A New Efficient Synthesis of Substituted Luminols Using Multicomponent Reactions*

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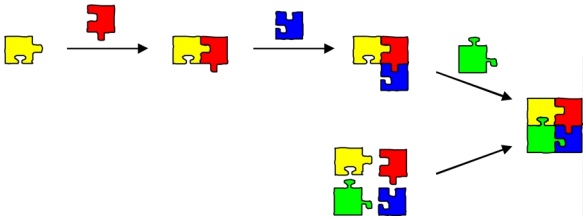
A new general synthesis of substituted luminols (5-amino-2,3-dihydrophthalazine-1,4-diones) is presented. Diversely substituted luminol derivatives can be synthesized in three steps. The products are of interest as new materials, which exhibit chemiluminescence.

Key words: Luminol, Multicomponent Reactions, Phthalhydrazides

Introduction

The ideal chemical synthesis should proceed with inexpensive, possibly renewable reagents, in standard equipment to give the desired product in quantitative yield and 100% atom-economy. Obviously, only very few known chemical transformations fulfill these criteria. Thus, the improvement of known synthetic methods and the invention of new reactions are still among the most important research areas in organic chemistry. Importantly, the number of reaction steps for a given substance should be as low as possible. Hence, the utilization of methodologies, which allow for minimization of reaction steps, offers significant advantages. In this regard, multicomponent reactions (MCR's) are of considerable interest owing to their exceptional synthetic efficiency [1]. Unlike the usual stepwise formation of individual bonds in the target molecule, the utmost attribute of MCR's is the inherent formation of several bonds in one operation without isolating the intermediates, changing the reaction conditions, or adding further reagents (Scheme 1). Since the products carry portions of all employed reactants in its structure, MCR's can result in a marked increase in molecular complexity and diversity. Upon wide variation of the starting materials of an MCR, opportunities also arise for the easy synthesis of compound libraries.



Scheme 1. Multi-step *vs.* multicomponent assembly.

Recently, we developed new multicomponent reactions of Amides and Aldehydes with Dienophiles (AAD reaction) for the straight forward synthesis of a large variety of carbo- and heterocyclic amides [2]. As shown in Scheme 2, the underlying mechanism of the AAD reaction involves the intermediacy of an 1(*N*-acylamino)-1,3-butadiene which easily undergoes Diels-Alder addition to an electron-deficient dienophile [3].

Interestingly, the sequential combination of a three-component coupling reaction of *O*-benzyl carbamate, aldehydes, and dienophiles and a subsequent domino deprotection – aromatization reaction allows for the synthesis of polysubstituted anilines with diverse substitution patterns [4]. Here, a palladium-catalyzed aromatization of the three-component coupling products, which is based on a new intramolecular-transfer hydrogenation reaction, is the key step

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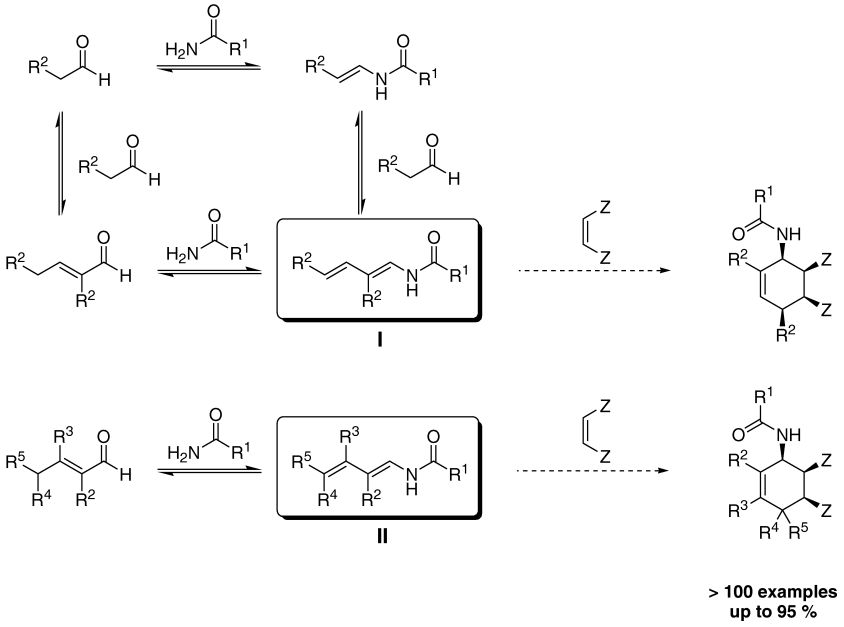
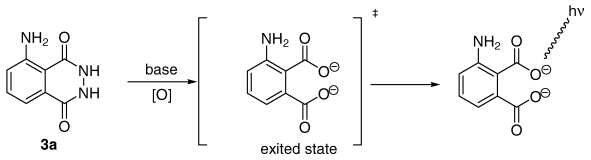


Scheme 2. The AAD-reaction.



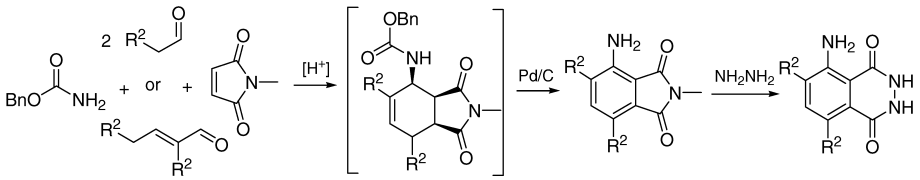
Scheme 3. Chemiluminescence of luminol.

of the described method. Apart from the synthesis of substituted anilines we considered our new reaction sequence also useful for the synthesis of 5-amino-2,3-dihydrophthalazine-1,4-diones (so-called luminols). This class of compounds is of special interest with regard to new materials which show chemiluminescence behavior. The prototype of this class of compounds, 5-amino-2,3-dihydrophthalazine-1,4-dione **3a**, was discovered by Albrecht [5] in 1928 and was named luminol, because oxidation of **3a** with H_2O_2 in the presence of a catalyst leads to the emission of light (Scheme 3) [6]. As a part of the energy escapes in form of light, this phenomenon is called chemiluminescence. Important applications of luminol include the determination of low concentrations of glucose in blood or urine [7, 8]. Also determination of H_2O_2 with luminol is extremely sensitive and in some cases subnanomolar concentrations can be measured [9].

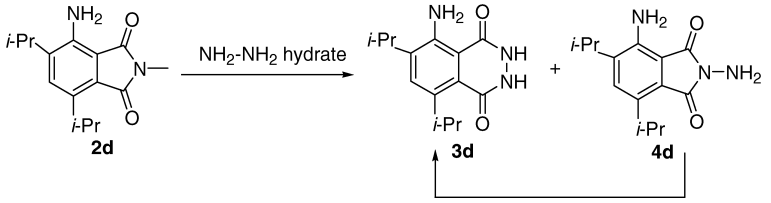
Structural variations to the luminol core were first investigated by Drew and Perman [10], who synthesized various 2,3-dihydrophthalazine-1,4-diones in order to examine the influence between constitution and chemiluminescence behavior. Accordingly, electron-donating substituents were shown to enhance the quantum yield of emitted light, whereas electron-withdrawing groups decrease it. Later on, White and Bursey [11] observed a similar beneficial effect of methoxy substituents in the arene core on the quantum yield depending on the solvent. Brundrett and White [12] as well as Gundermann and Drawert [13] studied the behavior of different alkyl-substituted luminols. Upon comparison of different syntheses of substituted luminols it is obvious that none of the known methods is general in terms of applicability, efficiency and scope. Often unselective and wasteful aromatic substitution reactions are applied. For example all known syntheses of luminol derivatives require electrophilic nitration with concentrated HNO_3 which is associated with the generation of (over)stoichiometric amounts of nitrates as byproducts.

Results and Discussion

Based on our three-component coupling reaction of aldehydes, *O*-benzyl carbamate and *N*-methylmaleimide [2, 4] we set up the topology of a valuable luminol precursor in one reaction step (Scheme 4). This strategy constitutes a synthetic approach rather different from the typical phthalic acid syntheses. Especially for polysubstituted derivatives, the envisioned reaction



Scheme 4. Three-component reaction of aldehydes, *O*-benzyl carbamate and *N*-methylmaleimide.



Scheme 5. Formation of **3d** and **4d**.

sequence can be shorter and may exhibit higher convergence. To the best of our knowledge, such a strategy has not been used for the synthesis of substituted phthalylhydrazine derivatives.

As shown in Table 1, ten different luminol derivatives have been prepared in only three reaction steps from commercially available substrates. Depending on the employed aldehyde, variation of alkyl and aryl substituents can be implemented in any desired position of the aromatic ring (C-6, C-7 and C-8). By employing 2 equivalents of simple aliphatic aldehydes the positions C-6 and C-8 are substituted by the same group. On the other hand the use of substituted α,β-unsaturated aldehydes affords *in situ* 1-acylamino-1,3-butadiene building blocks with four substitution centers along the 1,3-butadiene backbone. Clearly, this significantly increases the substrate diversity. Also anellated ring systems can be produced, which is nicely illustrated by the synthesis of **3f**. Aromatization of the MCR adducts **1a – j** to give substituted 3-aminophthalimides **2a – j** (56 – 91%) is easily achieved by heating the reaction mixture in triglyme at 140 °C in the presence of 10 mol% of Pd/C. Interestingly, the catalyst both removes hydrogen from the cyclohexene core to form the corresponding arene and cleaves the benzyl carbamate to the free amino group. Finally, the resulting 3-aminophthalimides **2a – j** are reacted with an excess of hydrazine in water to yield the luminol-type molecules **3a – j** in good yield (58 – 90%). In general, it was sufficient to heat the mixture in a pressure tube at 110 °C for 2 – 4 hours. However, in case of **2d** the formation of the *N*-aminophthalimide **4d** was observed as major product (Scheme 5) [10, 11, 13].

Obviously, the bulky isopropyl groups on the arene ring support the formation of **4d** instead of **3d**. Fortunately, **4d** can be converted in good yield to the thermodynamically more stable product **3d** by increasing the reaction time to 60 hours.

In summary, we have developed an efficient strategy for the synthesis of substituted luminols (5-amino-2,3-dihydrophthalazine-1,4-diones). Key reactions are the three-component coupling reaction of aldehydes, *O*-benzyl carbamate and maleimide, and a palladium-catalyzed domino deprotection-aromatization reaction. The overall procedure utilizes simple, ubiquitous available starting materials and allows the (regio)selective introduction of alkyl and aryl substituents in the benzene ring of luminol.

Experimental Section

General procedure for the synthesis of **1a – j**

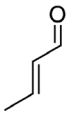
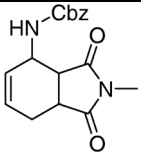
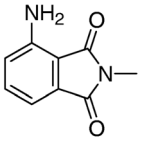
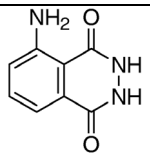
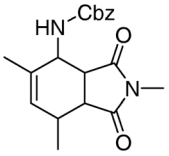
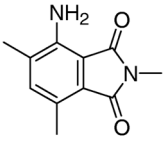
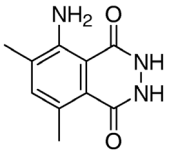
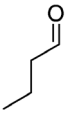
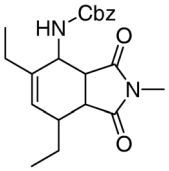
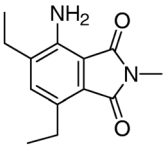
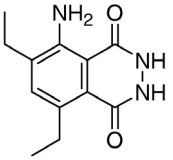
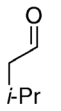
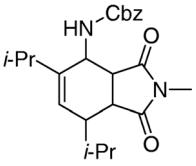
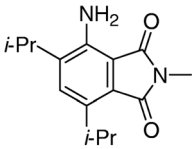
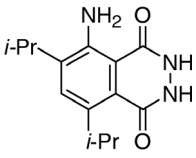
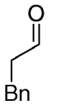
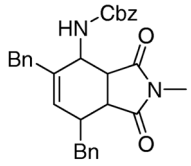
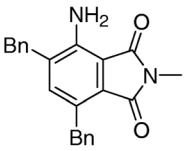
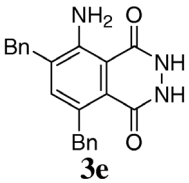
A mixture of *O*-benzyl carbamate (15 mmol), *p*-TSA·H_2O (2 mol%), aldehyde (15 mmol), Ac_2O (15 mmol), *N*-methylmaleimide (11 mmol), and NMP (10 ml) was confined to an ACE pressure tube and stirred at 120 °C [14]. After 24 – 48 h, the solvent and other volatile compounds were removed by high vacuum distillation. Silica gel flash chromatography (heptane/ethyl acetate) of the residue afforded the 3-CR adducts as air-stable solids.

With α,β-unsaturated aldehydes, reactions were run in the presence of 7.5 mmol aldehyde and without Ac_2O [15].

General procedure for the synthesis of **2a – j**

A 100 ml flask equipped with a reflux condenser was charged with a mixture of carbamate **1** (2.9 mmol), Pd/C (10% Pd on C, 8 mol%) and triglyme (20 ml) and heated to 140 °C. After 16 – 48 h, the solution was filtered through a celite pad and solvent and other volatile compounds were removed by high vacuum distillation. The residue was sub-

Table 1. Syntheses of luminols[a].

Entry	Aldehyde	MCR-Adducts	Yield [%]	Anilines	Yield [%]	Luminol	Yield [%]
1		 **1a**	80	 **2a**	68	 **3a**	70
2		 **1b**	89	 **2b**	91	 **3b**	80
3		 **1c**	89	 **2c**	79	 **3c**	74
4		 **1d**	81	 **2d**	80	 **3d**	58
5		 **1e**	80	 **2e**	91	 **3e**	81

jected to silica gel flash chromatography (heptane/ethyl acetate).

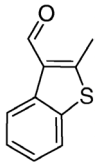
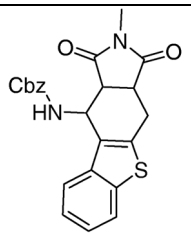
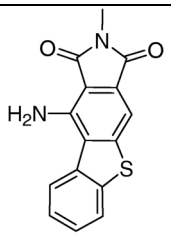
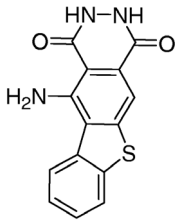
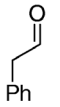
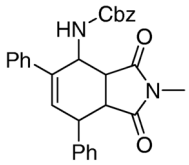
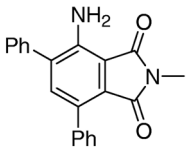
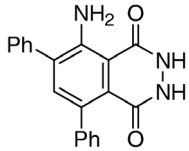
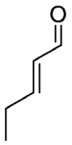
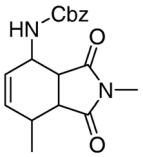
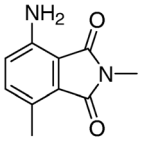
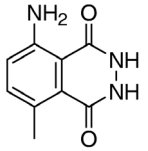
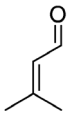
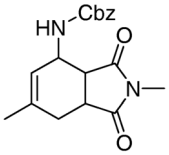
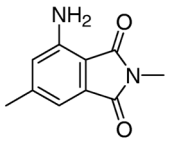
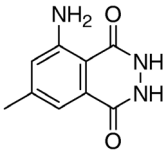
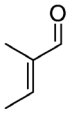
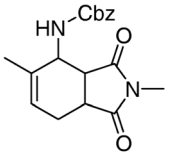
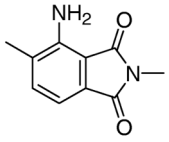
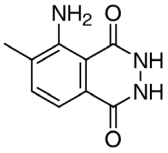
General procedure for the synthesis of **3a** – **j** [16]

3-Aminophthalimide **2** (1.25 mmol) and hydrazine hydrate (20.6 mmol, 1 ml) were transferred to a pressure tube. The mixture was heated at 110 °C for 2 – 4 hours [17]. After cooling to ambient temperature the volatile compounds were removed by high vacuum distillation and the residue was suspended in MeOH and filtered off. The collected product was suspended in 1N HCl, filtered again and washed with water. After drying in high vacuum slightly yellow solids were obtained.

*5-Amino-2,3-dihydrophthalazine-1,4-dione (***3a***)*

Yield: 70%; m. p. 320 °C. – IR (KBr): ν = 3423 (s, NH), 3335 (s, NH), 2920 (b), 1675 (C=O), 1604 (C=O), 1495 (s), 1451 (s), 1383 (m), 1324 (s), 1296 (s), 1246 (m), 1199 (w), 1098 (w), 1052 (w), 952 (m), 816 (m), 787 (m), 703 (m), 636 (m), 492 (m) cm^{-1}. – ^{1}H NMR (400.13 MHz, [D_6]-DMSO): δ = 11.18 (s, broad, 2 H, NH-NH), 7.44 (t, J = 7.9 Hz, 1 H, CHCHCH), 7.30 (s, broad, 2H, NH_2), 6.93 (d, J = 8.5 Hz, 1 H, CH), 6.87 (d, J = 9.0 Hz, 1H, CH). – ^{13}C NMR (100.63 MHz, [D_6]-DMSO): δ = 161.36/151.47 (2 C=O), 150.68, 126.57, 110.48 (3 C), 133.88, 116.41, 109.43 (3 CH). – MS (EI, 70 eV): m/z (%) =

Table 1 (continued).

Entry	Aldehyde	MCR-Adducts	Yield [%]	Anilines	Yield [%]	Luminol	Yield [%]
6		 **1f**	41	 **2f**	78	 **3f**	90
7		 **1g**	48	 **2g**	56	 **3g**	81
8		 **1h**	62	 **2h**	65	 **3h**	64
9		 **1i**	70	 **2i**	64	 **3i**	64
10		 **1j**	75	 **2j**	63	 **3j**	67

[a] In all cases isolated yields are reported.

177 (100) [M^+], 119 (52) [M^+-2NH-CO], 91 (46), 65 (21). – $C_8H_7N_3O_2$ (177.16): calcd. C 54.24, H 3.98, N 23.72; found C 54.27, H 3.99, N 23.56.

*5-Amino-6,8-dimethyl-2,3-dihydrophthalazine-1,4-dione (**3b**)*

Yield: 80%; m. p. 302 dec. – IR (KBr): $\nu = 3476$ (m, NH), 3317 (s, NH), 1646 (s, C=O), 1597 (s), 1573 (s), 1486 (s), 1455 (m), 1438 (m), 1381 (s), 1308 (s), 1261 (m), 1225 (w), 1140 (w), 1033 (s), 910 (w), 881 (m), 792 (s), 695 (w), 663 (w), 574 (w), 526 (m), 461 (w) cm^{-1}. – ^1H NMR (400.13 MHz, [D_6]-DMSO): $\delta = 11.04$ (s, broad, 2 H, NH-NH), 7.19 (s, 1 H, CH), 7.09 (s, broad, 2H, NH_2), 2.05 (s, 3 H, CH_3), 2.1 (s, 3 H, CH_3). – ^{13}C NMR (100.63 MHz, [D_6]-DMSO): $\delta = 161.71/153.38$ (2 C=O), 147.15, 124.47, 122.65, 121.26, 110.93 (5 C), 138.67 (CH). – MS (EI, 70 eV): m/z (%) = 205 (100) [M^+], 189 (29) [M^+-NH_2], 160 (15), 147 (8) [M^+-2NH-CO), 132 (21), 119 (32), 104 (8), 91 (10), 77 (11), 65 (7), 51 (8), 39 (6). – HRMS ($C_{10}H_{11}N_3O_2$): calcd. 205.08513, found 205.08602.

*5-Amino-6,8-diethyl-2,3-dihydrophthalazine-1,4-dione (**3c**)*

Yield: 74%; m. p. 281 – 282 °C. – IR (KBr): ν = 3476 (s, NH), 3307 (s, NH), 2965 (b), 1630 (s, C=O), 1602 (s), 1567 (s), 1537 (s), 1492 (s), 1457 (w), 1441 (w), 1422 (m), 1329 (s), 1235 (m), 1195 (m), 1068 (w), 1041 (w), 906 (m), 894 (m), 854 (s), 802 (w), 662 (w), 501 (w) cm^{-1}. – ^{1}H NMR (400.13 MHz, [D_6]-DMSO): δ = 11.02 (s, broad, 2 H, NH-NH), 7.21 (s, broad, 2H, NH_2), 7.15 (s, 1 H, CH), 2.93 (q, J = 7.3 Hz, 2 H, CH_2), 2.47 (q, J = 7.5 Hz, 2H, CH_2), 1.11 (t, J = 7.3 Hz, 3 H, CH_3), 1.06 (t, J = 7.5 Hz, 3 H, CH_3). – ^{13}C NMR (100.63 MHz, [D_6]-DMSO): δ = 161.85/152.80 (2 C=O), 146.86, 129.93, 128.13, 121.80, 110.87 (5 C), 135.97 (CH), 27.69, 23.33 (2 CH_2), 17.59, 12.47 (2 Me). – MS (EI, 70 eV): m/z (%) = 233 (53) [M^+], 218 (100) [M^+-NH], 132 (7), 117 (6), 91 (5). – $C_{12}H_{15}N_3O_2$ (233.27): calcd. C 61.79, H 6.48, N 18.01; found C 61.49, H 6.55, N 18.02.

*5-Amino-6,8-diisopropyl-2,3-dihydrophthalazine-1,4-dione (**3d**)*

Yield: 58%; m. p. 224 – 227 °C. – IR (KBr): ν = 3481 (s, NH), 3300 (s, NH), 2960 (b), 1649 (s, C=O), 1594 (m), 1569 (s), 1489 (s), 1427 (w), 1399 (w), 1380 (w), 1335 (s), 1301 (s), 1249 (m), 1192 (w), 1092 (w), 1055 (w), 998 (w), 992 (w), 855 (w), 827 (m), 806 (w), 781 (w), 704 (w), 661 (w), 560 (w) cm^{-1}. – ^{1}H NMR (400.13 MHz, [D_6]-DMSO): δ = 11.09 (s, broad, 2 H, NH-NH), 7.43 (s, 1 H, CH. arom.), 7.39 (s, broad, 2H, NH_2), 4.39 (sept, J = 6.9 Hz, 1 H, $CHMe_2$), 3.06 (sept, J = 6.7 Hz, 1H, $CHMe_2$), 1.18 (d, J = 6.7 Hz, 6 H, $CHMe_2$), 1.15 (d, J = 6.9 Hz, 6 H, $CHMe_2$). – ^{13}C NMR (100.63 MHz, [D_6]-DMSO): δ = 161.94/152.99 (2 C=O), 146.18, 134.11, 132.76, 121.30, 110.63 (5 C), 127.94 (CH arom.), 27.62, 26.31 (2 $CHMe_2$), 24.58, 21.84 (2 $CHMe_2$). – MS (EI, 70 eV): m/z (%) = 261 (36) [M^+], 246 (100) [M^+-NH], 232 (5). – HRMS ($C_{14}H_{19}N_3O_2$): calcd. 261.14774, found 261.14661.

*2,4-Diamino-5,7-diisopropylisoindole-1,3-dione (**4d**)*

SiO_2 chromatography (heptane/EtOAc 3:1): R_f = 0.11. – Yield: 42%; m. p. 133 – 135 °C. – IR (KBr): ν = 3462 (s, NH), 3360 (s, NH), 2963 (s), 2870 (s), 1746 (s), 1703 (s, CO), 1637 (s), 1610 (s), 1487 (s), 1426 (m), 1365 (m), 1288 (w), 1241 (m), 1188 (w), 1166 (w), 1130 (w), 1050 (m), 1007 (w), 901 (w), 880 (w), 799 (w), 759 (m), 655 (w), 633 (w), 586 (w) cm^{-1}. – ^{1}H NMR (400.13 MHz, [D_6]-DMSO): δ = 7.29 (s, 1 H, CH. arom.), 6.18 (s, 2 H, C-NH_2), 4.74 (s, 2H, N-NH_2), 3.83 (sept, J = 6.9 Hz, 1 H, $CHMe_2$), 3.10 (sept, J = 6.7 Hz, 1H, $CHMe_2$), 1.18 (d, J = 6.7 Hz, 6 H, $CHMe_2$), 1.15 (d, J = 6.9 Hz, 6 H, $CHMe_2$). – ^{13}C NMR (100.63 MHz, [D_6]-DMSO): δ = 168.91/167.53 (2 C=O), 142.17, 140.62, 136.04, 122.48, 107.54 (5 C), 128.12 (CH arom.), 26.79, 26.46 (2 $CHMe_2$), 22.80, 22.06 (2 $CHMe_2$). – MS (EI, 70 eV): m/z (%) = 261 (100) [M^+], 246 (87) [M^+-NH], 229 (56), 215 (21), 201 (13), 185 (21), 173 (43), 158 (15), 143 (17), 130 (17), 115 (15), 91 (11), 77 (11), 41 (11). – HRMS ($C_{14}H_{19}N_3O_2$): calcd. 261.14774, found 261.14733.

*5-Amino-6,8-dibenzyl-2,3-dihydrophthalazine-1,4-dione (**3e**)*

Yield: 81%; m. p. 278-280 °C. – IR (KBr): ν = 3473 (s, NH), 3315 (s,NH), 3026 s, 2900 (b), 1631 (s), 1619 (s), 1571 (s), 1535 (m), 1492 (s), 1452 (m), 1422 (m), 1394 (m), 1322 (s), 1251 (m), 878 (m), 799 (m), 746 (s), 697 (s) cm^{-1}. – ^{1}H NMR (400.13 MHz, [D_6]-DMSO): δ = 11.16 (s, broad, 2 H, NH-NH), 7.37 (s, broad, 2H, NH_2),7.26 (m, 2 H, CH), 7.18 (m, 6 H, CH), 7.07 (m, 1 H, CH), 7.01 (d, J = 7.00 Hz, 2 H, CH), 4.38 (s, 2H, CH_2), 3.89 (s, 2 H, CH_2). – ^{13}C NMR (100.63 MHz, [D_6]-DMSO): δ = 161.70/151.64 (2 C=O), 147.45, 127.29, 123.78, 123.02, 111.39 (5 C), 142.82, 138.95 (2 *i*-CH), 139.24 (CH, phenyl), 128.68, 128.35, 128.11, 128.01 (4 *o*-CH, 4 *m*-CH), 126.13, 125.26 (2 *p*-CH), 38.96, 35.96 (2 CH_2). – MS (EI, 70 eV): m/z (%) = 357 (100) [M^+], 280 (12) [M^+-Ph], 266 (15) [M^+-Bn], 180 (7), 165 (5), 91 (15). – $C_{22}H_{19}N_3O_2$ (357.41): calcd. C 73.93, H 5.36, N 11.76; found C 73.52, H 5.37, N 11.52.

*5-Amino-7,8-dihydro-11-thia-7,8-diazabenzo[b]fluorene-6,9-dione (**3f**)*

Yield: 90%; m. p. > 350 °C. – IR (KBr): ν = 3300 (NH), 3052 (b), 1645 (s, C=O), 1589 (s), 1483 (m), 1430 (m), 1407 (m), 1346 (m), 1310 (m), 1262 (w), 1216 (w), 1187 (w), 1087 (w), 1063 (w), 992 (w), 820 (m), 761 (m), 732 (s), 706 (m), 672 (w), 627 (w), 561 (w) cm^{-1}. – ^{1}H NMR (400.13 MHz, [D_6]-DMSO): δ = 11.33 (s, broad, 2 H, NH-NH), 8.44 (d, J = 8.13 Hz, 1 H, *o*-CH), 8.10 (d, J = 7.73 Hz, 1 H, *o*-CH), 8.00 (s, 1 H, CH), 7.83 (s, broad, 2 H, NH_2), 7.57 (m, 2 H, *m*-CH). – ^{13}C NMR (100.63 MHz, [D_6]-DMSO): δ = 161.61/152.02 (2 C=O), 145.59, 139.58, 139.28, 135.35, 125.27, 123.89, 106.89 (7 C), 128.37, 125.24, 123.40, 123.24, 103.93 (5 CH). – MS (EI, 70 eV): m/z (%) = 283 (100) [M^+], 268 (7) [M^+-NH], 225 (8), 197 (43) [M^+-2CO-2NH], 171 (8), 126 (8). HRMS ($C_{14}H_9N_3O_2S$): calcd. 283.04153; found 283.04230.

*5-Amino-6,8-diphenyl-2,3-dihydrophthalazine-1,4-dione (**3g**)*

Yield: 81%; m. p. 266 °C. – IR (KBr): ν = 3484 (m), 3301 (m), 3160 (s), 3025 (vs, br), 2675 (m), 1648 (vs), 1588 (s), 1562 (s), 1484 (vs), 1445 (s), 1377 (m), 1305 (vs), 1240 (w), 1202 (w), 1081 (m), 1060 (w), 1025 (w), 962 (vw), 912 (vw), 871 (w), 825 (s), 808 (m), 786 (m), 760 (m), 700 (vs), 671 (m), 635+(vw), 608 (vw), 583 (m),

566 (w), 516 (vw), 487 (vw), 469 (vw), 433 (vw) cm^{-1}. – ^1H NMR (400.13 MHz, $CDCl_3$): $\delta = 12.96$ (s, 1H, NH), 11.54 (s, 1H, NH), 7.42 – 7.35 (m, 5H, Ph), 7.28 (s, 1H, CH), 7.25 – 7.20 (m, 5H, Ph), 6.62 (s, 2H, NH_2). – ^{13}C NMR (100.63 MHz, $CDCl_3$): $\delta = 164.0/154.6$ (2 C=O), 147.0, 142.2 (2C), 139.6 (CH), 137.5 (C), 129.5 (2CH), 129.2 (2CH), 129.0 (C), 128.9 (2CH), 128.2 (CH), 128.1 (C), 127.2 (2 CH), 126.3 (CH), 122.3, 111.2 (C). – MS (EI, 70 eV): m/z (%) = 392 (100) [M^+], 243 (18) [M^+-CONHNHCO], 215 (6), 77 (7) [Phenyl], no other peaks < 5%. $C_{20}H_{15}N_3O_2$ (329.35): calcd. C 72.95, H 4.59, N 12.76; found C 72.24, H 4.73 N 12.73.

*5-Amino-8-methyl-2,3-dihydrophthalazine-1,4-dione (***3h***)*

Yield: 64%; dec. 310 °C. – IR (KBr): $\nu = 3476$ (s, NH), 3332 (s, NH), 2967 (b), 1649 (s, C=O), 1591 (s), 1573 (s), 1499 (s), 1448 (m), 1381 (m), 1312 (s), 1244 (m), 1193 (w), 1095 (w), 1023 (w), 902 (w), 827 (m), 790 (m), 662 (w), 542 (w), 496 (w), 469 (w) cm^{-1}. – ^1H NMR (400.13 MHz, [D_6]-DMSO): $\delta = 10.70$ (s, broad, 2 H, NH-NH), 6.90 (s, broad, 2H, NH_2), 6.93 (d, $J = 8.4$ Hz, 1H, CH), 6.51 (d, $J = 8.4$ Hz, 1H, CH), 2.21 (s, 3H, Me). – ^{13}C NMR (100.63 MHz, [D_6]-DMSO): $\delta = 161.26/153.26$ (2 C=O), 149.14, 124.70, 121.51, 111.29 (4 C), 137.52 and 116.97 (2 CH), 22.01 (Me). – MS (EI, 70 eV): m/z (%) = 191 (100) [M^+], 175 (33) [M^+-NH_2], 146 (16), 133 (13) [M^+-CONHNH], 118 (24), 105 (45), 89 (10), 77 (20), 63 (9), 51 (13), 39 (8). – $C_9H_9N_3O_2$ (191.07): calcd. C 56.54, H 4.74, N 21.98; found C 56.61, H 4.76, N 22.07.

*5-Amino-7-methyl-2,3-dihydrophthalazine-1,4-dione (***3i***)*

Yield: 64%; dec. 310 °C. – IR (KBr): $\nu = 3483$ (s, NH), 3353 (s, NH), 2925 (b), 1663 (s, C=O), 1635 (s), 1599 (s), 1494 (s), 1326 (s), 1294 (m), 1262 (w), 1200 (w), 1167 (w), 1110 (w), 1028 (w), 818 (s), 703 (m), 659 (w), 500 (w), 476 (w) cm^{-1}. – ^1H NMR (400.13 MHz, [D_6]-DMSO): $\delta = 11.08$ (s, broad, 2 H, NH-NH), 7.20 (s, broad, 2H, NH_2), 6.77 (s, 1 H, CH), 6.68 (s, 1H, CH), 2.28 (s, 3H, Me). – ^{13}C NMR (100.63 MHz, [D_6]-DMSO): $\delta = 161.29/151.27$ (2 C=O), 150.64, 144.05, 126.51, 108.03 (4 C), 116.67 and 110.22 (2 CH), 21.61 (Me). – MS (EI, 70 eV): m/z (%) = 191 (100) [M^+], 133 (51) [M^+-CONHNH], 105 (37), 77 (10), 65 (6). – HRMS ($C_9H_9N_3O_2$): calcd. 191.06947; found 191.07012.

*5-Amino-6-methyl-2,3-dihydrophthalazine-1,4-dione (***3j***)*

Yield: 67%; dec. 304 – 306 °C. – (KBr): $\nu = 3484$ (s, NH), 3325 (s, NH), 2970 (b), 1654 (s, C=O), 1612 (s), 1584 (s), 1485 (s), 1385 (m), 1339 (s), 1311 (s), 1244 (w), 1225 (w), 1100 (w), 1023 (w), 964 (w), 872 (m), 813 (s), 706 (w), 642 (w), 526 (w), 499 (w), 496 (w) cm^{-1}. – ^1H NMR (400.13 MHz, [D_6]-DMSO): $\delta = 11.04$ (s, broad, 2 H, NH-NH), 7.81 (s, broad, 2H, NH_2), 7.41 (d, $J = 7.7$ Hz, 1H, CH), 6.96 (d, $J = 7.9$ Hz, 1H, CH), 2.16 (s, 3H, Me). – ^{13}C NMR (100.63 MHz, [D_6]-DMSO): $\delta = 161.72/151.64$ (2 C=O), 148.12, 124.53, 110.31 (4 C), 134.88 and 109.80 (2 CH), 17.66 (Me). – MS (EI, 70 eV): m/z (%) = 191 (100) [M^+], 175 (7) [M^+-NH_2], 146 (5) 133 (47) [M^+-CONHNH], 118 (7) 105 (50), 89 (5), 77 (15), 65 (9), 51 (10), 39 (9). – HRMS ($C_9H_9N_3O_2$): calcd. 191.06947; found 191.06822.

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[1] a) L. F. Tietze, Chem. Rev. **96**, 115 (1996); b) L. F. Tietze, F. Haunert, in M. Shibasaki, J. F. Stoddart, F. Vögtle (eds): Stimulating Concepts in Chemistry, pp. 39, Wiley-VCH, Weinheim, (2000); c) H. Bienaymé, C. Hulme, G. Oddon, P. Schmitt, Chem. Eur. J. **6**, 3321 (2000); d) L. F. Tietze, A. Modi, Med. Res. Rev. **20**, 304 (2000); e) G. H. Posner, Chem. Rev. **86**, 831 (1986); f) R. W. Armstrong, A. P. Combs, P. A. Tempest, S. D. Brown, T. A. Keating, Acc. Chem. Res. **29**, 123 (1996).

[2] a) H. Neumann, A. Jacobi von Wangelin, D. Gördes, A. Spannenberg, M. Beller, J. Am. Chem. Soc. **123**, 8398 (2001); b) A. Jacobi von Wangelin, H. Neumann, D. Gördes, A. Spannenberg, M. Beller, Org. Lett. **3**, 2895 (2001); c) H. Neumann, A. Jacobi von Wangelin, D. Gördes, A. Spannenberg, W. Baumann, M. Beller, Tetrahedron **58**, 2381 (2002); d) A. Jacobi von Wangelin, H. Neumann, D. Gördes, S. Klaus, H. Jiao, A. Spannenberg, M. Beller, T. Krüger, C. Wendler, K. Thurow, N. Stoll, Chem. Eur. J. **9**, 2273 (2003); e) A. Jacobi von Wangelin, H. Neumann, D. Gördes, S. Klaus, D. Strübing, M. Beller, Chem. Eur. J. **9**, 4286 (2003); f) D. Strübing, H. Neumann, A. Jacobi von Wangelin, D. Gördes, M. Beller, P. Braiuca, C. Ebert, L. Gardossi, U. Kragl, Tetrahedron **60**, 683 (2004).

[3] a) J. Janey, T. Iwama, S. Kozmin, V. H. Rawal, J. Org. Chem. **65**, 9059 (2000); b) M. B. Smith, Org. Prep. Proced. Int. **22**, 315 (1990); c) L. E. Overman, R. L. Freerks, C. B. Petty, L. A. Clizbe, R. K. Ono, G. F. Taylor, P. J. Jessup, J. Am. Chem. Soc. **103**, 2816 (1981); d) W. Oppolzer, L. Bieber, E. Francotte, Tetrahedron Lett. **16**, 4537 (1979).

[4] H. Neumann, A. Jacobi von Wangelin, S. Klaus, D. Strübing, D. Gördes, M. Beller, Angew. Chem. Int. Ed. **42**, 4503 (2003).
[5] H. O. Albrecht, Z. Phys. Chem. **136**, 321 (1928).
[6] a) K. D. Gundermann, Chimia **25**, 261 (1971); b) For a review of hydrazide chemiluminescene see: E. H. White, D. F. Roswell, Acc. Chem. Res. **3**, 54 (1979).
[7] D. Bostick, D. Hercules, Anal. Chem. **47**, 447 (1975).
[8] D. Pilosof, T. Nieman, Anal. Chem. **54**, 1698 (1982).
[9] J. Yuan, A. Shiller, Anal. Chem. **71**, 1975 (1999).
[10] H. D. K. Drew, F. H. Pearman, J. Chem. Soc. (London) 1841 (1937).
[11] E. H. White, M. M. Bursey, J. Org. Chem. **31**, 1912 (1966).
[12] a) R. B. Brundrett, E. H. White, J. Am. Chem. Soc. **96**, 7497 (1974); b) R. B. Brundrett, D. F. Roswell, E. H. White, J. Am. Chem. Soc. **94**, 7536 (1972).
[13] K.-D. Gundermann, M. Drawert, Chem. Ber. **95**, 2018 (1962).
[14] In case of phenylacetaldehyde increased yields in the AAD reaction were observed when toluene was used as solvent.
[15] In case of 3-methylbenzo[*b*]thiophene-2-carboxaldehyde 1 equiv. Ac_2O was added to the reaction mixture to yield **1f**.
[16] L. R. Caswell, G. Cavasos, J. Heterocycl. Chem. **32**, 907 (1995).
[17] When **2d** was employed, we obtained the isomer **4d** as main product. Increasing the reaction time to 60 hours the desired **3d** was obtained.