer, S. Zbaida, *Tetrahedron* **1975**, *31*, 499.
[9] G. W. Gribble, D. A. Johnson, *Tetrahedron Lett.* **1987**, *28*, 5259; G. Büchi, R. E. Manning, F. A. Hochstein, *J. Am. Chem. Soc.* **1962**, *84*, 3393.
[10] F. G. Holliman, *J. Chem. Soc. (C)* **1999**, 2514; R. B. Herbert, F. G. Holliman, *South African Ind. Chem.* **1961**, *15*, 233.
[11] E. Ali, V. S. Giri, S. C. Pakrashi, *Tetrahedron Lett.* **1976**, *17*, 4887.
[12] A. R. Katritzky, H. M. Faid-Allah, *Synthesis* **1983**, 149; A. R. Katritzky, R. Awartani, R. C. Patel, *J. Org. Chem.* **1982**, *47*, 498; H. Quast, E. Schmitt, *Justus Liebigs Ann. Chem.* **1970**, *732*, 43; H. Quast, E. Schmitt, *Justus Liebigs Ann. Chem.* **1970**, *732*, 64.
[13] N. Kuhn, M. Steimann, G. Weyers, *Z. Naturforsch. Teil B* **1999**, *54*, 427; K. Ishiguro, K. Hirabayashi, T. Nojima, Y. Sawaki, *Chem. Lett.* **2002**, 796; J. D. Holbrey, W. M. Reichert, I. Tkatchenko, E. Bouajila, O. Walter, I. Tommasi, R. D. Rogers, *Chem. Commun.* **2003**, 28.
[14] Atta-ur-Rahman, S. Malik, H. Cun-heng, J. Clardy, *Tetrahedron Lett.* **1985**, *26*, 2759.
[15] cf. Matthaeus, *The Holy Bible, New Testament*, Math. 23,23.
[16] Atta-ur-Rahman, S. Malik, S. S. Hasan, M. I. Choudhary, C.-Z. Ni, J. Clardy, *Tetrahedron Lett.* **1995**, *36*, 1993.
[17] A. Schmidt, A. Gholipour Shilabin, M. Nieger, *Org. Biomol. Chem.* **2003**, *1*, 4342; A. Schmidt, T. Mordhorst, T. Habeck, *Org. Lett.* **2002**, *4*, 1375.
[18] S. Hemmen. A. Schmidt, A. Gholipour Shilabin, J. C. Namyslo, M. Nieger, *Eur. J. Org. Chem.* **2005**, accepted for publication; A. Schmidt, T. Mordhorst, M. Nieger, *Nat. Prod. Res.* **2005**, in press; A. Schmidt, A. Gholipour Shilabin, *Heterocycles* **2004**, *63*, 2851; Schmidt, T. Mordhorst, *ARKIVOC* **2003**, *XIV*, 233.
[19] A. Schmidt, N. Kobakhidze, *Heterocycles* **2002**, *57*, 2231; A. Schmidt, N. Kobakhidze, M. K. Kindermann, *J. Chem. Soc., Perkin Trans. 1* **2002,** *7*, 982; A. Schmidt, M. K. Kindermann, P. Vainiotalo, M. Nieger, *J. Org. Chem.* **1999**, *64*, 9499.
[20] A. Schmidt, T. Habeck, *Lett. Org. Chem.* **2005**, *2*, 37; A. Schmidt, T. Habeck, M. K. Kindermann, M. Nieger, *J. Org. Chem.* **2003**, *68*, 5977.
[21] All calculations were performed at DFT B3LYP/6-31Gd level of theory as implemented in the Gaussian03 program, Gaussian 03, Revision B.01.[22] Geometries were fully optimized and stationary points were characterized as true minima by frequency calculations. The results of the frequency calculations were also used for the computation of the Gibbs free energy at different temperatures for a standard pressure of 1 atm.
[22] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery, Jr., T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez, J. A. Pople, Gaussian, Inc., Wallingford CT, **2004**.

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