Second Generation Protocol for Multicomponent Coupling Reactions of Aldehydes, Amides and Dienophiles

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Dedicated to Prof. Dr. J. Bargon on the occasion of his 65th birthday.

Abstract: An improved one-pot procedure for the three-component coupling reaction of aldehydes, amides and dienophiles (AAD reaction) has been developed. Compared to known protocols for this type of reaction, the use of aromatic solvents in the presence of dehydrating reagents allows an efficient synthesis of previously not accessible products. Condensation of ubiquitous available aldehydes and amides and subsequent Diels–Alder reactions with dienophiles furnishes *endo*-selective amino-functionalized hexahydroisoindole-1,3-dione and tetrahydrophthalic acid derivatives in good yield.

Keywords: aldehydes; aldol reaction; Diels–Alder reaction; enamides; multicomponent coupling reactions; *N*-dienyl amides

Introduction

The ideal chemical transformation from A to B should proceed with inexpensive, easily available reagents, in standard equipment to give the desired product B at a fast rate in quantitative yield and 100% atom-economy. By comparing the various synthetic possibilities for more complicated products, the number of reaction steps is one of the most important indicators for the attractiveness and practicability of a given synthetic route. Obviously, the number of reaction and purification steps should be as low as possible. In this regard, domino[1] and multicomponent reactions (MCRs)[2] are of considerable interest owing to their high synthetic efficiency (Figure 1). Unlike the stepwise formation of individual bonds in the target molecule, the advantageous attribute of MCRs (or domino reactions) is the inherent formation of several bonds in one operation without isolating the intermediates, changing the reaction conditions, or adding any further reagents. Since the obtained product carries portions of all employed reactants in its structure, MCRs can result in a marked increase in molecular complexity and diversity.

Upon wider variation of the starting materials, opportunities also arise for the easier synthesis of compound libraries. Thus, in recent years, research in academia and industry has increasingly emphasized the use of MCRs as well as domino reaction sequences for various products.[3] For some time we have been especially interested in the development of transition metal-catalyzed three- and four-component coupling reactions. Examples include the hydroaminomethylation of olefins,[4] and the amidocarbonylation of aldehydes.[5] Based on the latter work[6] we discovered a new multicomponent methodology in which *a*mides and *a*ldehydes react with *di*enophiles (AAD reaction) to give a large variety of carbo- and heterocyclic amides in unprecedented efficiency (Scheme 1).[7]

The underlying mechanism of the AAD reaction involves 1-(*N*-acylamino)-1,3-butadienes as key intermediates. In the past several groups have elegantly demonstrated the synthetic versatility of isolated 1-acylamino-1,3-dienes for Diels–Alder chemistry.[8] Here, prominent examples include the total syntheses of pumiliotoxin C,[9] gephyrotoxin,[10] dendrobine,[11] and tabersonine.[12] More recently, we have been able to demon-

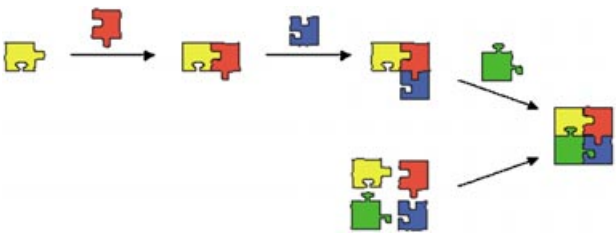

Figure 1. Schematic representation of multi-step *vs.* multicomponent assembly.

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strate the synthetic power of *in situ*-generated 1-amido-1,3-dienes for the synthesis of highly substituted anilines[13] and luminol derivatives.[14]

Here, we report an improved protocol for the multicomponent coupling reaction of aldehydes or α,β-unsaturated aldehydes with various amides and reactive dienophiles providing an easy synthesis of 1-acylamino-2-cyclohexene derivatives, which were previously not accessible or only accessible in lower yield by the method.

Results and Discussion

Based on the history of the discovery of the AAD-MCR,[15] so far all successful reactions were carried out in dipolar aprotic solvents, typically NMP. Despite the general applicability of these conditions, sometimes purification of the desired product is troublesome. In addition, sterically more hindered amides reacted only sluggishly or not at all. By studying the condensation of amides with sensitive arylacetaldehydes more carefully, we observed that the presence of toluene or xylene dramatically improves the yield of the corresponding MCR product. As an example the reaction of phenylacetaldehyde, *O*-methyl carbamate, and *N*-methylmaleimide is shown in Figure 2.

The reaction in NMP, with or without the addition of acetic anhydride, gave the MCR product only in very low yields ($<5\%$). To our surprise similar reactions in toluene gave the 4-*N*-carbamoyl-3a,4,7,7a–hexahydroisoindole-1,3-dione derivative in 86–94% yield! Apparently, due to the better stabilization of polar intermediates in NMP, the reaction stopped at the state of the *N*-carbamoylstyrene, and almost no formation of the desired *N*-carbamoyl-1,3-diene took place. In the less polar solvent toluene this inhibiting effect was not observed. To our delight, for larger scale reactions, it was also possible to use toluene together with a simple Dean–Stark apparatus to obtain the target compound in 70% yield. This opens up an easy possibility to obtain the corresponding product on a multi-100 g-scale in an easy and practical manner.

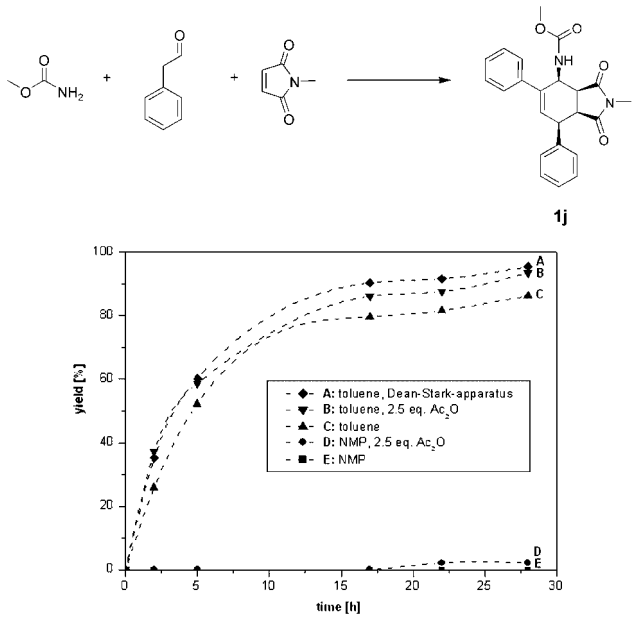
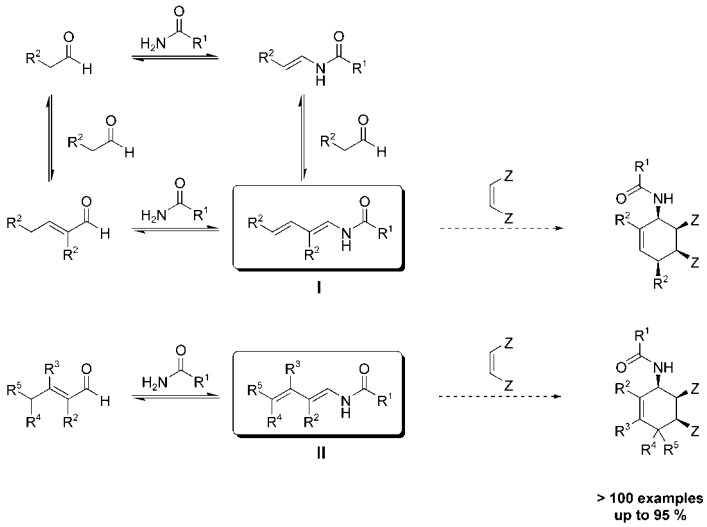


Figure 2. AAD reaction of phenylacetaldehyde, *O*-methyl carbamate and *N*-methyl maleimide. Reaction conditions **A**: *O*-methyl carbamate (5 mmol), phenylacetaldehyde (3 equivs.), *N*-methylmaleimide (1.5 equivs.), *p*-TSA (2 mol %), 110 °C, toluene (25 mL). Reaction conditions **B, C, D, E**: *O*-methyl carbamate (2 mmol), phenylacetaldehyde (2 equivs.), *N*-methylmaleimide (1.5 equivs.), *p*-TSA (2 mol %), 110 °C, solvent (10 mL). Yields by GC. Curves fitted spline.

Next, we set out to extend the novel protocol to other starting materials. Therefore, different amide derivatives were reacted with aliphatic aldehydes or α,β-unsaturated aldehydes in the presence of a dienophile providing a series of 1-acylamino-2-cyclohexene derivatives. With regard to the dienophile we focused on the synthesis of hexahydroisoindole-1,3-dione derivatives or tetrahydrophthalic acid derivatives by employing maleimides and maleic acid anhydride as truly powerful dienophiles. For a number of reactions the use of NMP (first generation protocol) and toluene (second generation protocol) as solvent was compared under optimized conditions, respectively. As shown in Table 1 in all cases studied, the new protocol gave a significantly higher yield compared to our previous procedure. For example, aliphatic and aromatic amides, sulfonamides, cyclic carbamates react well (61–85% yield) with α,β-unsaturated aldehydes and *N*-methylmaleimide (entries 1–4, 6–8). Also aliphatic aldehydes furnish the corresponding product in moderate to good yield (40–70% yield; entries 5, 9–11). Due to solubility problems when employ-



Scheme 1. The AAD reaction.

ing 2,5-dihydroxybenzamide it was necessary to use a solvent mixture of toluene and NMP (7:2). Again this mixture gave significantly better product yields than employment of pure NMP. Especially noteworthy are the reactions of sensitive substrates such as maleic acid anhydride (entries 12 and 13), which were not possible previously due to subsequent imide formation of the cyclic anhydride. Apart from toluene similar reactions were performed using xylene. Here, also the beneficial effect of the aromatic solvent is observed.

For all products one- and two-dimensional NMR experiments unambiguously established the stereochemical structure. As with our previously reported multicomponent coupling reactions, we observe the selective *endo* addition of the dienophile during the Diels–Alder step. Thus, analyses of the ^{1}H-^{1}H coupling constants of the amide moiety as well as of the alkyl substituents on the cyclohexene ring revealed the exclusive formation of the all-*syn* products. This results in bowl- or crown-shaped cyclohexenes with all substituents on one side of the ring.

Conclusion

Here, we have presented an improved multicomponent reaction of aldehydes, amides and dienophiles, which features the domino formation of three carbon-carbon bonds and one carbon-nitrogen bond. Using toluene as solvent and acetic acid anhydride or a Dean–Stark apparatus for water removal significantly improved product yields were obtained compared to our previous protocol. Although up to four stereogenic centers are created, only one diastereomer is formed selectively. The described methodology constitutes the most simple and direct high-yield approach to a variety of amido-functionalized hexahydroisoindole-1,3-dione and tetrahydrophthalic acid derivatives. With regard to practicability it is interesting to note that the ubiquitous, off-shelf starting materials readily react even without special exclusion of air or water.

Experimental Section

General

All reactions were run in ACE pressure tubes from Aldrich. Unless otherwise noted, all reagents were used as received from commercial suppliers. Silica gel column chromatography was performed with 230–400 mesh ASTM silica gel from Merck. Melting points were recorded on a Galen III (Cambridge Instruments) and are uncorrected. IR spectra of solids were recorded as nujol mulls using KBr plates or KBr pellets on a Nicolet Magna 550, liquids were analyzed as capillary films. MS were obtained on an AMD 402/3 from AMD Intectra (EI, 70 eV). NMR data were recorded on a Bruker ARX 400 with QNP probe head (^{1}H, 400.13 MHz; ^{13}C, 100.61 MHz) at 25 °C. GC analyses were performed on an HP 6890 equipped with a HP-5 capillary column (5% phenylmethylsiloxane, L = 30 m, d = 250 μm, d_{film} = 0.25 μm) and an FID detector. Quantitative GC analyses were referenced to internal hexadecane or dodecane.

Procedure A (α,β-Unsaturated Aldehydes)

Amide (5 mmol), dienophile (7.5 mmol), and *p*-toluenesulfonic acid monohydrate (2 mol %) were combined in a threaded tube, and toluene (20 mL), aldehyde (5 mmol), and acetic anhydride (5 mmol) were added. Then, the reaction mixture was stirred at 110 °C for 16 to 24 h. After cooling, all volatile compounds were removed under reduced pressure. Silica gel flash chromatography (*n*-heptane/EtOAc) afforded the corresponding products. For reaction times, see paragraph pertinent to the corresponding product.

Procedure B (2,5-Dihydroxybenzamide Derivatives)

Amide (5 mmol), dienophile (7.5 mmol), and *p*-toluenesulfonic acid monohydrate (2 mol %) were combined in a threaded tube, and toluene/NMP (9 mL, 7/2) and aldehyde (5 mmol) were added. Then, the reaction mixture was stirred at 120 °C for 18 h. After cooling, all volatile compounds were removed under reduced pressure. Silica gel flash chromatography (*n*-heptane/EtOAc) afforded the corresponding products. For purification reasons, compounds **1f** and **1g** were subsequently recrystallized from ethanol and toluene/ethanol, respectively.

Procedure C (Saturated Aldehydes)

Amide (3 mmol), dienophile (6 mmol), and *p*-toluenesulfonic acid monohydrate (2 mol %) were combined in a threaded tube, and toluene (14 mL), aldehyde (6 mmol), and acetic anhydride (3 mmol) were added. Then, the reaction mixture was stirred at 120 °C for 24 h. After cooling, all volatile compounds were removed under reduced pressure. Silica gel flash chromatography (*n*-heptane/EtOAc) afforded the corresponding products.

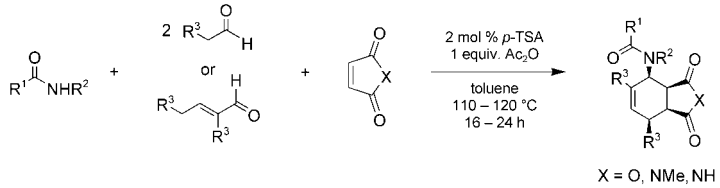
Procedure D (Dean–Stark Apparatus)

In a 250 mL two-necked, round-bottom flask *O*-methyl carbamate (1.9 g, 25 mmol), phenylacetaldehyde (5.9 mL, 50 mmol), *N*-methylmaleimide (2.8 g, 25 mmol), and *p*-toluenesulfonic acid monohydrate (95 mg, 0.5 mmol, 2 mol %) in toluene (125 mL) were refluxed on a Dean–Stark apparatus for 24 h. Then, all volatile compounds were removed under reduced pressure. Silica gel flash chromatography (*n*-heptane/EtOAc) afforded the corresponding product.

N-Ethyl-*N*-(2-methyl-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1*H*-isoindol-4-yl)-acetamide (1a)

Procedure A. 24 h; R_f (SiO_2, *n*-heptane/EtOAc, 1/4) = 0.13; yield: 69%; colorless solid; mp 94–96 °C; ^{1}H NMR

Table 1. Second generation AAD-MCR.



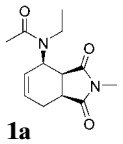
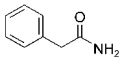
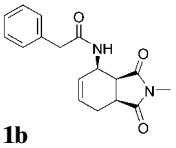
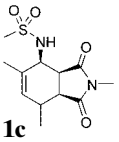
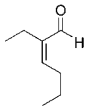
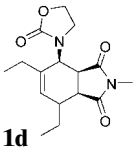
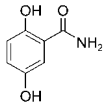
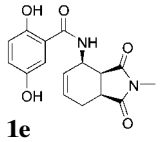
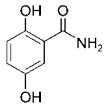
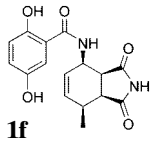
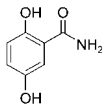
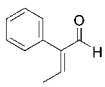
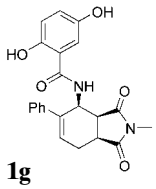
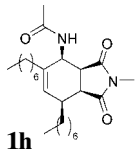
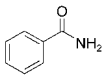
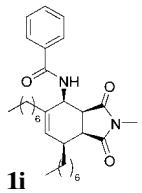
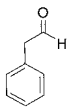
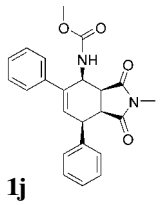
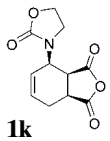
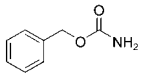
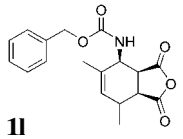
Entry	Amide	Aldehyde	Dienophile	MCR product	Second generation yield [%]	First generation yield [%]
1				 **1a**	69[a]	0
2				 **1b**	72[a]	58
3				 **1c**	88[a]	nd
4				 **1d**	73[a]	nd
5					40[c]	27
6				 **1e**	70[b]	14
7				 **1f**	61[b]	16
8				 **1g**	51[b]	nd

Table 1 (cont.)

Entry	Amide	Aldehyde	Dienophile	MCR product	Second generation yield [%]	First generation yield [%]
9				 **1h**	66[c]	nd
10				 **1i**	70[c]	nd
11				 **1j**	70[d]	5
12				 **1k**	76[a]	nd
13				 **1l**	72[16]	0

Reaction conditions:
[a] Amide (5 mmol), aldehyde (5 mmol), dienophile (7.5 mmol), toluene (20 mL), Ac_2O (5 mmol), *p*-TSA (2 mol %), 16–24 h, 110 °C.
[b] Amide (5 mmol), aldehyde (5 mmol), dienophile (7.5 mmol), toluene/NMP (9 mL, 7/2), *p*-TSA (2 mol %), 18 h, 120 °C. NMP was added for better solubility of the amide. Reaction was carried out without addition of Ac_2O.
[c] Amide (3 mmol), aldehyde (6 mmol), dienophile (6 mmol), toluene (14 mL), Ac_2O (3 mmol), *p*-TSA (2 mol %), 24 h, 120 °C.
[d] Dean–Stark-apparatus, amide (25 mmol), dienophile (50 mmol), toluene (125 mL), *p*-TSA (2 mol %), 24 h, 110 °C (reflux).

(400 MHz, $CDCl_3$): δ = 6.01–5.87 (m, 2H, NCHC*H*=C*H*), 4.92 (m, 1H, NC*H*), 3.61 (t*, *J* = 8.7 Hz, *J* = 8.3 Hz, 1H, NCHC*H*), 3.58–3.46 (m, 1H, NCHCHC*H*), 3.15–3.03 (m, 1H, NCH_2 CH_3), 2.90 (s, 3H, NCH_3), 2.84–2.76 (m, 1H of CH_2CH), 2.18 (s, 3H, CH_3CO), 2.20–2.12 (m, 1H of CH_2CH), 1.24 (t, *J* = 7.1 Hz, 3H, NCH_2CH_3); $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ = 179.5, 177.2 and 171.4 (3*C*O), 128.2 and 127.0 (*C*=*C*), 51.5, 41.1 and 38.8 (3*C*H), 42.5 (NCH_2CH_3), 23.1 (CH_2CH), 24.9, 21.9 and 16.4 (3CH_3); IR (KBr): 1/λ = 3046 (w), 2979 (w), 2948 (w), 2923 (w), 1773 (m), 1692 (s), 1648 (s), 1478 (m), 1430 (s), 1384 (m), 1356 (m), 1328 (m), 1282 (s), 1212 (m), 1188 (m), 1122 (m), 1084 (m), 1053 (w), 1032 (w), 1003 (m), 948 (m), 892 (w), 858 (w), 822 (w), 784 (m), 754 (w), 701 (m), 671 (m), 619 (w), 583 (m), 562 (m), 498 (m), 449 (m)

cm^{-1}; MS (EI, 70 eV): *m/z* (%) = 250 (9) [M]$^+$, 207 (100) [M – Ac]$^+$, 139 (20), 122 (19), 97 (55), 94 (14), 88 (10), 86 (12), 82 (40), 79 (29), 78 (17), 77 (24), 68 (14), 44 (22), 43 (52) [Ac], no other peaks > 10%; HR-MS (EI): calcd. for $C_{13}H_{18}N_2O_3$: 250.13174; found: 250.13109 [M]$^+$.

N-(2-Methyl-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1*H*-isoindol-4-yl)-2-phenylacetamide (1b)

Procedure A. 16 h; R_f (SiO_2, *n*-heptane/EtOAc, 1/1) = 0.32; yield: 72%; colorless solid; mp 196 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.34 (d, *J* = 7.7 Hz, 1H, N*H*), 7.36–7.15 (m, 5H, *Ph*), 5.86 (m, 1H, NHCHC*H*=CH), 5.74 (m, 1H, NHCHCH=C*H*), 4.44 (m, 1H, NHC*H*), 3.51 (m, 2H, PhCH_2), 3.34 (m, 1H, NCHC*H*CO), 3.17 (m, 1H, NHCHCHC*H*CO), 2.76 (s, 3H, NCH_3), 2.47 and 2.16 (both m, both 1H, CHCH_2CH=CH); ^{13}C{^{1}H} NMR (100.6 MHz, DMSO-d_6): δ = 179.6 and 177.3 (*C*O), 169.9 (CH$_2$*C*ON), 136.3 (*i-C*) 130.9 and 129.2 (2*m-C*H and 2*o-C*H), 128.2 (*p-C*H), 129.7 and 126.4 (NHCH*C*H=*C*H), 45.3 (NH*C*H), 42.3 (Ph*C*H$_2$), 42.0 (NHCH*C*HCO), 38.5 (NHCHCH*C*HCO), 24.4 (N*C*H$_3$), 23.4 (CH*C*H$_2$CH=CH); MS (EI, 70 eV): *m/z* (%) = 298 (9) [M]$^+$, 207 (7), 179 (100) [M – PhAc]$^+$, 164 (40), 91 (67) [PhAc]$^+$, 79 (56), 69 (21), no other peaks > 10%; IR (KBr): 1/λ = 3297 (s), 3075 (m), 3029 (w), 2941 (w), 1773 (m), 1699 (s) cm^{-1}; HR-MS (EI): calcd. for $C_{17}H_{18}N_2O_3$: 298.13174; found: 298.13156 [M]$^+$.

N-(2,5,7-Trimethyl-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1*H*-isoindol-4-yl)-methansulfonamide (1c)

Procedure A. 16 h; R_f (SiO_2, *n*-heptane/EtOAc, 1/1) = 0.14; yield: 88%; colorless solid; mp 122–125 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 6.75 (d, *J* = 8.9 Hz, 1H, N*H*), 5.32 (m, 1H, NHCHC=C*H*), 4.13 (m, 1H, NHC*H*), 3.36 (dd, *J* = 5.9 Hz, *J* = 2.4 Hz, 1H, NHCHC*H*CO), 3.24 (m, 1H, NHCHCHC*H*CO), 3.10 (s, 3H, CH_3SO$_2$), 2.76 (s, 3H, NCH_3), 2.49 (m, 1H, CH$_3$C*H*), 1.68 (s, 3H, CH_3C=CH), 1.25 (d, *J* = 7.1 Hz, 3H, CH_3CH); ^{13}C{^{1}H} NMR (100.6 MHz, DMSO-d_6): δ = 178.6 and 177.0 (2*C*O), 137.5 (NHCH*C*=CH), 127.0 NHCHC=*C*H), 51.6 (NH*C*H), 45.0 (NHCH*C*HCO), 44.2 (NHCHCH*C*HCO), 40.6 (*C*H$_3$SO$_2$), 29.4 (CH$_3$*C*H), 24.3 (N*C*H$_3$), 18.9 (*C*H$_3$C=CH), 16.7 (*C*H$_3$CH); IR (KBr): 1/λ = 3439 (m), 3318 (s), 3024 (m), 2968 (m), 2943 (m), 1765 (s), 1696 (s) cm^{-1}; MS (EI, 70 eV): *m/z* (%) = 286 (2) [M]$^+$, 271 (1) [M – CH$_3$]$^+$, 207 (78), 191 (13) [M – CH$_3$SO$_2$]$^+$, 175 (46), 122 (23), 106 (34), 96 (100) [CH$_3$SO$_2$NH]$^+$, 91 (18), 79 (27), 43 (75), 28 (35), no other peaks > 10%; HR-MS: calcd. for $C_{12}H_{18}N_2O_4S$: 286.09873; found: 286.09886 [M]$^+$.

5,7-Diethyl-2-methyl-4-(2-oxooxazolidin-3-yl)-3a,4,7,7a-tetrahydroisoindole-1,3-dione (1d)

Procedure A. 24 h; R_f (SiO_2, *n*-heptane/EtOAc, 1/2) = 0.15; yield: 73%; colorless solid; mp 131–132 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 5.46–5.41 (m, 1H, NCHC=C*H*), 4.44 (d, *J* = 6.0 Hz, 1H, NC*H*), 4.31–4.22 (m, 2H, CH_2), 3.78 (td*, *J* = 8.8 Hz, *J* = 6.9 Hz, 1H of CH_2), 3.62 (td*, *J* = 8.8 Hz, *J* = 6.9 Hz, 1H of CH_2), 3.53 (dd, *J* = 8.1 Hz, *J* = 6.5 Hz, 1H, NCHC*H*CO), 3.25 (t*, *J* = 8.1 Hz, 1H, NCHCHC*H*CO), 2.73 (s, 3H, NCH_3), 2.31–2.22 (m, 1H, NCHC=CHC*H*), 2.00–1.91 (m, 2H, CH$_3$CH_2), 1.81–1.70 (m, 1H of CH$_3$CH_2), 1.47–1.36 (m, 1H of CH$_3$CH_2), 0.98 (t, *J* = 7.3 Hz, 3H, CH_3CH$_2$), 0.83 (t, *J* = 7.3 Hz, 3H, CH_3CH$_2$); ^{13}C{^{1}H} NMR (100.6 MHz, DMSO-d_6): δ = 176.9 (*C*O), 176.8 (*C*O), 158.5 (N*C*OO), 140.7 (NCH*C*=CH), 124.4 (NCHC=C*H*), 62.1 (*C*H$_2$), 51.2 (N*C*H), 44.9 (*C*H$_2$), 43.3 (NCH*C*HCO), 42.5 (NCHCH*C*HCO), 36.2 (NCHC=CH*C*H), 24.5 (CH$_3$*C*H$_2$), 24.3 (CH$_3$*C*H$_2$), 24.2 (N*C*H$_3$), 12.5 (*C*H$_3$CH$_2$), 11.5 (*C*H$_3$CH$_2$); IR (nujol): 1/λ = 3441 (m), 1769 (m), 1734 (m), 1699 (s), 1653 (m), 1559 (w), 1540 (w), 1336 (w), 1321 (w), 1273 (w), 1201 (w), 1118 (w), 1095 (m), 1068 (m), 1042 (m), 1026 (m), 976 (w), 955 (w), 910 (w), 846 (w), 815 (w), 767 (m), 748 (w), 724 (w), 691 (w), 675 (m), 636 (m), 609 (w), 574 (m) cm^{-1}; MS (EI, 70 eV): *m/z* (%) = 306 (84) [M]$^+$, 277 (47) [M – C$_2$H$_5$]$^+$, 263 (6), 247 (24), 233 (33), 219 (100) [M – C$_2$H$_5$NO$_2$]$^+$, 205 (20), 195 (48), 190 (31), 166 (10), 162 (15), 151 (44), 134 (83), 122 (33), 105 (82), 93 (34), 88 (53), 79 (41), 56 (20), 42 (16), 29 (13), no other peaks > 10%; HR-MS (EI): calcd. for $C_{16}H_{22}N_2O_4$: 306.15796; found: 306.15787 [M]$^+$.

2,5-Dihydroxy-*N*-(2-methyl-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1*H*-isoindol-4-yl)-benzamide (1e)

Procedure B. R_f (SiO_2, *n*-heptane/EtOAc, 1/1) = 0.15; yield: 70%; colorless solid; mp 226–229 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.01 (s, 1H, O*H*), 9.31 (d, *J* = 7.9 Hz, 1H, N*H*), 8.95 (s, 1H, O*H*), 7.28 (d, *J* = 3.0 Hz, 1H, *o*-C*H*), 6.78 (dd, *J* = 8.7 Hz, *J* = 3.0 Hz, 1H, *p*-C*H*), 6.70 (d, *J* = 8.7 Hz, 1H, *m*-C*H*), 5.86–5.75 (m, 2H, NHCHC*H*=C*H*), 4.66 (m, 1H, NHC*H*), 3.39 (dd, *J* = 8.7 Hz, *J* = 6.9 Hz, 1H, NHCHC*H*CO), 3.19 (m, 1H, NHCHCHC*H*CO), 2.74 (s, 3H, NCH_3), 2.49–2.41 (m, 1H of NCHC=CHCH_2), 2.24–2.14 (m, 1H of NCHC=CHCH_2); ^{13}C{^{1}H} NMR (100.6 MHz, DMSO-d_6): δ = 179.6 (*C*O), 178.1 (*C*O), 166.5 (*C*O), 150.8 and 149.5 (*o-C*OH and *m-C*OH), 117.1 (*i-C*), 132.3 and 127.3 (*C*H=*C*H), 120.9 (*p-C*H), 117.6 (*m-C*H), 114.7 (*o-C*H), 45.4 (NH*C*H), 42.4 (NHCH*C*HCO), 38.6 (NHCHCH*C*HCO), 24.5 (N*C*H$_3$), 23.5 (NCHC=CH*C*H$_2$); IR (KBr): 1/λ = 3217 (br, m), 2950 (w), 1772 (w), 1684 (s), 1619 (s), 1585 (m), 1538 (s), 1502 (s), 1447 (m), 1390 (m), 1330 (m), 1294 (m), 1217 (m), 1187 (m), 1138 (w), 100 (w), 1044 (w), 1005 (w), 819 (w), 778 (w), 697 (w), 660 (w), 586 (w), 555 (w) cm^{-1}; MS (EI, 70 eV): *m/z* (%) = 316 (49) [M]$^+$, 179 (47) [M – 2,5-dihydroxybenzoyl]$^+$, 164 (14) [M – 2,5-dihydroxybenzamide]$^+$, 153 (59), 136 (100), 108 (10), 94 (21), 81 (16), 79 (58), 77 (17), 69 (20), 58 (9), 53 (14), no other peaks > 10%; HR-MS (EI): calcd. for $C_{16}H_{16}N_2O_5$: 316.10593; found: 316.10461 [M]$^+$.

2,5-Dihydroxy-*N*-(2,7-dimethyl-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1*H*-isoindol-4-yl)-benzamide (1f)

Procedure B. R_f (SiO_2, *n*-heptane/EtOAc, 1/1) = 0.20; crystallized from toluene/ethanol; yield: 61%; colorless solid; mp 209 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.06 (s, 1H, O*H*), 9.41 (d, *J* = 7.7 Hz, 1H, N*H*), 9.00 (s, 1H, O*H*), 7.33 (d, *J* = 3.0 Hz, 1H, *o*-C*H*), 6.83 (dd, *J* = 8.7 Hz, *J* = 3.0 Hz, 1H, *p*-C*H*), 6.75 (d, *J* = 8.7 Hz, 1H, *m*-C*H*), 5.85–5.78 (m, 1H, NHCHC*H*=CH), 5.69–5.63 (m, 1H, NHCHCH=C*H*), 4.69

(m, 1H, NHC*H*), 3.42 (dd, $J=9.0$ Hz, $J=8.3$ Hz, 1H, NHCHC*H*CO), 3.14 (t*, $J=7.3$ Hz, 1H, NHCHCHC*H*CO), 2.76 (s, 3H, NCH_3), 2.53 (m, 1H, CH_3CH), 1.33 (d, $J=7.3$ Hz, 1H, CH_3CH); $^{13}C\{^1H\}$ NMR (100.6 MHz, DMSO-d_6): $\delta=$ 177.8 (*C*O), 177.2 (*C*O), 166.4 (*C*O), 150.8 and 149.5 (*o*-*C*OH and *m*-*C*OH), 117.1 (*i*-*C*), 133.7 and 131.4 (*C*H=*C*H), 120.8 (*p*-*C*H), 117.6 (*m*-*C*H), 114.7 (*o*-*C*H), 45.9 (NH*C*H), 43.6 (NHCHCH*C*HCO), 43.3 (NHCH*C*HCO), 29.8 (CH_3CH), 24.3 (NCH_3), 16.7 (CH_3CH); IR (KBr): $1/\lambda=3397$ (br, m), 2934 (w), 1768 (w), 1682 (s), 1601 (w), 1528 (m), 1487 (m), 1442 (m), 1387 (w), 1337 (m), 1292 (m), 1234 (w), 1205 (w), 1110 (w), 1021 (w), 980 (w), 832 (w), 788 (m), 713 (w), 670 (w) cm^{-1}; MS (EI, 70 eV): *m/z* (%) = 330 (67) $[M]^+$, 193 (66) $[M-2,5$-dihydroxybenzoyl$]^+$, 178 (13) $[M-2,5$-dihydroxybenzamide$]^+$, 153 (66), 136 (100), 112 (8), 108 (31), 93 (72), 83 (31), 82 (19), 81 (23), 80 (10), 79 (6), 77 (18), 69 (8), 65 (5), 58 (7), 55 (8), 54 (5), 53 (18), 52 (11), 51 (5), no other peaks > 10%; HR-MS (EI): calcd. for $C_{17}H_{18}N_2O_5$: 316.10592; found: 316.10461 $[M]^+$.

2,5-Dihydroxy-*N*-(2-methyl-1,3-dioxo-5-phenyl-2,3,3a,4,7,7a-hexahydro-1*H*-isoindol-4-yl)-benzamide (1g)

Procedure B. R_f (SiO_2, *n*-heptane/EtOAc, 1/1) = 0.20; crystallized from ethanol; yield: 51%; colorless crystals; mp 163–165 °C; ^1H NMR (400 MHz, DMSO-d_6): $\delta=10.63$ (s, 1H, O*H*), 9.15 (d, $J=9.1$ Hz, 1H, N*H*), 8.95 (s, 1H, O*H*), 7.26–7.19 (m, 5H, Ph), 7.18 (d, $J=2.8$ Hz, 1H, *o*-C*H*), 6.73 (dd, $J=$ 3.0 Hz, $J=8.8$ Hz, 1H, *p*-C*H*), 6.69 (d, $J=8.7$ Hz, 1H, *m*-C*H*), 6.07 (m, 1H, NHCHC=C*H*), 5.38 (m, 1H, NHC*H*), 3.48–3.39 (m, 1H, NHCHC*H*CO), 3.38–3.31 (m, 1H, NHCHCHC*H*CO), 2.80 (s, 3H, NCH_3), 2.64–2.57 (m, 2H, NHCHC=CHCH_2). $^{13}C\{^1H\}$ NMR (100.6 MHz, DMSO-d_6): $\delta=179.6$ (*C*O), 178.1 (*C*O), 164.9 (*C*O), 149.7 and 149.4 (*m*-*C*OH and *o*-*C*OH) 142.3 (NHCH*C*=CH), 138.3 (*i*-*C*), 138.0 (*i*-*C*), 128.0 and 127.2 (*m*-*C*H and *o*-*C*H) and 126.7 (*p*-*C*H), 125.3 (NHCHC=*C*H), 120.3 (*p*-*C*H), 117.5 (*m*-*C*H), 115.4 (*o*-*C*H), 46.1 (NH*C*H), 44.4 (NHCH*C*HCO), 38.0 (NHCHCH*C*HCO), 24.4 (NCH_3), 23.6 (NHCHC=CHCH_2); IR (KBr): $1/\lambda=3398$ (m), 2974 (w), 1774 (w), 1688 (s), 1649 (w), 1596 (m), 1536 (s), 1444 (s), 1366 (m), 1331 (w), 1286 (m), 1244 (m), 1138 (w), 1080 (w), 1046 (w), 1010 (w), 837 (w), 787 (m), 762 (m), 700 (w), 671 (w), 580 (w), 561 (w) cm^{-1}; MS (EI, 70 eV): *m/z* (%) = 392 (29) $[M]^+$, 255 (100) $[M-2,5$-dihydroxybenzoyl$]^+$, 239 (11) $[M-2,5$-dihydroxybenzamide$]^+$, 170 (22), 153 (77), 136 (43), 128 (6), 115 (9), 109 (8), 81 (14), 77 (14), 53 (10), no other peaks > 10%; HR-MS (EI): calcd. for $C_{22}H_{20}N_2O_5$: 392.13721; found: 392.13479 $[M]^+$.

N-(5,7-Diheptyl-2-methyl-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1*H*-isoindol-4-yl)-acetamide (1h)

Procedure C. R_f (SiO_2, *n*-heptane/EtOAc, 1/1) = 0.19; yield: 66%; colorless oil; ^1H NMR (400 MHz, DMSO-d_6): $\delta=7.67$ (d, $J=9.1$ Hz, 1H, N*H*), 5.25 (s, 1H, NHCHC=C*H*), 4.61–4.54 (m, 1H, CH, NHC*H*), 3.18–3.12 (m, 2H, COC*H*C*H*CO), 2.72 (s, 3H, NCH_3), 2.26–2.17 (m, 1H, CH, NHCHC=CHC*H*), 1.97 (s, 3H, CH_3CO), 1.87–1.84 (m, 2H, CH_2), 1.80–1.71 (m, 1H of CH_2), 1.61–1.52 (m, 1H of CH_2), 1.45–1.33 (m, 2H, CH_2), 1.32–1.06 (m, 18H, CH_2), 0.85 (t, $J=6.3$ Hz, 3H, CH_3 CH_2), 0.83 (t, $J=6.9$ Hz, 3H, CH_3CH_2); $^{13}C\{^1H\}$ NMR (100.6 MHz, DMSO-d_6): $\delta=178.7$ (*C*O), 177.2 (*C*O), 169.2 (CH_3*C*O), 141.1 (NHCH*C*=CH), 125.2 (NHCHC=*C*H), 47.7 (NH*C*H), 44.0 and 42.5 (CO*C*H*C*HCO), 35.3 (NHCHC=CH*C*H), 31.3 (*C*H_2), 31.2 (*C*H_2), 30.9 (*C*H_2), 30.8 (*C*H_2), 29.0 (*C*H_2), 28.7 (*C*H_2), 28.2 (*C*H_2), 28.4 (*C*H_2), 27.6 (*C*H_2), 27.2 (*C*H_2), 24.2 (N*C*H_3), 22.8 (CH_3*C*O), 22.1 (*C*H_2), 22.1 (*C*H_2), 14.0 (CH_3*C*H_2), 13.9 (CH_3*C*H_2); IR (capil.): $1/\lambda=$ 3396 (m), 2926 (s), 2856 (s), 1770 (m), 1694 (s), 1514 (s), 1437 (s), 1385 (m), 1336 (w), 1288 (m), 1126 (w), 1010 (w), 776 (w), 723 (w), 659 (w), 576 (w) cm^{-1}; MS (EI, 70 eV): *m/z* (%) = 418 (20) $[M]^+$, 375 (100) $[M-C_2H_3O]^+$, 319 (3) $[M-C_7H_{15}]^+$, 291 (5), 191 (8), 180 (4), 91 (8), 57 (17), 43 (48) $[C_2H_3O]^+$, no other peaks > 10%; HR-MS (EI): calcd. for $C_{25}H_{42}N_2O_3$: 418.31955; found: 418.31646 $[M]^+$.

N-(5,7-Diheptyl-2-methyl-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1*H*-isoindol-4-yl)-benzamide (1i)

Procedure C. R_f (SiO_2, *n*-heptane/EtOAc, 1/1) = 0.57; yield: 70%; colorless solid; mp 54–56 °C; ^1H NMR (400 MHz, DMSO-d_6): $\delta=8.34$ (d, $J=8.5$ Hz, 1H, N*H*), 7.83–7.81 (m, 2H, Ph), 7.60–7.52 (m, 3H, Ph), 5.41–5.32 (m, 1H, NHCHC=C*H*), 4.82–4.74 (m, 1H, NHC*H*), 3.36 (dd, $J=$ 8.0 Hz, $J=6.8$ Hz, 1H, NHCHC*H*CO), 3.21 (dd, $J=8.0$ Hz, $J=6.8$ Hz, 1H, NHCHCHC*H*CO), 2.76 (s, 3H, NCH_3), 2.37–2.27 (m, 1H, NHCHC=CH−C*H*), 1.91–1.85 (m, 2H, CH_2), 1.84–1.73 (m, 1H of CH_2), 1.66–1.55 (m, 1H of CH_2), 1.48–1.37 (m, 2H, CH_2), 1.34–1.02 (m, 18H, CH_2), 0.86 (t, $J=$ 6.3 Hz, 3H, CH_3CH_2), 0.76 (t, $J=6.6$ Hz, 3H, CH_3CH_2); $^{13}C\{^1H\}$ NMR (100.6 MHz, DMSO-d_6): $\delta=179.9$ (*C*O), 177.3 (*C*O), 165.7 (Ph*C*O), 140.9 (NHCH*C*=CH), 133.9 (*i*-*C*), 131.8 and 128.8 (2*o*-*C*H and 2*m*-*C*H), 126.6 (*p*-*C*H), 125.9 (NHCHC=*C*H), 48.3 (NH*C*H), 43.8 (NHCH*C*HCO), 42.4 (NHCHCH*C*HCO), 35.3 (NHCHC=CH*C*H), 31.3 (*C*H_2), 31.1 (*C*H_2), 31.0 (*C*H_2), 30.9 (*C*H_2), 29.0 (*C*H_2), 28.7 (*C*H_2), 28.3 (*C*H_2), 28.3 (*C*H_2), 27.6 (*C*H_2), 27.5 (*C*H_2), 24.3 (N*C*H_3), 22.1 (*C*H_2), 22.0 (*C*H_2), 14.0 (CH_3*C*H_2), 13.8 (CH_3*C*H_2); IR (nujol): $1/\lambda=3397$ (m), 3091 (w), 3045 (w), 1769 (m), 1694 (s), 1602 (w), 1580 (w), 1524 (s), 1487 (m), 1346 (w), 1289 (m), 1207 (w), 1188 (w), 1150 (w), 1116 (w), 1096 (m), 1073 (w), 997 (w), 927 (w), 799 (w), 763 (w), 714 (m), 692 (m), 641 (m), 626 (w), 594 (w), 576 (w), 546 (w) cm^{-1}; MS (EI, 70 eV): *m/z* (%) = 480 (12) $[M]^+$, 375 (100) $[M-C_7H_5O]^+$, 289 (3), 191 (6), 105 (90) $[C_7H_5O^+]$, 77 (27), 57 (10), 43 (15), no other peaks > 10%; HR-MS (EI): calcd. for $C_{30}H_{44}N_2O_3$: 480.33521; found: 480.33723 $[M]^+$.

(2-Methyl-1,3-dioxo-5,7-diphenyl-2,3,3a,4,7,7a-hexahydro-1*H*-isoindol-4-yl)-carbamic Acid Methyl Ester (1j)

Procedure D. R_f (SiO_2, *n*-heptane/EtOAc, 1/1) = 0.24; yield: 70%; colorless solid; mp 188 °C; ^1H NMR (400 MHz, $CDCl_3$): $\delta=7.33-7.28$ (m, 2H, Ph), 7.27–7.18 (m, 6H, Ph), 7.05–7.01 (m, 2H, Ph), 6.26 (d, $J=9.9$ Hz, 1H, N*H*), 6.11 (t*, $J=3.4$ Hz, 1H, NHCHC=C*H*), 4.92 (m, $J=2.6$ Hz, 1H, NHC*H*), 3.81 (m, $J=2.6$ Hz, 1H, NHCHC*H*CO), 3.54 (s, 3H, OCH_3), 3.41–3.32 (m, 2H, NHCHCHC*H*CO and PhC*H*), 2.84 (s, 3H,

NCH_3); $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ = 178.3 (*C*O), 175.4 (*C*O), 156.6 (*C*OO), 144.2, 138.3 and 137.5 (2*i*-*C* and NHCH*C*=CH), 128.6, 128.3, 128.1 and 128.0 (4*m*-*C*H and 4*o*-*C*H), 127.7, 127.6 and 127.3 (2*p*-*C*H and NHCHC=*C*H), 52.3 (NH*C*H), 50.0 (OCH_3), 45.8 and 44.7 (NHCH*C*HCO and NHCHCH*C*HCO), 41.9 (Ph*C*H), 24.7 (NCH_3); IR (KBr): 1/λ = 3426 (m), 3407 (m), 3032 (w), 2952 (w), 1765 (m), 1740 (s), 1722 (s), 1690 (vs), 1599 (w), 1517 (vs), 1440 (s), 1385 (m), 1344 (m), 1327 (s), 1289 (s), 1232 (m), 1192 (m), 1192 (w), 1101 (w), 1063 (m), 1040 (w), 762 (w), 700 (w) cm^{-1}; MS (EI, 70 eV): *m/z* (%) = 390 (35) $[M]^+$, 331 (100) $[M-COOCH_3]^+$, 315 (54), 279 (21), 246 (18), 230 (80), 204 (79), 115 (24), 91 (13), 59 (16), no other peaks > 10%; HR-MS (EI): calcd. for $C_{23}H_{22}N_2O_4$: 390.15796; found: 390.15806 $[M]^+$.

4-(2-Oxooxazolidin-3-yl)-3a,4,7,7a-tetrahydroisobenzofuran-1,3-dione (1k)

Procedure A. 24 h; R_f (SiO_2, *n*-heptane/EtOAc, 1/1) = 0.09; yield: 76%; colorless solid; mp 94–96 °C; ^1H NMR (400 MHz, $CDCl_3$): δ = 6.19–6.13 (m, 1H, NCHCH=C*H*), 6.08–6.04 (m, 1H, NCHC*H*=CH), 4.64–4.60 (m, 1H, NC*H*), 4.49–4.38 (m, 2H, OCH_2), 3.90–3.86 (m, 1H, NCHC*H*CO), 3.77–3.73 (m, 2H, NCH_2), 3.52 (ddd, *J* = 9.9 Hz, *J* = 8.1 Hz, *J* = 2.0 Hz, 1H, NCHCHC*H*CO), 2.83 (ddd, *J* = 16.4 Hz, *J* = 6.5 Hz, *J* = 2.0 Hz, 1H of NCHCH=CHCH_2), 2.34–2.26 (m, 1H of NCHCH=CHCH_2); $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ = 173.4 (*C*O), 171.1 (*C*O), 158.0 (N*C*OO), 129.8 and 125.8 (NCH*C*H=*C*H), 62.8 (OCH_2), 48.7 (N*C*H), 43.0 (NCH_2), 42.9 (NCH*C*HCO), 39.1 (NCHCH*C*HCO), 23.5 (NCHCH=CH*C*H_2); IR (nujol): 1/λ = 3594 (w), 3444 (w), 1841 (m), 1777 (vs), 1748 (vs), 1532 (w), 1347 (w), 1321 (m), 1271 (s), 1209 (s), 1200 (s), 1103 (s), 1085 (m), 1051 (s), 1033 (m), 993 (s), 982 (s), 962 (m), 935 (s), 922 (m), 897 (w), 862 (w), 838 (w), 766 (s), 751 (m), 715 (m), 674 (m), 632 (w), 582 (m), 551 (s), 486 (m), 470 (w), 408 (m) cm^{-1}; MS (EI, 70 eV): *m/z* (%) = 237 (13) $[M]^+$, 209 (2), 193 (17) $[M-CO_2]^+$, 164 (35), 139 (100) $[M-C_4H_2O_3]^+$, 120 (22), 106 (14), 95 (61), 88 (26), 80 (87), 79 (78), 78 (58), 77 (58), 67 (25), 53 (37), 41 (19), 39 (33), 28 (37), no other peaks > 10%; HR-MS (EI): calcd. for $C_{11}H_{11}NO_5$: 237.06372; found: 237.06347 $[M]^+$.

(5,7-Dimethyl-1,3-dioxo-1,3,3a,4,7,7a-hexahydro-isobenzofuran-4-yl)-carbamic Acid Benzyl Ester (1l)

Procedure A.[16] 24 h; R_f (SiO_2, *n*-heptane/EtOAc, 5/1) = 0.13; yield: 72%; colorless solid; mp 179–182 °C; ^1H NMR (400 MHz, DMSO-d_6): δ = 7.44–7.25 (m, 5H, Ph), 7.20 (d, *J* = 9.3 Hz 1H, NH), 5.45 (s, 1H, C*H*=), 5.10 (s, 2H, CH_2), 4.38 (m, 1H, NHC*H*), 3.63 (dd, *J* = 6.5 Hz, *J* = 9.3 Hz, 1H, NHCHC*H*), 3.44 (dd, *J* = 7.1 Hz, *J* = 9.1 Hz, 1H, MeCHC*H*), 2.56–2.44 (m, 1H MeC*H*), 1.67 (s, 3H, *Me*C=), 1.23 (d, *J* = 7.1 Hz, 3H, *Me*CH); $^{13}C\{^1H\}$ NMR (100.6 MHz, DMSO-d_6): δ = 172.7, 172.0 and 155.9 (3 *C*O), 137.4, 136.8 (2*C*), 128.4, 127.9, 127.7, and 127,7 (*C*H arom., *C*H=), 65.8 (CH_2), 49.2, 45.8, 45.2 and 29.0 (4*C*H), 18.4 and 16.5 (2 Me); IR (KBr): 1/λ = 3375 (m), 3038 (w), 2972 (m), 2881 (w), 2853 (w), 1856 (m), 1779 (s), 1704 (s), 1540 (s), 1456 (m), 1384 (m), 1338 (m), 1317 (w), 1254 (s), 1186 (m), 1071 (m), 1021 (m), 977 (m), 923 (s), 803 (w), 775 (w), 742 (m), 693 (m), 558 (m), 528 (w), 493 (w), 466 (w) cm^{-1}; MS (EI, 70 eV): *m/z* (%) = 329 (1) $[M]^+$, 194 (19), 122 (34), 107 (16), 91 (100) $[Bn]^+$, 65 (11), no other peaks > 10%; HR-MS (EI): calcd. for $C_{18}H_{19}NO_5$: 329.12631; found: 329.12619 $[M]^+$.

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[16] Procedure A with 2 equivs. of acetic anhydride.

