Facile Synthesis of Tetrahydroquinolines and Julolidines through **Multicomponent Reaction**

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Abstract: Aldehydes, anilines and enol ethers react in trifluoroethanol (TFE) through an aza-Diels-Alder reaction (Povarov reaction) to afford the corresponding substituted tetrahydroquinolines. This reaction occurs, without any catalyst, under sequential threecomponent conditions, allowing thus the use of aliphatic aldehydes. In the presence of formaldehyde and an excess of dienophile, the product undergoes a second Povarov reaction affording new julolidine derivatives.

Key words: domino reaction, cycloaddition, fluorous alcohols, heterocycles, solvent effect

Multicomponent reactions (MCRs) constitute a very attractive way to synthesize complex molecules due to their numerous advantages (atom economy, simplicity to implement, etc.).¹ In this connection, the aza-Diels-Alder reaction (also called imino-Diels-Alder or Povarov reaction) is a useful transformation that offers an easy entry to the tetrahydroquinoline family (Figure 1). This reaction is formally a [4+2] cycloaddition between a Schiff base (as diene) and an electron-rich olefin (as dienophile) in the presence of a Lewis or Brønsted acid as promoter.² The Schiff base can be either preformed or formed in the pot under three-component conditions. However, in the case of unstable alkyl aldimines their in situ generation is required, and there are only rare reports dealing with such substrates.^{2c,2e} In connection with our studies on the use of fluorinated alcohols (trifluoroethanol, TFE and hexafluoroisopropanol, HFIP) as reaction medium,3a-d,4 we now report herein the facile synthesis of tetrahydroquinolines under multicomponent conditions by using TFE as solvent.3e,3f







Previously, we showed that TFE and HFIP were able to promote, without any catalyst, the Povarov reaction between Schiff bases (aryl aldimines) and electron-rich di-

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enophiles.^{3b,3c} We now found that the reaction gives also nice results under domino conditions with alkyl aldehydes. By mixing the aldehyde with the dienophile in TFE, then followed by the slow addition of the aniline, the expected reaction occurs, affording thus tetrahydroquinolines in good to very good yields (56-88%, Scheme 1).



Scheme 1

The results reported in Table 1 show that the use of enolizable aldehydes such as isobutyraldehyde (entry 2), isovaleraldehyde (entries 3-5) and hexanal (entry 6) gives satisfactory to very good results. In all cases, the products are obtained with the cis-configuration for the major isomer. It is worth mentioning that the reaction conditions are attractive: they are mild (neutral conditions and at r.t. in open vessels for 2 h), no other effluent than water is released and only a slight excess of reagents is required (1.2 equiv). Thus this process could be interesting for largescale synthesis. However, one of the limitation of the reaction stems from the dienophile: only electron-rich olefins (vinyl ethers) are able to react in the reaction.⁵ This method offers thus a simple alternative to access to 3alkyl substituted tetrahydroquinolines, whose access was rather limited (see Figure 1 for the tetrahydroquinoline numbering).

Having in hand a straightforward and simple method to synthesize tetrahydroquinolines, we decided to further explore its potential in view to access to structurally more complex structures. In 1988, it was reported by Grieco and Bahsas that the Povarov reaction between formaldehyde (in excess), aniline, and an electron-rich olefin (in excess) under strong acidic conditions (CF₃CO₂H, 1 equiv), afforded tricyclic compounds related to the benzoquinolizine family (julolidines, Figure 1).⁷ Julolidine and its derivatives have found various applications: fluorescent probes,⁸ photoconductive materials, potential antidepressants and tranquilizers.9 The classical ways to prepare julolidines involve the N-alkylation of tetrahydroquinolines or anilines followed by intramolecular electro-

Entry	R ¹	Dienophile	Ar	Product	cis:trans ^b	Yield (%)
1	Ph	OEt	Ph	Ph HN OEt	85:15	85
2	<i>i</i> -Pr	OEt	Ph	la <i>i</i> -Pr HN OEt	85:15	78
3	<i>i</i> -Bu		Ph	1b HN HN O	80:20	56
4	<i>i</i> -Bu	OEt	Ph	Ic <i>i</i> -Bu HN OEt	85:15	70
5	<i>i</i> -Bu	OEt	4-MeO-C ₆ H ₄	1d <i>i</i> -Bu HN OEt OMe	70:30	60
6	<i>n</i> -C ₅ H ₁₁	OEt	Ph	1e n-C ₅ H ₁₁ HN OEt 1f	85:15	88

 Table 1
 Synthesis of Tetrahydroquinolines through Three-Component Reaction^a

^a According to Scheme 1.⁶

^b Measured by ¹H NMR.

philic cyclization.¹⁰ However, both these methods offer only few possibilities to introduce substituents on the skeleton. Later on, some other synthetic paths have been used, allowing the synthesis of few julolidines with substituents on 3- and 1-positions.¹¹

According to Grieco's report and to our work, we reasoned that we could use our method to prepare 1,3,7trisubstituted julolidines (see Figure 1 for the julolidine numbering). Indeed, by adding formaldehyde and a dienophile to a crude tetrahydroquinoline in TFE, the fluorous alcohol could also promote the second aza-Diels–Alder reaction. In order to check our hypothesis, we prepared tetrahydroquinolines **1b** and **1f** according to our conditions (see Table 1) and, without isolating the product, a solution of formaldehyde (35% aq) and of olefin was added in the medium. After only 1 hour reaction time, we were delighted to see that the reaction was completed and that the julolidines were formed (Scheme 2).¹²

By this protocol we obtained three new substituted julolidines 2, 3 and 4. Products 2 and 4 (with the same substituent on the positions 1 and 7) were obtained in good yields (72% and 80%, respectively) while the compound 3 (with two different substituents) was obtained in low yield (35%). However, considering that the product is the result



Scheme 2

of four reaction steps, a 35% yield means more than 75% yield per step. Concerning the relative configuration of the julolidines, the last reaction step always afforded a single stereomer, which had the groups in 3- and 7-positions of the *cis*-configuration.¹³

In conclusion, we have reported a useful method to synthesize tetrahydroquinolines with alkyl substituents in the position 3 through three-component Povarov reaction, by using TFE as solvent. Such compounds are still challenging to synthesize by this path. In the presence of aqueous formaldehyde and of a dienophile these tetrahydroquinolines undergo a second reaction in the pot to yield new *cis,cis*-trisubstituted julolidines as major isomers. The reaction conditions are mild (no catalyst) and very simple to implement.

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- (6) Typical Procedure for the Synthesis of cis-4-Ethoxy-1,2,3,4-tetrahydro-2-isopropylquinoline (1b). Isobutyraldehyde (1.2 mmol, 86 mg) and ethyl vinyl ether (1.2 mmol, 86 mg) were dissolved in TFE (1 mL) in a 5 mL test tube. A solution of aniline (1 mmol, 93 mg) in TFE (1 mL) was then slowly added over 15 min to the previous mixture under stirring. After stirring for 2 h, the solvent was evaporated in vacuo. The crude product was then purified by chromatography on florisil (cyclohexane-EtOAc, 9:1) to afford 1b as yellow crystals (171 mg, 78%); mp 74-76 °C. ¹H NMR (300 MHz, CDCl₃): $\delta = 1.02$ (d, 3 H, J = 6.7 Hz), 1.03 (d, 3 H, J = 6.7 Hz), 1.33 (t, 3 H, J = 7.0 Hz), 1.75 (m, 2 H), 2.24 (ddd, 1 H, J = 2.5, 5.5, 12.1 Hz), 3.23 (ddd, 1 H, *J* = 2.5, 5.3, 11.2 Hz), 3.63 (m, 1 H), 3.79 (m, 1 H), 4.68 (dd, 1 H, J = 5.6, 10.2 Hz, 6.51 (d, 1 H, J = 7.8 Hz), 6.71 (t, 1 H, J = 7.8 Hz), 6.J = 7.4 Hz), 7.04 (t, 1 H, J = 7.6 Hz), 7.36 (d, 1 H, J = 7.6 Hz), NH not observed. ¹³C NMR (300 MHz, CDCl₃): $\delta = 15.6, 18.0, 18.3, 30.3, 32.4, 56.1, 63.4, 74.1, 113.8,$ 117.1, 122.8, 126.9, 127.91, 144.6. Anal. Calcd for C14H21NO (219.32): C, 76.67; H, 9.65; N, 6.39. Found: C, 76.33; H, 9.99; N, 6.35.
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- (12) Typical Procedure for the Synthesis of *cis,cis*-1,7-Diethoxy-3-isopropyljulolidine (2). Isobutyraldehyde (1.2 mmol, 103 mg) and ethyl vinyl ether (1.2 mmol, 86 mg) were dissolved in TFE (0.5 mL) in a 5 mL test tube. A solution of aniline (1 mmol, 93 mg) in TFE (0.5 mL) was then slowly added over 15 min to the previous mixture under stirring. After stirring for 2 h, a solution of formaldehyde (35% aq; 2 mmol, 172 mg) and ethyl vinyl ether (1.2 mmol, 86 mg) in TFE (1 mL) was added to the reaction mixture. After further stirring for 1 h, the solvent was evaporated in vacuo. The crude product was then

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Figure 2