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Consecutive Three-Component Synthesis of Ynones by Decarbonylative Sonogashira Coupling

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Dedicated to Armin de Meijere on the occasion of his 70th birthday

Alkynones are important intermediates in organic syntheses,[1] and due to their bifunctional electrophilicity they have found broad application as three-carbon building blocks in heterocyclic synthesis. Therefore, efficient, mild, and catalytic methodologies for their preparation are highly desirable. Besides catalytic acylations of terminal[2] and silylated[3] alkynes the carbonylative alkynylation of aryl iodides following the Sonogashira protocol represents an elegant three-component synthesis of alkynones, which were as well elaborated into one-pot syntheses of pharmaceutically relevant heterocycles such as pyrazoles[4] and pyrimidines.[5]

Carbonylations of aryl halides usually require carbon monoxide or molybdenum hexacarbonyl as suitable CO sources. However, the effective concentration of CO in the reaction medium plays a crucial role for the outcome of carbonylative alkynylation. An alternative mode, which also dispenses the use of aryl halides, could be a decarbonylation of an α-dicarbonyl compound. Rhodium-mediated decarbonylations of aldehydes (Tsuji–Wilkinson reaction) are well precedented,[6] however, the process becomes catalytic only at temperatures over 200 °C and most applications in total syntheses have remained stoichiometric.[7] Decarbonylations of acid chlorides are less common.[8] In 2002, iridium-catalyzed decarbonylative homologizations of aroyl chlorides in boiling xylene were reported.[9] Palladium complexes are not commonly used for decarbonylations. Besides decarbonylative carbostannylations,[10] Gooßen has reported decarbonylative Heck reactions with reaction times of 16 h at 160 °C in NMP as a solvent.[11] Just recently, the same group has introduced Pd/Cu-catalyzed decarboxylative cross-couplings of α-oxocarboxylates with aromatic bromides[12] and chlorides[13] at high temperatures and long reaction times. Interestingly, although oxalyl chloride has been applied in the presence of aluminium chloride as a phosgene surrogate for Friedel–Crafts acylations[14] or as a source of carbon monoxide in stoichiometric copper-mediated synthesis of cyclopentadienones from organolithium and organozirconium compounds[15] there is no report of its use in any catalytic application. In continuation of our program to develop transition metal catalyzed multicomponent syntheses of heterocycles[16] and functional organic materials,[17] we report our first findings on consecutive three-component synthesis of alkynones by decarbonylative Sonogashira coupling starting from electron-rich heterocycles and oxalyl chloride as a source of the CO building block via intermediary glyoxylyl chlorides. Conceptually, this methodology complements the carbonylative alkynylation of halides of heterocycles with diminished electron density.[5]

It has been known for quite some time that many indole derivatives directly and without Lewis acid activation react with oxalyl chloride in a Friedel–Crafts acylation to furnish indole-3-glyoxylyl chlorides **1** in high yields.[18] Due to the generality and smoothness of this glyoxylation the idea was now to use the notoriously unstable and reactive indole-3-glyoxylyl chlorides **1** as synthetic equivalents of acid chlorides in transition metal catalyzed cross-coupling reactions. Therefore, for establishing a decarbonylative alkynylation we first tested indole-3-glyoxylyl chlorides **1** without substitution (**1a**) and with a benzyl substituent (**1b**) on the indole nitrogen atom in a model reaction with 1-hexyne (**2a**) under modified Sonogashira conditions[19] (Scheme 1, Table 1). Immediately, it was apparent that only the benzyl derivative **1b** can be transformed into the corresponding alkynone **3b** (entries 3–9).

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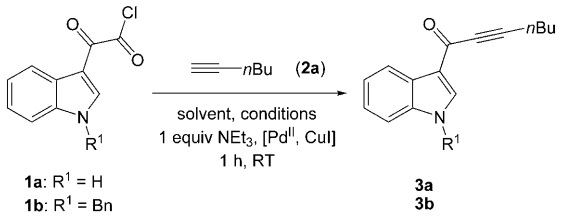


Scheme 1. Optimization of the decarbonylative Sonogashira coupling of indole-3-glyoxylyl chlorides **1** and 1-hexyne (**2a**).

Table 1. Optimization of the decarbonylative Sonogashira coupling of indole-3-glyoxylyl chlorides **1** and 1-hexyne (**2a**).[a]

Entry	Compound **1**	Solvent	Catalyst system	Ynone **3** (isolated yield/%)
1	**1a**: R^1 = H	THF	2 mol % $[PdCl_2(PPh_3)_2]$ 4 mol % CuI	**3a** (–, no reaction)
2[b]	**1b**: R^1 = Bn	THF	2 mol % $[PdCl_2(PPh_3)_2]$ 4 mol % CuI	**3b** (–, no reaction)
3	**1b**	THF	1 mol % $[PdCl_2(PPh_3)_2]$ 2 mol % CuI	**3b** (n.i.)[c]
4	**1b**	THF	2 mol % $[PdCl_2(PPh_3)_2]$ 4 mol % CuI	**3b** (n.i.)[c]
5	**1b**	DME	2 mol % $[PdCl_2(PPh_3)_2]$ 2 mol % CuI	**3b** (61)
6[d,e]	**1b**	DME	5 mol % $[PdCl_2(PPh_3)_2]$ 2 mol % CuI	**3b** (n.i.)[c]
7	**1b**	CH_2Cl_2	2 mol % $[PdCl_2(PPh_3)_2]$ 4 mol % CuI	**3b** (n.i.)[c]
8	**1b**	THF	1 mol % $[PdCl_2(PPh_3)_2$ 1 mol % CuI	**3b** (80)
9[f]	**1b**	THF	1 mol % $[PdCl_2(PPh_3)_2]$ 1 mol % CuI	**3b** (70)
10[f,g]	**1b**	THF	1 mol % $[PdCl_2(PPh_3)_2]$ 1 mol % CuI	**3b** (–, no reaction)
11	**1b**	THF	0.1 mol % $[PdCl_2(PPh_3)_2]$ 1 mol % CuI	**3b** (–, no reaction)
12	**1b**	THF	1 mol % $[PdCl_2(dppf)]$ 1 mol % CuI	**3b** (–, no reaction)

[a] The reactions were performed in 5 mL of solvent (c(**1**) = 0.2 M) using 1.5 equiv of **2a** for 1 h and at room temperature unless otherwise stated. [b] Reaction performed at 0 °C. [c] TLC indicates coupling without decarbonylation and the formation of compound **3b** which was not isolated. [d] The reaction time was 48 h. [e] The reaction was performed under 1 atm of CO. [f] 1.0 equiv of **2a** was applied. [g] 2 mol % of PPh_3 were added to the reaction mixture.

Although the desired alkynone **3b** could be immediately detected by TLC monitoring of the reaction it was only isolable if the formation of the non-decarbonylated byproduct could be suppressed. Therefore, the influence of the ratios of the substrates, the catalysts and the solvent were studied qualitatively. Besides spectroscopic and combustion analytical characterization the structure of compound **3b** was unambiguously corroborated by an X-ray structure analysis (Figure 1).[20]

The most crucial point for the successful transformation and high conversion is the well-balanced equimolar ratio of $[PdCl_2(PPh_3)_2]$ and CuI (entries 5, 8, and 9). Dimethoxyethane (DME) and THF are both good solvents. Performing the reaction under a CO atmosphere to block the decarbonylation resulted in the formation of the ynone (entry 6), whereas the addition of 2 mol % of PPh_3 completely stopped the conversion (entry 10). Switching the palladium catalyst precursor to $[PdCl_2(dppf)]$ did not result in ynone formation (entry 12). Therefore, the most favorable conditions for the development of a sequence with the decarbonylative Sonogashira coupling suggest the use of an equimolar ratio of glyoxylyl chloride **1b** and alkyne **2a** giving a clean reaction and 70 % isolated yield of alkynone **3b** (entry 9). Hence, the mechanistic rationale of this new decarbonylative Sonogashira coupling can be rationalized as follows (Scheme 2).

After the oxidative addition of indole-3-glyoxylyl chloride (**1**), adduct **4** undergoes a migratory de-insertion and elimination of carbon monoxide furnishing the acyl–Pd species **5**. The driving force of this reaction is the apparent relative instability of the dicarbonyl species **4** compared with the acyl species **5**. Then, transmetalation of the in situ generated copper acetylide to **5** gives rise to the formation of the acyl-alkynyl-Pd complex **6**, which undergoes reductive elimination to give the alkynone **3** and the catalytically active Pd^0 species to start a new catalytic cycle.

Encouraged by these initial successful experiments we decided to combine the formation of relatively labile glyoxylyl chloride **1** and the subsequent decarbonylative alkynylation to a consecutive three-component reaction in a one-pot transformation. Indeed, *N*-substituted indoles (X = CH) and 7-aza-indoles (X = N) **7** or pyrroles **8** were glyoxylated with oxalyl chloride in THF or DME on a 5 mmol scale and the transient glyoxylyl chlorides **1** were reacted with equimolar amounts of the alkynes **2** for 1 h at room temperature

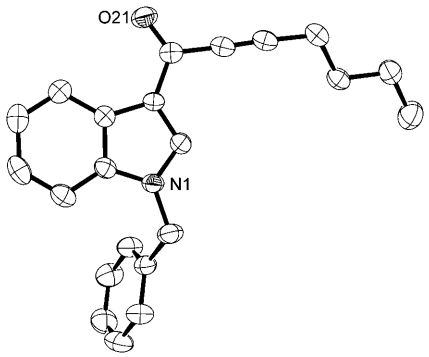
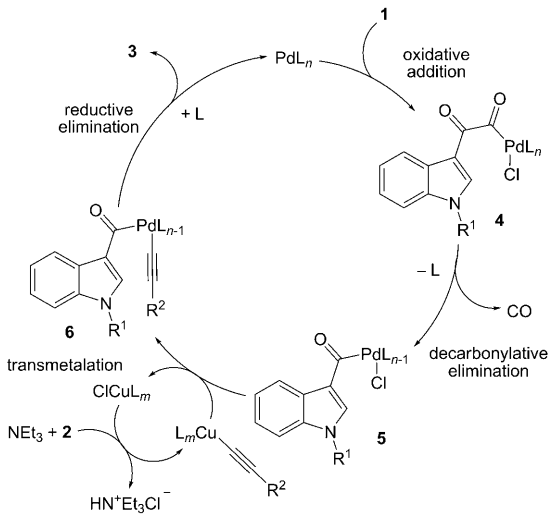
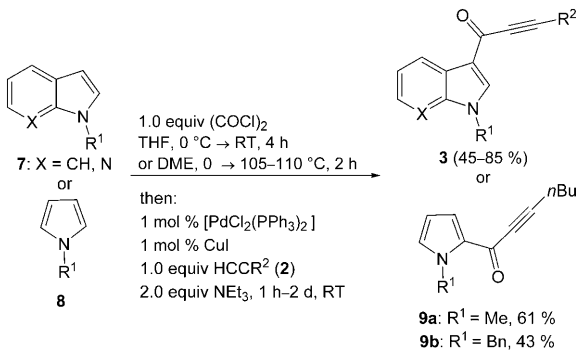


Figure 1. Molecular structure of alkynone **3b** (hydrogen atoms were omitted for clarity).



Scheme 2. Mechanistic rationale of the decarbonylative Sonogashira coupling of indole-3-glyoxylyl chlorides **1** and terminal alkynes **2**.

for 1–48 h in the presence of two equivalents of triethylamine and catalytic amounts of $[PdCl_2(PPh_3)_2]$ and CuI to give the corresponding alkynones **3** and **9** in moderate to good yields (Scheme 3, Table 2). The presence of two stoichiometrically necessary equivalents of triethylamine assures that the hydrogen chloride formed upon glyoxylation is bound and that the decarbonylative Sonogashira coupling occurs by scavenging the hydrochloric acid from the catalytic cycles. Expectedly, as a consequence of the regioselective glyoxylation of pyrroles in the 2-position the ynones **9** were obtained by the same protocol, simultaneously illustrating the methodological potential for the application to electron-rich π systems.



Scheme 3. Three-component glyoxylation-decarbonylative alkynylation synthesis of alkynones **3** and **9**.

With this versatile alkynone synthesis in hand, we tested the application of the products in pyrimidine synthesis. As previously shown, 4-(indol-3-yl)- and 4-(7-aza-indol-3-yl)-2-amino pyrimidines, which are structurally related to the marine natural products class of meridianins, have displayed a considerable potential as kinase inhibitors.[5] Therefore,

Table 2. Three-component glyoxylation-decarbonylative alkynylation synthesis of alkynones **3** and **9**.[a]

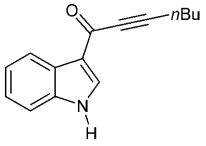
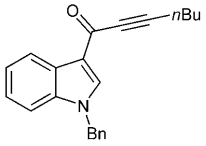
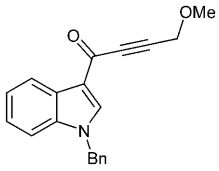
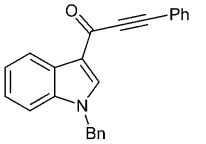
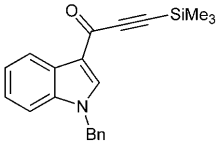
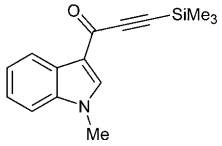
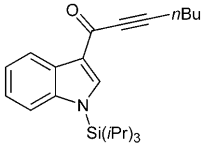
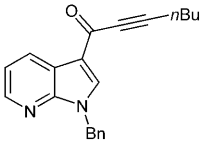
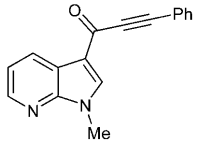
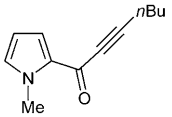
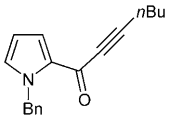
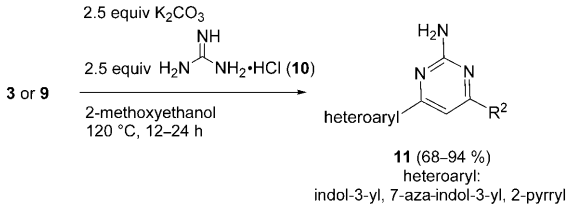
Entry	*N*-Substituted indole or 7-aza-indole **7**	Alkyne **2**	Ynone **3** (isolated yield/%)	
1	**7a**: X = CH, R^1 = Si(*i*Pr)$_3$	**2a**: R^2 = *n*Bu		**3a** (43)[b]
2	**7b**: X = CH, R^1 = Bn	**2a**		**3b** (74)
3	**7b**	**2b**: R^2 = CH$_2$OMe		**3c** (66)
4	**7b**	**2c**: R^2 = Ph		**3d** (85)
5	**7b**	**2d**: R^2 = SiMe$_3$		**3e** (76)
6	**7c**: X = CH, R^1 = Me	**2d**		**3f** (64)
7	**7a**	**2a**		**3g** (45)
8[c]	**7d**: X = N, R^1 = Bn	**2a**		**3h** (63)
9[c]	**7e**: X = N, R^1 = Me	**2c**		**3i** (61)
10[d]	**8a**: R^1 = Me	**2a**		**9a** (61)

Table 2. (Continued)

Entry	*N*-Substituted indole or 7-aza-indole **7**	Alkyne **2**	Ynone **3** (isolated yield/%)
11[e]	**8b**: R^1 = Bn	**2a**	 **9b** (43)

[a] The sequences were performed in 25 mL of solvent (c(**7**) = 0.2 M) and in the acylation step the reaction vessel was allowed to come from 0 °C (external water/ice cooling) to room temperature for 4 h unless otherwise stated. For the subsequent decarbonylative alkynylation step, 1 mol % of $[PdCl_2(PPh_3)_2]$, 1 mol % of CuI, 1.0 equiv of alkyne **2** and 2.0 equiv of triethylamine were added. [b] After addition of 1.1 equiv of TBAF (1 M in THF) to the reaction mixture and stirring at room temperature the product **3a** was obtained. [c] The reaction was performed in DME as a solvent and the acylation step was carried out at 105-110 °C for 2 h. [d] The decarbonylative alkynylation step was carried out for 2 d. [e] The decarbonylative alkynylation step was carried out overnight.

upon reacting indolyl (X = CH) and 7-aza-indolyl (X = N) substituted alkynones **3** or the pyrrolyl ynones **9** with an excess of guanidinium hydrochloride (**10**) and potassium carbonate in 2-methoxyethanol at 120 °C for 12–24 h the 2-amino pyrimidines **11** were obtained in good to excellent yields (Scheme 4, Table 3).



Scheme 4. Cyclocondensation of alkynones **3** and **9** to 4-(indol-3-yl)-, 4-(7-aza-indol-3-yl)-, and 4-(pyrrol-2-yl)-2-amino pyrimidines **11**.

Compounds **11e** and **11f** can be considered as *N*-alkyl derivatives of the naturally occurring meridianin G.[21] The structures of the 2-amino pyriminidines **11** were unambiguously supported by NMR spectroscopy and mass spectrometry, and later by an X-ray structure analysis of compound **11b** (Figure 2).[20]

In conclusion, we have disclosed a new consecutive three-component synthesis of alkynones by glyoxylation of very easily accessible indole, 7-aza-indole, and pyrrole derivatives with oxalyl chloride and subsequent Pd/Cu-catalyzed decarbonylative alkynylation of the heteroaryl glyoxylyl chlorides with terminal alkynes. This new Sonogashira protocol proceeds considerably faster than carbonylative alkynylations of (hetero)aryl iodides with carbon monoxide[5] and a lower catalyst loading is needed. The mild conditions for decarbonylations are unprecedented, and the reagents are only applied in equimolar quantities with a high tolerance for various substituents. The application of the alkynones in a subsequent transformation to pyrimidines also illustrates the

Table 3. Synthesis of 4-(indol-3-yl)-, 4-(7-aza-indol-3-yl)-, and 4-(pyrrol-2-yl)-2-amino pyrimidines **11**.[a]

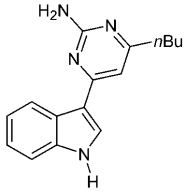
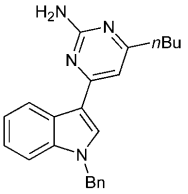
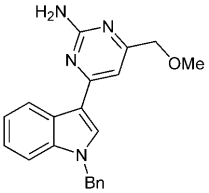
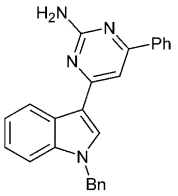
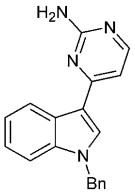
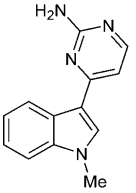
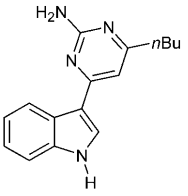
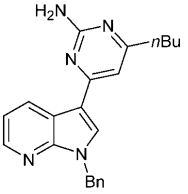
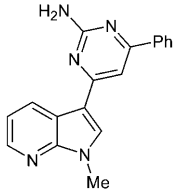
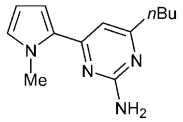
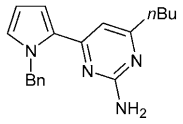
Entry	Ynone **3** or **9**	2-Amino pyimindine **11** (isolated yield/%)
1	**3a**	 **11a** (81)
2	**3b**	 **11b** (86)
3	**3c**	 **11c** (88)
4	**3d**	 **11d** (82)
5	**3e**	 **11e** (88)[b]
6	**3f**	 **11f** (68)[b]
7	**3g**	 **11a** (68)[b]
8	**3h**	 **11g** (81)

Table 3. (Continued)

Entry	Ynone **3** or **9**	2-Amino pyimindine **11** (isolated yield/%)
9	**3i**	 **11h** (86)
10	**9a**	 **11i** (92)
11	**9b**	 **11j** (94)

[a] The reactions were performed at c(**3** or **9**) = 0.2 M in 2-methoxyethanol. [b] TMS and TIPS were deprotected in the course of the reaction.

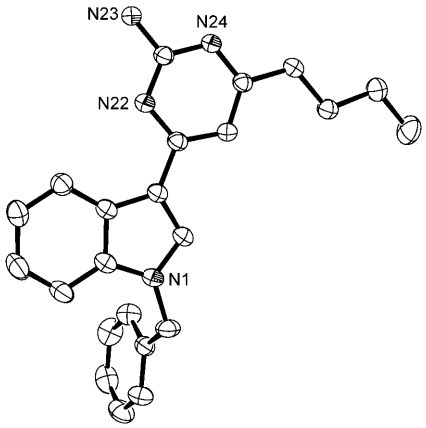


Figure 2. Molecular structure of 2-amino pyrimidine **11b** (hydrogen atoms were omitted for clarity).

vast potential to diversity-oriented syntheses of heterocycles. Studies expanding the scope of this novel access to alkynones and their elaboration towards multi-component syntheses of heterocycles are currently underway. In addition, the stage has been set for the methodological expansion to further decarbonylative cross-couplings that are currently under investigation.

Experimental Section

General methods and further reactions are given in the Supporting Information.

Three-component synthesis of alkynone 3b: *N*-Benzyl-1*H*-indole (**7a**) (1.04 g, 5.00 mmol) in dry THF (25 mL) was placed under argon in a screw-cap vessel with septum, degassed with argon and cooled to 0 °C (water/ice). Then, oxalyl chloride (0.44 mL, 5.00 mmol) was added to the reaction mixture at 0 °C. The mixture was allowed to come to room temperature and was stirred for 4 h. Then, $[PdCl_2(PPh_3)_2]$ (35 mg, 0.05 mmol), CuI (10 mg, 0.05 mmol), 1-hexyne (**2a**) (0.59 mL, 5.00 mmol), and dry triethylamine (1.39 mL, 10.0 mmol) were successively added to the mixture and stirring at room temperature was continued for 1 h. The evolution of CO can be observed. After complete conversion (monitored by TLC) saturated brine (25 mL) was added, and the mixture was extracted with dichloromethane (3×25 mL). The combined organic layers were dried with anhydrous sodium sulfate. After removal of the solvents in vacuo the residue was absorbed onto Celite and chromatographed on silica gel with hexanes/ethyl acetate to give the alkynone **3b** (1.17 g, 74 %) as a yellow solid. M.p. 84–85 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 8.44–8.38 (m, 1H), 7.90 (s, 1H), 7.39–7.13 (m, 8H), 5.35 (s, 2H), 2.44 (t, J = 7.5 Hz, 2H), 1.62 (quint, J = 8.3 Hz, 2H), 1.47 (sext, J = 8.3 Hz, 2H), 0.94 ppm (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = 171.8 (C_{quat}), 138.1 (CH), 137.3 (C_{quat}), 135.5 (C_{quat}), 129.1 (CH), 128.3 (CH), 127.1 (CH), 126.1 (C_{quat}), 123.8 (CH), 123.0 (CH), 122.6 (CH), 118.9 (C_{quat}), 110.3 (CH), 91.0 (C_{quat}), 80.6 (C_{quat}), 50.9 (CH_2), 30.0 (CH_2), 22.1 (CH_2), 18.7 (CH_2), 13.6 ppm (CH_3); EI+MS: m/z (%): 315 (100) [M^+], 91 (40) [$C_7H_7^+$]; IR (KBr): $\tilde{\nu}$ = 730, 752, 771, 827, 1027, 1184, 1237, 1360, 1386, 1440, 1453, 1465, 1486, 1495, 1522, 1576, 1607, 2226, 2870, 2932, 2955 3119 cm^{-1}; elemental analysis calcd (%) for $C_{22}H_{21}NO$: C 83.78, H 6.71, N 4.44; found: C 83.64, H 6.71, N 4.43.

2-Aminopyrimidine 11b: In a screw-cap vessel under argon the alkynone **3b** (315 mg, 1.00 mmol) was dissolved in 2-methoxyethanol (5 mL). Then, potassium carbonate (346 mg, 2.50 mmol), and guanidinium hydrochloride (**10**) (239 mg, 2.50 mmol) were added and the mixture was stirred at 120 °C over night. Then, after cooling to room temperature saturated brine (20 mL) was added, and the mixture was extracted with dichloromethane (5×20 mL). The combined organic layers were dried with anhydrous sodium sulfate. After removal of the solvents in vacuo the residue was absorbed onto Celite and chromatographed on silica gel with dichloromethane and dichloromethane/methanol/aqueous ammonia (100:1:1) to give the 2-amino pyrimidine **11b** (305 mg, 86 %) as a pale yellow solid. M.p. 174–175 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 27 °C, TMS): δ = 8.40–8.33 (m, 1H), 7.84 (s, 1H), 7.35–7.18 (m, 6H), 7.18–7.11 (m, 2H), 6.89 (s, 1H), 5.35 (s, 2H), 5.05 (s, 2H, NH_2), 2.60 (t, J = 7.5 Hz, 2H), 1.72 (quint, J = 7.5 Hz, 2H), 1.42 (sext, J = 7.5 Hz, 2H), 0.95 ppm (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 27 °C, TMS): δ = 171.4 (C_{quat}), 163.1 (C_{quat}), 162.5 (C_{quat}), 137.4 (C_{quat}), 136.5 (C_{quat}), 130.3 (CH), 128.9 (CH), 127.9 (CH), 126.9 (CH), 126.3 (C_{quat}), 122.6 (CH), 121.7 (CH), 121.2 (CH), 114.8 (C_{quat}), 110.3 (CH), 106.4 (CH), 50.5 (CH_2), 37.8 (CH_2), 31.2 (CH_2), 22.6 (CH_2), 14.0 ppm (CH_3); EI+MS: m/z (%): 356 (27) [M^+], 341 (3) [M^+-CH_3], 268 (7) [$M^+-C_2H_5$], 314 (100) [$M^+-C_3H_6$], 223 (5) [$M^+-C_{10}H_{13}$], 91 (14) [$C_7H_7^+$]; IR (KBr): $\tilde{\nu}$ = 743, 1175, 1385, 1456, 1469, 1521, 1577, 1628, 1645, 2860, 2927, 2956, 3442, 3463 cm^{-1}; elemental analysis calcd (%) for $C_{23}H_{24}N_4$: C 77.50, H 6.79, N 15.72; found: C 77.45, H 6.75, N 15.77.

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[20] CCDC 710258 (**3b**) and CCDC 710259 (**11b**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
[21] The NMR-spectroscopic data of compound **11e** are identical with *N*-benzyl meridianin G, see G. Simon, H. Couthon-Gourves, J.-P. Haelters, B. Corbel, N. Kervarec, F. Michaud, L. Meijer, *J. Heterocycl. Chem.* **2007**, *44*, 793–801.

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