Assembly of 1,3-Dihydro-2*H*-3-benzazepin-2-one Conjugates via Ugi Four-Component Reaction and Palladium-Catalyzed Hydroamidation[1]

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Abstract: The Ugi four-component reaction (U-4CR) of a number of 2-aminophenols was carried out with 2-alknylbenzaldehydes, benzyl isocyanide, and 2-chloro-5-nitrobenzoic acid in MeOH under microwave heating (MW, 80 °C, 20 min). The reaction mixture was then directly treated with aqueous K_2CO_3 (MW, 100 °C, 10 min) to promote an intramolecular nucleophilic aromatic substitution (S_NAr), resulting in the formation of highly functionalized dibenz[*b*,*f*][1,4]oxazepin-11(10*H*)-ones. The *N*-benzyl amide and arylalkynyl moieties, derived from benzyl isocyanide and 2-alkynylbenzaldehydes, allow for further assembly of 1,3-dihydro-2*H*-3-benzazepin-2-one scaffold via an intramolecular 7-*endo*-*dig* hydroamidation catalyzed by 10 mol% $Pd(PhCN)_2Cl_2$ (THF, 60 °C, 24 h, 61–74%). This new post-Ugi annulation enables an expeditious access to the C–N bond-linked conjugates of two benzannulated seven-membered-ring heterocycles.

Key words: alkynes, hydroamidation, microwaves, palladium, Ugi four-component reaction

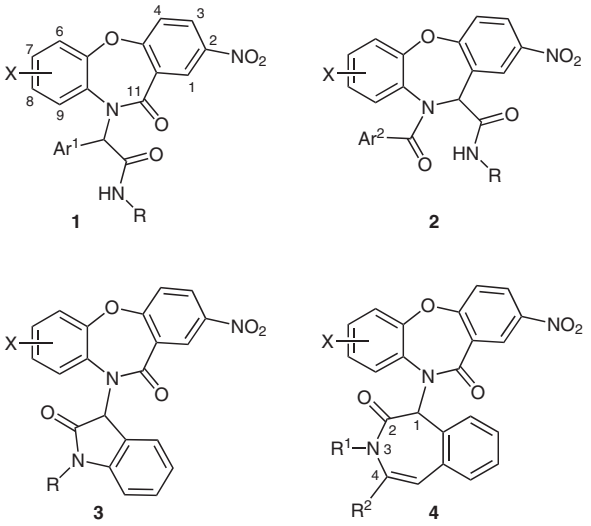

Figure 1 Structures of dibenz[*b*,*f*][1,4]oxazepin-11(10*H*)-ones (**1**), dibenz[*b*,*f*][1,4]oxazepine-11(10*H*)-carboxamides (**2**), and the C–N bond-linked conjugates **3** and **4** with 2-oxindole and 1,3-dihydro-2*H*-3-benzazepin-2-one

Alkynes are a family of organic compounds both of biological significance and diverse synthetic applications.[2,3] Under transition-metal catalysis, alkynes undergo a variety of addition reactions[4] among which the intramolecular hydroamidation (IMHAD) process has been used for the synthesis of the nitrogen-containing heterocycles.[5–7] In our previous studies on microwave-assisted generation of heterocyclic skeletal diversity starting from 2-aminophenols,[8] we have developed synthetic methodologies featuring intramolecular O-alkylation (S_N2),[9a] O-arylation (S_NAr),[9b] N-arylation (amidation),[9a–9c] and Heck reaction[9d] as the post-Ugi transformations.[10] A microwave-assisted intramolecular direct arylation catalyzed by palladium has also been established for the synthesis of novel fused hetereocycles.[11] The high efficiency of our methodologies is illustrated by the one-pot construction of the cleft scaffolds of dibenz[*b*,*f*][1,4]oxazepin-11(10*H*)-ones (**1**) and dibenz[*b*,*f*][1,4]oxazepine-11(10*H*)-carboxamides (**2**) as shown in Figure 1. Moreover, the compounds **1** (Ar^1 = 2-BrC_6H_4) could be transformed into the helical conjugates **3** with 2-oxindole by the palladium-catalyzed intramolecular amidation under controlled microwave heating.[9b] We report here on synthesis of the C–N-bond-linked conjugates **4** with 1,3-dihydro-2*H*-3-benazepin-2-one[7,12] via a novel U-4CR–S_NAr–IMHAD sequence.[13,14]

2-Aminophenols **5** are the readily available and inexpensive starting materials for our microwave-assisted synthesis of heterocyclic scaffolds.[9,11,15] In Scheme 1, we used six 2-aminophenols **5** for the Ugi four-component reaction with 2-alknylbenzaldehydes **6**,[13,16] 2-chloro-5-nitrobenzoic acid **7**, and benzyl isocyanide **8**.

The reaction was carried out in MeOH at 80 °C in closed vials under microwave heating for 20 minutes to form the acyclic product **9**. The latter was then treated with 1.2 equivalents of aqueous K_2CO_3 at 100 °C for another 10 minutes to promote the intramolecular nucleophilic aromatic substitution between the phenolic OH and the 4-nitrophenyl chloride moieties. The resultant products **10a**–**g** possess the 6,7,6-fused tricyclic skeleton and have a cleft molecular shape as characterized by an X-ray structural analysis in our previous work.[9b] Table 1 summarizes the structures and one-pot synthesis yields of **10a**–**g**.[17] The results indicate that the microwave-assisted one-pot U-4CR–S_NAr sequence tolerates diverse substitution patterns on 2-aminophenols **5** and affords the highly functionalized products **10a**–**g** in 57–81% overall yields.

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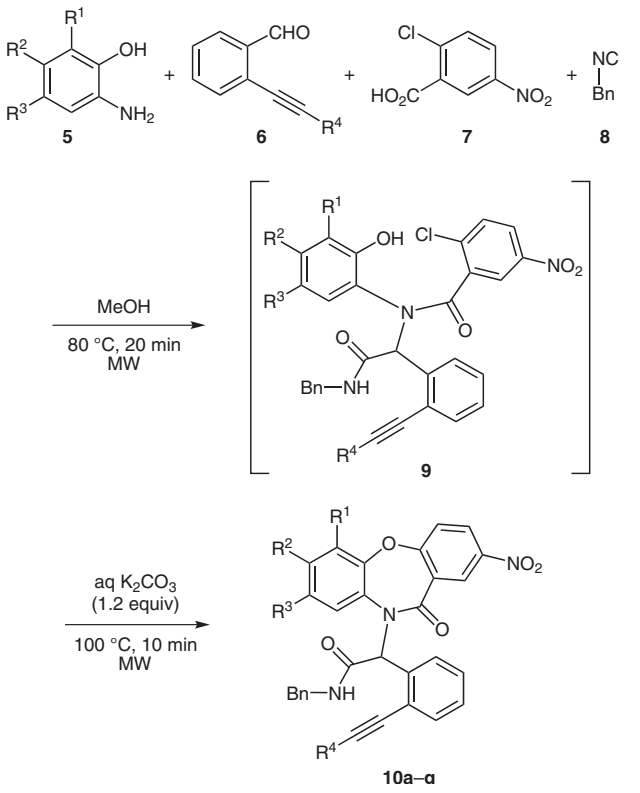


Scheme 1 Synthesis of dibenz[*b*,*f*][1,4]oxazepin-11(10*H*)-ones **10a**–**g**

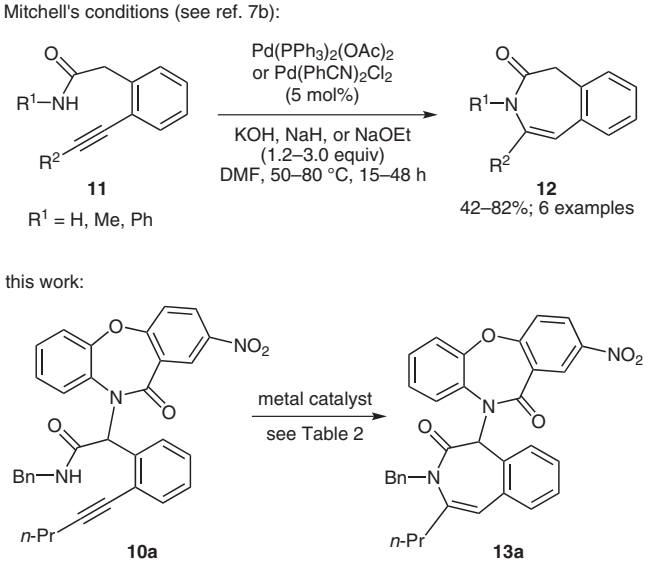
Table 1 One-Pot Synthesis of Dibenz[*b*,*f*][1,4]oxazepin-11(10*H*)-ones **10a**–**g** via Microwave-Assisted U-4CR and Post Intramolecular S_NAr[a]

Entry	Product	R^1	R^2	R^3	R^4	Yield (%)	mp (°C)
1	**10a**	H	H	H	*n*-Pr	69	96–98
2	**10b**	H	Me	H	*n*-Pr	80	118–120
3	**10c**	H	H	*t*-Bu	*n*-Pr	78	149–151
4	**10d**	H	H	Cl	*n*-Pr	57	184–186
5	**10e**	Me	H	Me	*n*-Pr	73	188–190
6	**10f**	H	H	Ph	*n*-Pr	81	191–193
7	**10g**	H	H	H	$(CH_2)_4CO_2Me$	71	128–130

[a] The one-pot synthesis was carried out by heating a MeOH solution of **5**–**8** at 80 °C for 20 min and the U-4CR mixture, after adding 1.2 equiv of aq K_2CO_3, at 100 °C for 10 min. All reactions were performed on a technical microwave reactor in a closed pressurized vial with the temperature measured by an IR sensor.
[b] Recrystallized from CH_2Cl_2–hexane.

Mitchell and co-workers[7b] screened reaction conditions for the intramolecular hydroamidation of **11** (R^1 = Me, R^2 = *n*-Bu) and found that a hydroxide base such as KOH in DMF (60 °C, 16 h) could, albeit not efficiently, promote the formation of **12** (Scheme 2). KO*t*-Bu gave complete conversion but it also promoted carbocyclization through the amide enolate species. Metal reagents such as $Cu(OTf)_2$, AgOTf, and $ZnCl_2$ together with KOH failed to improve both the conversion of **11** and the yield of **12**.

When $Ph(PPh_3)_2(OAc)_2$ (5 mol%) and KOH or NaOEt (2 equiv) were used, the product **12** (R^1 = Me, R^2 = *n*-Bu) was obtained in 80–82% yield. For the primary amide **11** (R^1 = H), NaH and higher temperature at 80 °C were used while longer reaction time (48 h) was required for cyclization of the anilide **11** (R^1 = Ph). We tried Mitchell's reaction conditions for IMHAD of **10a** but it failed (Scheme 2 and entry 1 of Table 2). The alkoxide base, KO*t*-Bu, did not work as well (entry 2, Table 2). These results suggest that the bulky 6,7,6-fused tricyclic skeleton in **10a** renders formation of **13a** much more difficult. After a systematic examination over the reaction parameters, we found that a base is not necessary for IMHAD of **10a**. Polar and nonpolar solvents such as DMF, DMSO, and toluene were inferior (entries 3, 4, and 8–10 in Table 2). THF and CH_2Cl_2 were the suitable solvents and gave similar results (entries 6 and 7, Table 2). Temperature at 60 °C in THF afforded the best yield of 71% when 10 mol% of $Pd(PhCN)_2Cl_2$ were used (entry 5, Table 2).



Scheme 2 Screening of reaction conditions for IMHAD

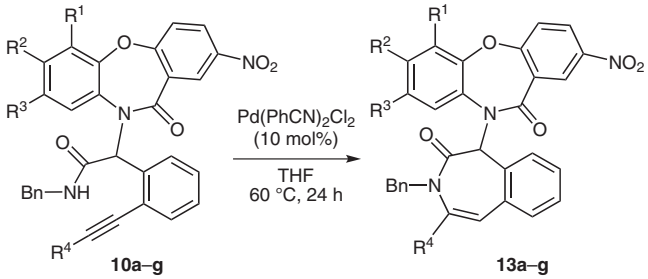
The IMHAD of **10a** was catalyzed by $PdCl_2$ at 60 °C in THF (62% yield after 40 h) but this catalyst was inactive at 150 °C under microwave heating, indicating that $Pd(PhCN)_2Cl_2$ is more robust than $PdCl_2$ (entries 5 and 6 vs. entries 13 and 14). We found that the phosphine complexes of palladium(II) lost catalytic activity in THF with thermal (60 °C) and microwave (150 °C) heating (entries 11, 12, and 15). AgOTf and $Cu(OTf)_2$ were examined in THF and formation of **13a** was confirmed only for AgOTf at 150 °C (entries 16–18, Table 2).

Next, we applied the conditions in entry 5 of Table 2 to the IMHAD of other substrates (Scheme 3). The results are summarized in Table 3. In general, the novel conjugates **13a**–**g** could be obtained in 61–74% yields regardless the bulky (R^3 = *t*-Bu, Ph) or reactive (R^3 = Cl) substituents

Table 2 Screening of Reaction Conditions for Intramolecular Hydroamidation of **13a**

Entry	Catalyst (10 mol%)	Base	Solvent	Temp (°C)	Time (h)	Yield (%)[a]
1	$Pd(PhCN)_2Cl_2$	KOH (1 equiv)	DMF	60	18	–[b]
2	none	KO*t*-Bu (1 equiv)	DMF	60	18	trace
3	$Pd(PhCN)_2Cl_2$	none	DMF	60	24	–[b]
4	$Pd(PhCN)_2Cl_2$	none	DMSO	110	18	–[b]
5	$Pd(PhCN)_2Cl_2$	none	THF	60	24	71
6	$Pd(PhCN)_2Cl_2$	none	THF	150 (MW)	0.5	35
7	$Pd(PhCN)_2Cl_2$	none	CH_2Cl_2	120 (MW)	0.33 + 0.5	30
8	$Pd(PhCN)_2Cl_2$	none	DMF	150 (MW)	0.5	–[b]
9	$Pd(PhCN)_2Cl_2$	none	DMSO	150 (MW)	0.5	–[b]
10	$Pd(PhCN)_2Cl_2$	none	PhMe	150 (MW)	0.5	–[b]
11	$Pd(PPh_3)_2Cl_2$	none	THF	60	18	–[b]
12	$Pd(PPh_3)_2Cl_2$	none	THF	150 (MW)	0.5	–[b]
13	$PdCl_2$	none	THF	60	40	62
14	$PdCl_2$	none	THF	150 (MW)	0.5	–[b]
15	$Pd(OAc)_2$ + dppf (1:1)	none	THF	150 (MW)	0.5	–[b]
16	AgOTf	none	THF	60	24	–[b]
17	AgOTf	none	THF	150 (MW)	0.5	<35[c]
18	$Cu(OTf)_2$	none	THF	60	22	–[b]

[a] Isolated yield.
[b] No reaction was noted by TLC analysis.
[c] A substantial amount of SM remained and the conversion was poor as compared to entry 6 using $Pd(PhCN)_2Cl_2$.



Scheme 3 Synthesis of 1,3-dihydro-2*H*-3-benzazepin-2-ones **13a–g**

(entries 3, 4, and 6 in Table 3). Moreover, our nonbasic conditions tolerates the base-labile methyl ester in **13g** (entry 7, Table 3). As seen in the 2-oxindole conjugates of 3,4-dihydro-3-oxo-2*H*-1,4-benzoxazines[9a] and dibenz[*b*,*f*]-[1,4]oxazepin-11(10*H*)-ones,[9b] the conjugates **13** also show atropisomerism in solution. Peak broadening was generally observed in their ^{1}H NMR and ^{13}C NMR spectra taken at 80 °C in DMSO-d_6. Formation of the seven-membered ring in compounds **13** is evident by disappearance of the IR absorptions at ca. 3400 and 3320 cm^{-1} [C(O)N(Bn)H] and ca. 2230 cm^{-1} (C≡C). The N–H signal

Table 3 Synthesis of 1,3-Dihydro-2*H*-3-benzazepin-2-ones **13a–g**[18] via Palladium-Catalyzed Intramolecular Hydroamidation

Entry	Product	R^1	R^2	R^3	R^4	Yield (%)[a]	mp (°C)[b]
1	**13a**	H	H	H	*n*-Pr	71	230–231
2	**13b**	H	Me	H	*n*-Pr	67	199–201
3	**13c**	H	H	*t*-Bu	*n*-Pr	61	223–225
4	**13d**	H	H	Cl	*n*-Pr	68	234–236
5	**13e**	Me	H	Me	*n*-Pr	72	247–249
6	**13f**	H	H	Ph	*n*-Pr	66	238–240
7	**13g**	H	H	H	$(CH_2)_4CO_2Me$	74	123–125

[a] Isolated yield.
[b] Recrystallized from CH_2Cl_2–hexane.

of **10** in the ^{1}H NMR spectra (for example, a triplet at δ = 6.35 ppm for **10c**) was not found after cyclization to **13**, instead, whose vinyl proton was observed (for example, a broad singlet at δ = 6.27 ppm for **13c**). However, the six-membered-ring product formed by the 6-*exo*-*dig* pathway

was not detected in accordance with the observation in the reaction of the simple substrates **11**.[7b]

In summary, we have developed a novel sequence for synthesis of the conjugates of 1,3-dihydro-2*H*-3-benzazepin-2-ones with dibenz[*b*,*f*][1,4]oxazepine-11(10*H*)-ones by taking advantage of the one-pot microwave-assisted U-4CR–S_NAr protocol[9b] and the palladium-catalyzed intramolecular hydroamidation of arylalkynes.[7] The current work expands the scope of our studies on skeletal diversity of the C–N-bond-linked conjugates of various benzannulated heterocycles.[9a–9c] These helical molecules show atropisomerism and their flexible molecular architectures may be of interest for chemical genetics studies.[19]

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(17) **General Procedure for the Synthesis of 10a–g**
A 10 mL pressurized process vial was charged with 0.25 mmol each of 2-aminophenol **5**, 2-alknylbenzaldehyde **6**, 2-chloro-5-nitrobenzoic acid (**7**), and benzyl isocyanide (**8**), and MeOH (2 mL). The loaded vial was then sealed with a cap containing a silicon septum, and put into the microwave cavity, and heated at 80 °C for 20 min. Then, an aq soln of K_2CO_3 (1 mL, 0.30 mmol) was added to the reaction vial through a syringe followed by heating at 100 °C for 10 min in the microwave cavity. Water was added to the reaction mixture, and the organic layer was extracted with EtOAc (3 × 10 mL). The combined organic layer was washed with brine, dried over anhyd Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography over SiO_2 with elution by 20% EtOAc in PE (60–90 °C) to afford **10**. The structures and yields of the products **10a–g** are given in Table 1.
Characterization Data for Compound 10c
White crystalline solid; mp 149–151 °C (CH_2Cl_2–hexane). R_f = 0.45 (20% EtOAc–hexane). IR (KBr): 3399, 3322, 2964, 2230, 1651, 1529, 1345, 1272, 1225 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.84 (d, *J* = 2.4 Hz, 1 H), 8.28 (dd, *J* = 8.4, 2.4 Hz, 1 H), 7.59–7.55 (m, 1 H), 7.45 (br s, 1 H), 7.37–7.25 (m, 7 H), 7.18–7.12 (m, 2 H), 7.04 (d, *J* = 8.8 Hz, 1 H), 7.00 (dd, *J* = 8.8, 2.4 Hz, 1 H), 6.41 (br s, 1 H), 6.35 (t, *J* = 5.6 Hz, 1 H), 4.66 and 4.59 (ABqd, *J* = 14.8, 6.0 Hz, 2 H), 2.21 (t, *J* = 7.2 Hz, 2 H), 1.48–1.37 (m, 2 H), 1.11 (s, 9 H), 0.88 (t, *J* = 7.6 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.9, 165.4, 165.2, 151.9, 148.9, 144.7, 137.8, 135.4 (br), 132.4, 129.7 (br), 129.0, 128.6 (2×), 128.4, 128.3, 127.6 (2×), 127.5, 127.4, 127.2, 124.9, 124.2, 121.1, 120.2, 97.4, 77.6, 66.6, 43.9, 34.4, 31.0 (3×), 21.9, 21.4, 13.5 (two aromatic carbons were not seen). MS (+ESI): *m/z* (%) = 624 (100) [M + Na^+]. Anal. Calcd for $C_{37}H_{35}N_3O_5$: C, 73.86; H, 5.86; N, 6.98. Found: C, 73.85; H, 5.83; N, 7.01.

(18) **General Procedure for the Synthesis of 13a–g**
A 10 mL flask was charged with **10** (0.25 mmol) and $Pd(PhCN)_2Cl_2$ (2.5×10^{-2} mmol, 10 mol%). The flask was evacuated and backfilled with N_2 (repeated three times). To the degassed flask was added degassed anhyd THF (2.5 mL) followed by heating at 60 °C for 24 h. Water was added to the reaction mixture, and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layer was washed with brine, dried over anhyd Na_2SO_4, and evaporated under reduced pressure. The residue was purified by flash column chromatography over SiO_2 with elution by 20% EtOAc in PE (60–90 °C) to give **13**. The structures and yields of **13a**–**g** are given in Table 3. Full characterization data for compounds **13a**,**b** and **13d**–**g** can be found in the Supporting Information.

Characterization Data for Compound 13c
White crystalline solid; mp 223–225 °C (CH_2Cl_2–hexane). R_f = 0.47 (20% EtOAc–hexane). IR (KBr) 2961, 1661, 1529, 1346, 1274 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6, 80 °C): δ = 8.63 (s, 1 H), 8.39 (dd, *J* = 8.5, 2.0 Hz, 1 H), 7.58 (d, *J* = 9.0 Hz, 2 H), 7.37–6.90 (m, 9 H), 6.75 (d, *J* = 7.0 Hz, 2 H), 6.42 (br s, 1 H), 6.27 (br s, 1 H), 5.02 (br s, 1 H), 4.55 (br s, 1 H), 2.30–2.10 (m, 2 H), 1.50–1.30 (m, 2 H), 1.01 (s, 9 H), 0.78 (br s, 3 H). ^{13}C NMR (125 MHz, DMSO-d_6, 80 °C): δ = 165.1, 164.6, 163.6, 151.8, 148.2, 144.7, 140.0(br), 137.8, 133.5, 130.8, 130.0(br), 129.1, 128.1, 127.9 (3×), 127.7, 126.6, 126.5 (2×), 126.2, 124.3 (br), 124.0, 121.9, 120.2, 116.6 (br), 67.4 (br), 46.90, 35.9, 34.2, 30.8 (3×), 20.2, 13.7 (two aromatic carbons were not seen). MS (+ESI): *m/z* (%) = 624 (32) [M + Na^+], 602 (100) [M + H^+]. Anal. Calcd for $C_{37}H_{35}N_3O_5$: C, 73.86; H, 5.86; N, 6.98. Found: C, 73.86; H, 5.91; N, 6.86.

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