Латвийский институт органического синтеза

*Химия гетероциклических соединений* **2016**, *52*(2), 84–86

ГЕТЕРОЦИКЛЫ В ФОКУСЕ

Химия гетероциклических соединений

# Synthesis of 1,3-dihydro-2*H*-benzo[*d*]azepin-2-ones (microreview)

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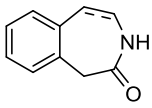
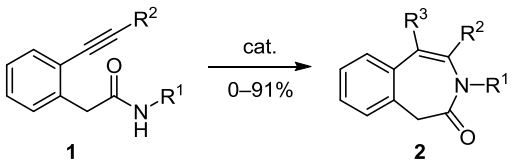
Submitted February 1, 2016
Accepted February 29, 2016



Benzazepinones display a wide range of pharmacological activity, and are used for treatment of heart diseases,[1,2] cancer,[3] and Alzheimer's disease.[4] They are also found in naturally-occurring alkaloids.[5,6] Furthermore, benzazepinones are used as building blocks for synthesis of benzazepines useful for treatment of various neurological conditions.[7–13] Structurally analogous dibenzazepinones are also found in pharmaceutically-relevant organic molecules.[14,15] Here, methods of synthesis of benzazepinones – hydroamination, carbopalladation, amidation, Friedel–Crafts alkylation, rearrangements with cycle enlargement are reviewed.

## Hydroamination

Metal-catalyzed intramolecular hydroamination of alkyne function by amide moiety in compound **1** leads to a formation of benzazepinones **2** in good yields.[16–18] Yu et al. developed a Pd-catalyzed addition of tethered amides to phenyl acetylenes.[16] Zhang et al. presented a similar procedure with gold catalysts.[17] Under the employed conditions, $AuBr_3$ not only activates the substrate but also performs as a brominating agent.

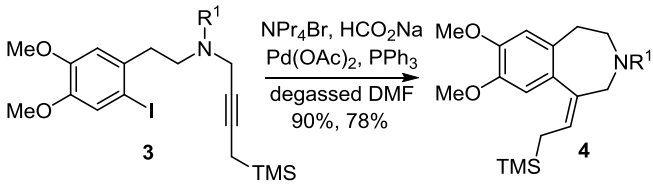



**1** **2**

$R^1$ = H, Alk, Ar; $R^2$ = Alk, Ar, HetAr, $CH_2OMe$, $(CH_2)_3CO_2Me$; $R^3$ = H, Br; cat. = $Pd(OAc)_2(PPh_3)_2$, $Pd(PhCN)_2Cl_2$, $Au(PPh_3)Cl/AgSbF_6$ or $AuBr_3$/AcOH, if $R^3$ = Br

## Carbopalladation

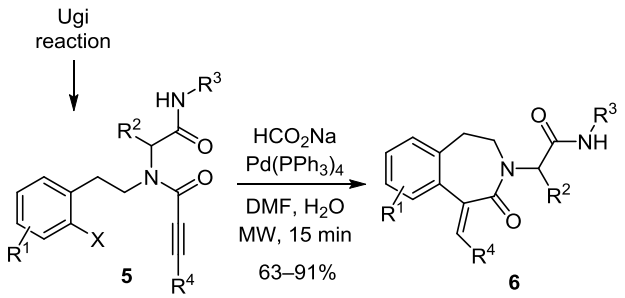
Reductive Heck conditions were employed to furnish benzazepinones and benzazepines in moderate to high yields.[19,20] Tietze et al. gained an access to benzazepinones **4** from silylated alkynes **3**.[19]




**3** **4**

$R^1$ = $SO_2Mes$, $COCF_3$

Recently, Peshkov et al. provided a more general and efficient method for preparation of benzazepinones **6** from Ugi reaction products **5**.[20] This finding opened a route to new substitution patterns and diversity points in resulting heterocycles. Modifications to the reaction protocol simplified the reaction conditions and shortened the reaction time.[20]




**5** **6**

$R^1$ = H, 4,5-$(MeO)_2$; $R^2$ = Alk, HetAr, Ar; $R^3$ = Alk, Ar; $R^4$ = Alk, Ar; X = Br, I

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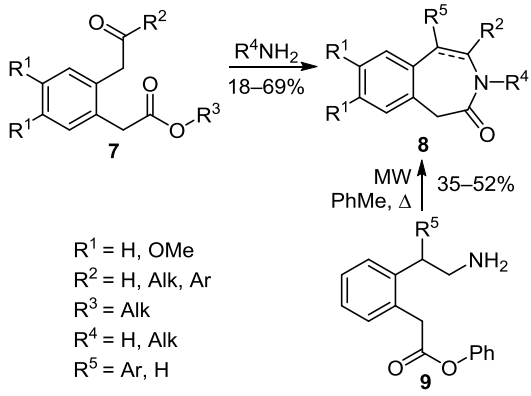
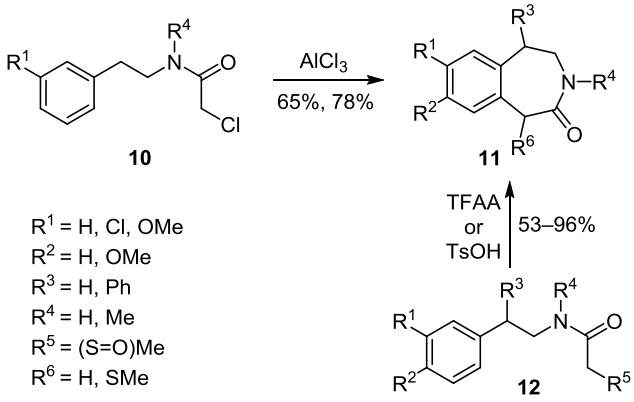
## Amidation

Various amidation approaches allow obtaining of both saturated[21,22] and unsaturated[23–25] benzazepinones. Guastavino et al. provided an improved version of the process,[23] described earlier by Beugelmans et al., where benzazepinones **8** are synthesized by cyclization of ketoesters **7**.[24] Sarkar et al. described a route to benzazepinones through microwave-assisted condensation of ketoesters **7** with primary amines.[25] Saturated benzazepinones **8** are less explored and usually are products of intramolecular cyclization of aminoesters **9**.[21,22]

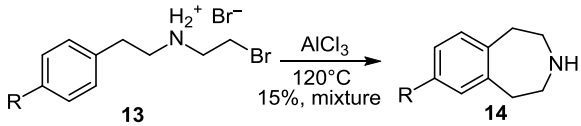



## Friedel–Crafts alkylation

By employing Friedel–Crafts conditions, it is possible to obtain benzazepinones **11** in good yields.[26,27] However they require high reaction temperatures and very reactive Lewis acids. Mitchell et al. performed the cyclization of compound **10** on a multigram scale, while heating it with $AlCl_3$ at 165°C for 2 h.[26] Similar method is used to deliver dibenzazepinones.[28] Milder conditions were found by Ishibashi et al., who employed a modified Pummerer/Friedel–Crafts protocol on compound **12**.[29] It allowed to synthesize the target benzazepinones **11** at 0°C.




Benzazepines **14** can also be prepared under Friedel–Crafts conditions, but with significantly lower yields.[30]

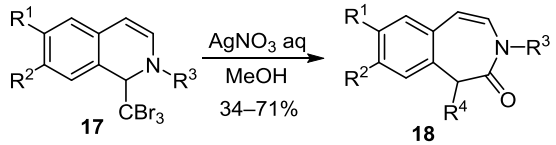



## Rearrangements with ring enlargement

There are several ways to synthesize benzazepines **16** *via* rearrangements.[31–35] In a Schmidt reaction, rearrangement occurs in tetralones **15** employing hydrazoic acid, which is generated from sodium azide in the presence of a protic acid (such as sulfuric acid).[31] The reaction yields a mixture of two regioisomers (carbonyl group in positions 2 and 3). Beckmann rearrangement *via* oximes is also prone to formation of both regioisomers from compound **15**.[31] Additionally, stability of the intermediate oxime might be an extra issue. Yadav et al. provided a milder and safer way to access benzazepinones **16** from compounds **15** while excluding the formation of dangerous hydrazoic acid.[32]


Beckmann: $R^1$ = OMe, $R^2$ = H; $R^3$ = 3,4-$(MeO)_2C_6H_3CH_2$; 23–70%
Schmidt: $R^1$ = H, $R^2$ = OMe, H; $R^3$ = H; $R^1$ = H, 39–73%

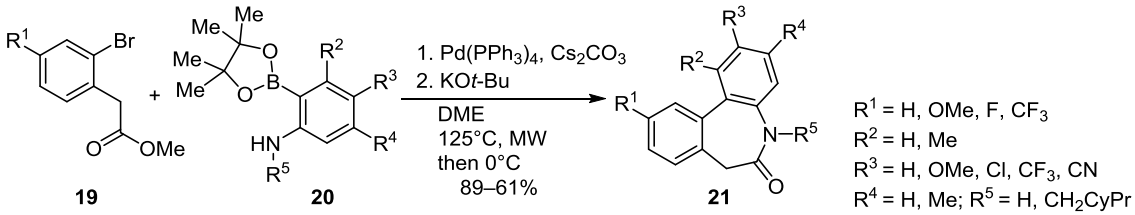
Another method, developed by Jean-Gerard et al., leads to the target compounds **18** by homologation of isoquinoline **17** *via* formation of an aziridinium intermediate and its rearrangement to benzazepinones in moderate to good yields.[36]




$R^1$ = H, OMe; $R^2$ = H, OMe; $R^3$ = Ar
$R^4$ = OH, OMe; X = Cl, Br

**Suzuki cross coupling**

Synthesis of acyclic intermediates by Suzuki cross coupling is specific to preparation of dibenzazepinones. Deb et al. provided a robust one-pot synthetic method for dibenzazepinones **21** from commercially available reagents.[37]




**19** **20** **21**

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