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One-Pot, Multicomponent Route to Pyrazoloquinolizinones

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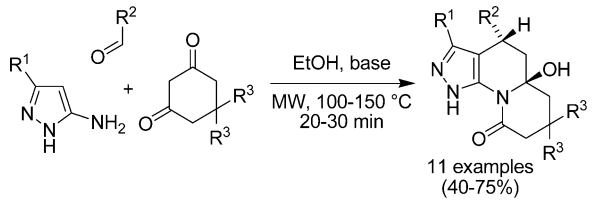
ABSTRACT



An efficient synthesis of 5a-hydroxy-4,5,5a,6,7,8-hexahydropyrazolo[4,3-*c*]quinolizin-9-ones based on the three-component condensation of 5-aminopyrazoles, aromatic aldehydes, and cyclic 1,3-diketones is described. The multicomponent reaction is performed under strongly basic conditions applying controlled microwave heating in a sealed vessel and involves an unusual base-mediated ring-opening/recyclization of the cyclic 1,3-diketone moiety.

Heterocycles containing the pyrazole ring are important targets in synthetic and medicinal chemistry because this fragment is a key moiety in numerous biologically active compounds,[1] among them such prominent drug molecules as Viagra, Celebrex, Analginum, and many others. Similarly, many pharmacologically active alkaloids of the berberine, lupine, sarpagine, and protopine type contain the quinolizine structure.[2] For example, berberine alkaloids such as allocryptopine (**1**) were successfully tested as antibacterial agents against *Staphylococcus aureus*, *Candida albicans*, and *Escherichia coli*,[2a,b] and the related alkaloid clathrotropine (**2**) is the toxic component of the curare arrow poison (Figure 1).[2e] Despite the importance of the quinolizine fragment, known approaches for obtaining this bicyclic nitrogen

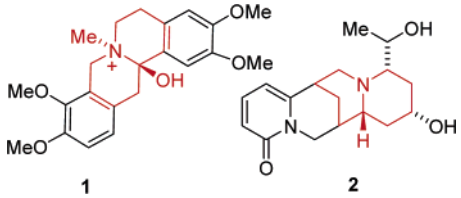


Figure 1. Selected examples of biologically active quinolizines.

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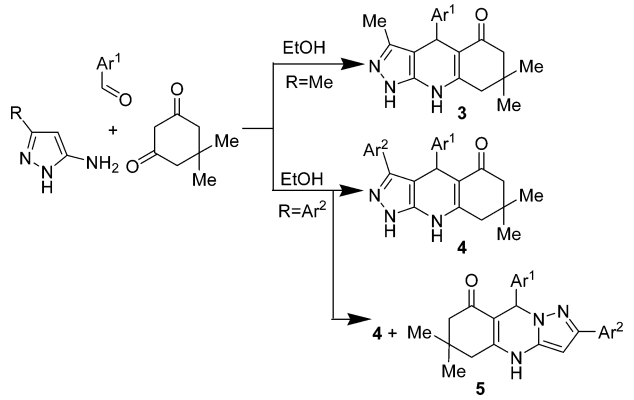
heterocycle are based either on isolation from natural plant sources[2d,e,3] or on multistep synthetic routes.[4]

The development of new synthetic methods for the efficient preparation of heterocycles containing quinolizine and/or pyrazole ring fragments is therefore an interesting challenge. Herein, we report the rapid, microwave-assisted formation of pyrazolo[4,3-*c*]quinolizin-9-ones via three-component condensation of 5-aminopyrazoles, aromatic aldehydes, and cyclic 1,3-diketones.

Multicomponent reactions (MCRs) of 5-aminopyrazoles with cyclic 1,3-diketones and aromatic aldehydes have recently attracted the interest of the synthetic community because the formation of different condensation products can be expected depending on the specific conditions and structure of the building blocks.[5−7] In the case of 1- and 4-substituted 5-aminopyrazoles, this MCR always leads to the formation of either dihydropyridine[5] or dihydropyrimidine[6] heterocycles, respectively. In contrast, the behavior of 1,4-unsubstituted 5-aminopyrazoles is somewhat ambiguous. For example, it has been demonstrated[6b,c] that in a three-component condensation with cyclic 1,3-diketones and aldehydes 3-methyl-5-aminopyrazole forms exclusively pyrazoloquinolinones **3**, whereas 3-aryl-substituted 5-aminopyrazoles can yield both pyrazoloquinolinones **4**[6b] and pyrazoloquinazolinones **5**,[7] or mixtures of both heterocyclic systems (Scheme 1).

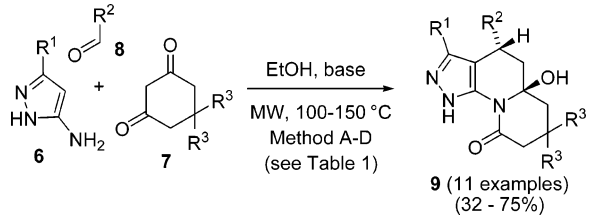
Scheme 1



Our own independent investigations in this area[5] confirmed that the formation of mixtures of both possible isomers **4** and **5** in these three-component condensation reactions is indeed the most common scenario when the reaction is carried out in refluxing ethanol at ca. 80 °C. Employing a high-temperature microwave irradiation protocol (150 °C, 25 min, EtOH, Et_3N), the reaction can be effectively tuned toward the exclusive formation of dihydropyridine derivatives **4**.[8]

In the context of these investigations, we noted that in the presence of a strong base such as KOH the three-component reaction proceeded via a different pathway and led to the formation of novel, hitherto undisclosed reaction products. For example, microwave-assisted condensation (EtOH, 150 °C, 25 min) of 3-phenyl-5-aminopyrazole **6a** (R^1 = Ph) with cyclic diketones **7** and substituted benzaldehydes **8** in the presence of an equimolar amount of KOH led to tricyclic structures that on the basis of ^1H, ^{13}C NMR, HSQC, and ROESY spectra were ultimately assigned as pyrazolo[4,3-*c*]quinolizin-9-ones **9** (Scheme 2, Table 1, method A). As compound **9** contained two chiral centers, the formation of two diastereomeric pairs was expected. On the basis of NMR data, in particular on the absence of an NOE between the OH group and the *ortho*-protons on the aryl ring in position 4, we were able to assign the relative configuration of the stereogenic centers as trans. Final confirmation for the formation of these unusual reaction products was derived from an X-ray analysis of compound **9d** (Figure 2).

Scheme 2



After evaporation of the solvent and recrystallization from an EtOH−H_2O mixture (1:1), the product yields in this

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(8) The detailed results on the scope and limitations of this muticomponent reaction will be published elsewhere.

Table 1. Synthesis of 5a-Hydroxy-4,5,5a,6,7,8-hexahydropyrazolo[4,3-*c*]quinolizin-9(1*H*)-ones **9a**−**k** (Scheme 2)

building blocks						quinolizine	yield
amine	R^1	diketone	R^3	aldehyde	R^2	**9**	(%)
6a	Ph	**7a**	Me	**8a**	Ph	**9a**	40[a]
							60[b]
							65[c]
							57[d]
6a	Ph	**7a**	Me	**8b**	4-MeC_6H_4	**9b**	38[a]
							75[b]
							60[d]
6a	Ph	**7a**	Me	**8c**	4-$MeOC_6H_4$	**9c**	39[a]
							65[b]
							71[c]
6a	Ph	**7a**	Me	**8d**	4-BrC_6H_4	**9d**	45[a]
							70[b]
							58[d]
6a	Ph	**7a**	Me	**8e**	4-FC_6H_4	**9e**	38[b]
							40[c]
							38[d]
6a	Ph	**7b**	H	**8a**	Ph	**9f**	44[a]
							58[b]
							62[c]
							55[d]
6a	Ph	**7b**	H	**8b**	4-MeC_6H_4	**9g**	35[a]
							60[b]
							51[d]
6a	Ph	**7b**	H	**8c**	4-$MeOC_6H_4$	**9h**	32[a]
							58[b]
							65[c]
6a	Ph	**7b**	H	**8d**	4-BrC_6H_4	**9i**	43[a]
							59[b]
							55[d]
6b	Me	**7a**	Me	**8d**	4-BrC_6H_4	**9j**	54[c]
							50[d]
6b	Me	**7b**	H	**8a**	Ph	**9k**	60[c]
							48[d]

[a] Method A (one-pot, one-step procedure): equimolar mixtures of **6**, **7**, and **8**, KOH/EtOH, MW, 150 °C, 25 min. [b] Method B (one-pot, one-step procedure): mixture of **6**, **7**, and **8** (1:2:1), EtONa/EtOH, MW, 150 °C, 20 min. [c] Method C (one-pot, two-step procedure): (i) mixture of **7** and **8** (2:1), EtONa/EtOH, MW, 100 °C, 2 min; (ii) addition of 1 equiv of **6**, EtONa/EtOH, MW, 150 °C, 15 min. [d] Method D (one-pot, two-step procedure): (i) mixture of **6** and **7** (1:1), EtONa/EtOH, MW, 150 °C, 10 min; (ii) add 1 equiv of **8**, EtONa/EtOH, MW, 150 °C, 10 min.

transformation according to method A (Scheme 2, Table 1) were in the range of 32−45%. Additional experiments revealed that formation of heterocycles **9** in yields up to 75% was possible when 2 equiv of the 1,3-diketone building block was employed. In addition, the use of 2 equiv of sodium ethoxide instead of potassium hydroxide also increased the yields and improved the purity of the formed pyrazolo[4,3-*c*]quinolizin-9-ones **9a**−**i** (Table 1, method B).

On the basis of these observations, it appears that this unusual three-component reaction involves the initial formation of Michael adduct **10** (Figure 3) derived from condensation of the aldehyde and 1,3-diketone components. This assumption was supported by the spectroscopic (^{1}H NMR) identification of intermediate **10** in the crude reaction mixture. Additional evidence was also obtained by subjecting

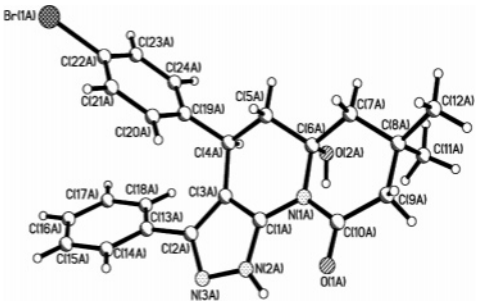

Figure 2. Molecular structure (X-ray diffraction data) of **9d**.

independently synthesized Michael adduct **10**[9] to the standard reaction conditions (method C) in the presence of 3-phenyl-5-aminopyrazole **6a**. The anticipated quinolizinones **9** were obtained in high isolated yields.

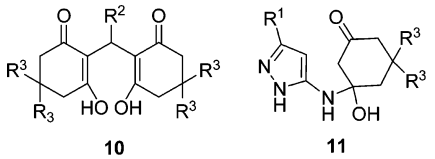

Figure 3. Possible reaction intermediates in the formation of pyrazolo[4,3-*c*]quinolizin-9-ones **9**.

On the basis of our mechanistic hypothesis, an alternative one-pot, two-step procedure was elaborated (Table 1, method C). This protocol involved the initial in situ formation of Michael adducts **10** via condensation of cyclic 1,3-diketones **7a**,**b** with the appropriate aldehydes **8a**,**c**−**e** (MW, 100 °C, 2 min). Subsequent addition of the 5-aminopyrazole component **6a** or **6b** to the microwave process vial and resubjection to microwave irradiation at 150 °C for 15 min provided the target compounds **9** in good yields. Importantly, this protocol must be employed when 3-methyl-5-aminopyrazole **6b** is used as a building block. In this case, the application of both one-pot, one-step methods A and B exclusively provides the "classical" Hantzsch dihydropyrazolo[3,4-*b*]quinolin-5-ones of type **3** and **4** (Scheme 1).

As an additional one-pot, two-step alternative, it was discovered that precondensation of 5-aminopyrazoles **6a**,**b** with cyclic 1,3-diketones **7a**,**b** in ethanol in the presence of sodium ethoxide (MW, 150 °C, 10 min), followed by addition of the appropriate aldehyde building blocks **8** (MW, 150 °C, 10 min), also led to the formation of target structures **9a**,**b**,**e**−**g**,**j**,**k** (Table 1, method D). This procedure, generally providing high product yields, can be used for both types of aminopyrazoles and cyclic 1,3-diketones and possibly proceeds through an intermediate of type **11** (Figure 3).

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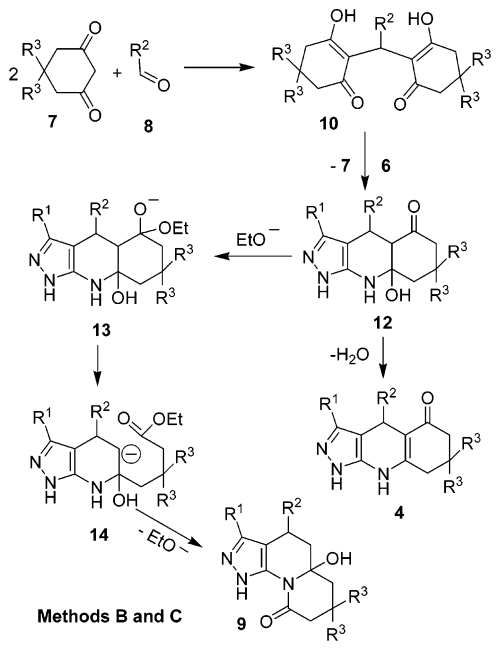
Although the exact reaction mechanism for this novel three-component condensation reaction has not been confirmed, our current working hypothesis is shown in Scheme 3 (for methods B and C). The three-component process is

Scheme 3



likely to involve the initial base-catalyzed formation of Michael adduct **10**. This intermediate subsequently reacts with the aminopyrazole component **6** to furnish the tricyclic intermediate **12**. The formation of **12** may occur either (i) by nucleophilic addition of the NH_2 group of the aminopyrazole to one of the carbonyl centers in adduct **10** and concomitant elimination of one molecule of cyclic diketone **7** or (ii) via nucleophilic substitution of the diketone moiety in adduct **10** by 5-aminopyrazole.

In any event, elimination of water from the tricyclic intermediate **12** may now lead to the formation of the classical Hantzsch-type tricyclic dihydropyridine derivatives **4** (an observed byproduct in the formation of pyrazolo[4,3-*c*]quinolizin-9-ones **9**). In the presence of a strong base at high temperatures, however, the cyclic 1,3-dicarbonyl fragment in **12**—after nucleophilic attack of the ethoxide (or hydroxide) ion to the carbonyl group—apparently undergoes ring opening (**13** → **14**) in accordance with previously reported mechanisms for the cleavage of β-diketones.[10] In the particular case reported here, the intermediate ester **14** is able to efficiently recyclize to provide the observed fused quinolizinones **9**. It should be noted that intramolecular heterocyclizations involving 1,3-diketone ring opening/recyclization are very rare, and only a few examples for this type of transformation can be found in the literature.[11]

In summary, we have reported an efficient synthetic route to 5a-hydroxy-4,5,5a,6,7,8-hexahydropyrazolo[4,3-*c*]quinolizin-9-ones based on the multicomponent condensation of 5-aminopyrazoles with cyclic 1,3-diketones and aromatic aldehydes. Preliminary studies seem to indicate that this novel MCR tolerates diversity in all three building blocks. The key step in the suggested mechanistic pathway involves an unprecedented base-mediated ring opening/recyclization of the cyclic 1,3-diketone component. The generality of this synthetic strategy for the synthesis of related quinolizinone derivatives is currently under investigation in our laboratories.

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Supporting Information Available: Experimental procedures and characterization of new compounds (including X-ray and 2D NMR). This material is available free of charge via the Internet at http://pubs.acs.org.

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