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Monoterpene amino alcohols in multicomponent synthesis of chiral hetero- and carbocycles

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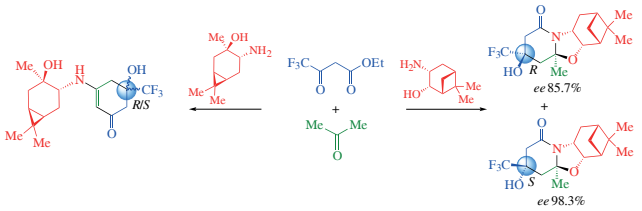
The reaction between ethyl trifluoroacetoacetate, acetone and 4-amino-3-hydroxycarane having tertiary hydroxy group affords the 5-hydroxy-5-(trifluoromethyl)cyclohex-2-en-1-one derivative bearing 3-positioned (3-hydroxycaran-4-yl)amino moiety. The analogous reaction with 3-amino-2-hydroxyapopinane having functional groups at the secondary carbon atoms gives the product of further heterocyclization with perhydro 6,8-methanobenz[4,5]-oxazolo[3,2-*a*]pyridine framework.



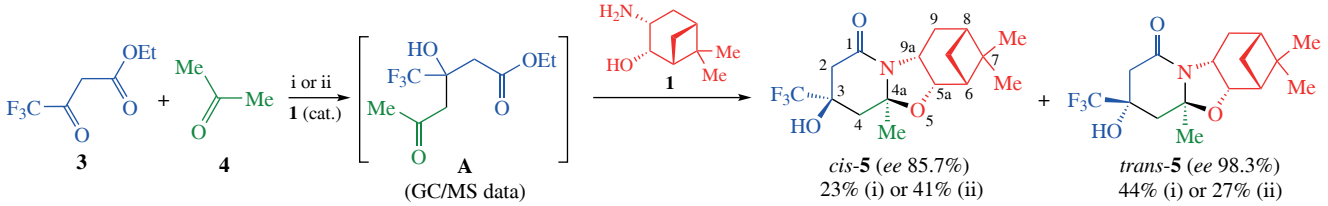
Keywords: monoterpenes, amino alcohols, β-pinene, 3-carene, ethyl trifluoroacetoacetate, acetone, multicomponent reactions, organofluorine compounds, cyclohex-2-en-1-one, 6,8-methanobenz[4,5]oxazolo[3,2-*a*]pyridine.

Monoterpenes belong to a large group of secondary plant metabolites.[1,2] Both natural monoterpenes and their synthetic derivatives have various pharmacological properties,[3] which finds medical applications.[4] In addition, monoterpenes are key reagents in the development of chiral oxa- and azaheterocyclic compounds.[5,6] In this regard, compounds derived from readily available 3-carene and β-pinene, having high enantiomeric purity, are promising reagents to produce chiral compounds,[7–9] including different hetero-[10–12] and carbocycles.[13] The practical attractiveness of their derivatives is due to a wide range of biological activity,[14] such as antibacterial,[15,16] antimicrobial,[17,18] anti-inflammatory[19] and insecticidal.[20]

Herein, the applicability of our previously developed three-component one-pot approach[21–24] to terpenoid hetero- and carbocycles based on the cyclization of enantiomerically pure β-amino alcohols **1**, **2** with ethyl trifluoroacetoacetate **3** and acetone **4** was investigated. β-Amino alcohol **1**, 3-amino-2-hydroxyapopinane, is synthesized from β-pinene,[25] while compound **2**, 4-amino-3-hydroxycarane, is obtained from 3-carene.[26]

First, we studied the reaction of apopinane amino alcohol **1** with ethyl trifluoroacetoacetate **3** and acetone **4** in 1,4-dioxane at room temperature, and diastereomeric products *cis*-**5** and *trans*-**5** in a ratio of ~1 : 2 were isolated (Scheme 1). Monitoring of the reaction by GC/MS and ^{19}F NMR spectroscopy showed that aldol **A** (δ_F 81.94, *m/z* = 242) was also formed along with the main products *cis*-**5** (δ_F 81.15) and *trans*-**5** (δ_F 79.86, *m/z* = 333). As we have shown previously,[21–24] aldol **A** was a key intermediate in similar three-component transformations, and its generation was an autocatalytic process. The ability of terpene amino alcohols **1**, **2** to catalyze aldol reactions was established previously.[26,27]

The reaction in weakly polar 1,4-dioxane at room temperature proceeded very slowly for 20 days (Table 1, entry 1). Thus, more polar MeCN and EtOH were tested to intensify the process. However, even under these conditions, after 14 days, unreacted aldol **A** still remained in the reaction mixture (entries 2, 3), and the formation of large amounts of by-products in EtOH was also observed (entry 3). Varying the time mode showed that the formation of aldol **A** in 1,4-dioxane at room temperature occurred within two days (entry 5), and further generation of the cyclic system proceeded very slowly. Hence, we decided to carry out the reaction in two stages (entry 4). In the first stage, after loading all the reactants, the mixture was stirred at room temperature for 2 days until complete conversion of ester **3** and ketone **4** into aldol **A**. In the second stage, the reaction mixture was heated at 80 °C, which significantly accelerated the reaction of aldol **A** with amino alcohol **1** and reduced the total reaction



Scheme 1 *Reagents and conditions*: i, 1,4-dioxane, room temperature, 20 days; ii, 1,4-dioxane, room temperature, 2 days and 80 °C, 3 days.

Table 1 Optimization of conditions for the three-component reaction between **1**, **3** and **4**.[a]

Entry	Solvent	Time/ days	*T*/°C	Composition of the reaction mixture[b] (%)			
				A	*cis*-**5**	*trans*-**5**	by-products
1	1,4-Dioxane	20	25	9	30	50	11
2	MeCN	14	25	23	21	44	12
3	EtOH[c]	14	25	12	11	54	23
4	1,4-Dioxane	2	25	95	3	1	1
5	1,4-Dioxane	3	80	5	49	37	9

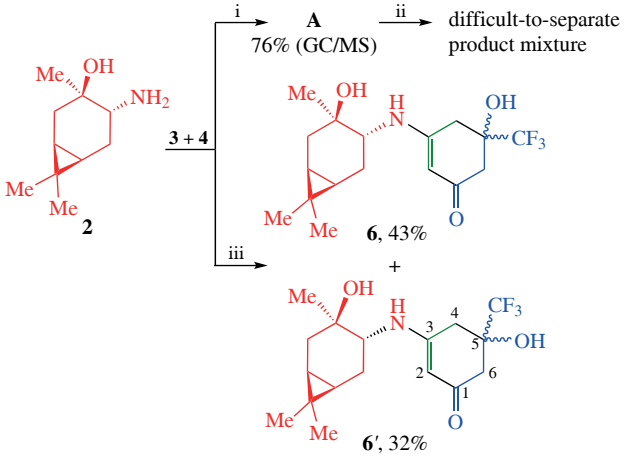
[a] **1**, **3** and **4** (0.5 mmol each), solvent (1 ml). [b] Determined by ^{19}F NMR: **A** (δ_F 81.94), *cis*-**5** (δ_F 81.15) and *trans*-**5** (δ_F 79.86). [c] Anhydrous EtOH.

time to 5 days. Heating the reaction led to a change in the diastereomer ratio: heterocycle *cis*-**5** predominated over *trans*-**5** (see Scheme 1). We were able to separate diastereomers *cis*-**5** and *trans*-**5** due to their different solubility. The *cis*-diastereomer precipitated upon crystallization from MeCN while *trans*-diastereomer was isolated from the filtrate and purified by crystallization from Et_2O.

A similar reaction was carried out with (1*S*,3*R*,4*R*,6*R*)-4-amino-3-hydroxycarane **2**. However, initially formed in 1,4-dioxane at room temperature aldol **A** was not converted into the expected fused heterocycle even in small quantities upon heating at the next stage, but underwent decomposition into a difficult-to-separate mixture of products (GC/MS and ^{19}F NMR, Scheme 2). Apparently, the methyl substituent geminal to the hydroxy group in β-amino alcohol **2** sterically hinders its participation in the formation of a new heterocyclic system.

Since the involvement of β-amino alcohol **2** in the pyridone formation was unsuccessful, the reaction medium was switched to ethanol and zeolites. We employed such an approach in the three-component synthesis of cyclohexenones from ester **3**, acetone **4**, and monoamines.[22] Indeed, these conditions favored the formation of caranylamino-substituted 5-hydroxy-5-(trifluoromethyl)cyclohex-2-en-1-one as a mixture of two diastereomers **6** (δ_F 80.39) and **6′** (δ_F 80.25) in good total yield (see Scheme 2), which were separated by crystallization from MeCN.

The structure of the synthesized compounds **5**, **6** was confirmed by IR, ^{1}H, ^{19}F, ^{13}C NMR spectroscopy and X-ray diffraction analysis for *trans*-**5**. Complete assignment of signals in the ^{1}H and ^{13}C NMR spectra was performed based on two-dimensional experiments 2D ^{1}H–^{1}H COSY, ^{1}H–^{13}C HSQC and ^{1}H–^{13}C HMBC. A comparison of the NMR spectra of diastereomers *cis*/*trans*-**5** shows that, similar to the known *cis*/*trans*-diastereomers of hexahydrooxazolo[3,2-*a*]pyridin-5-ones,[24] the characteristic difference is also the magnitude of the non-equivalence of the diastereotopic protons at C^4: the value $\Delta\delta_{AB}$ is 0.45 ppm for *cis*-**5**, and this value is much smaller (0.10 ppm) for *trans*-**5**. The 2D NOESY data also confirm the structure of these diastereomers. In the *trans*-**5**, the OH proton at C^3 and the methyl protons at C^{4a} have cross peaks with the same proton C^{4}H$_A$ from the diastereotopic pair at C^4. As for isomer *cis*-**5**, cross peaks (HO–C^3, C^{4}H$_B$) and (Me–C^{4a}, C^{4}H$_A$) are observed, which is consistent with its *cis*-configuration.



Scheme 2 *Reagents and conditions*: i, 1,4-dioxane, room temperature, 2 days; ii, 1,4-dioxane, 80 °C, 3 days; iii, EtOH (anhydrous), zeolites, room temperature, 10 days.

The absolute 3*S*,4a*S*,6*R*,8*R*-configuration of the stereocenters in compound *trans*-**5** was determined using X-ray diffraction analysis data (Figure 1).† Based on analysis of the entire set of NOE correlations of the *cis*-**5** in comparison with *trans*-**5**, the configuration of the nodal atom C^{4a} is assumed to retain in heterocycle *cis*-**5**, while the configuration of the atom C^3 changes. Thus, the 3*R*,4a*S*,6*R*,8*R* stereo configuration should be assigned to isomer *cis*-**5**. The enantiomeric purity of *trans*-**5** (*ee* 98.3%) and *cis*-**5** (*ee* 85.7%) was determined by HPLC using chiral columns.

The NMR spectra of cyclohexenones **6** and **6′** correspond to the proposed structure, but the diastereomers differ slightly in chemical shifts in the ^{1}H and ^{13}C NMR spectra. The main differences are in the magnitude of non-equivalence of the diastereotopic protons C^{4}H$_2$ and C^{6}H$_2$ in the ^{1}H NMR spectra, which indicates a change in the configuration of the CF$_3$- and HO-substituents at the asymmetric center C^5. Unfortunately, we were unable to grow monocrystals to determine the *R*/*S*-configuration of **6** and **6′**, as well as to select conditions to determine their enantiomeric purity owing to poor solubility.

To summarize, we showed different variants of cyclizations of terpene β-amino alcohols with ethyl trifluoroacetoacetate and acetone. Depending on the terpene component structure, tetracyclic pyridone derivatives or cyclohexenes with an aminoterpene moiety were obtained. The β-amino alcohol is a dinucleophile during a heterocycle formation; as for a carbocycle

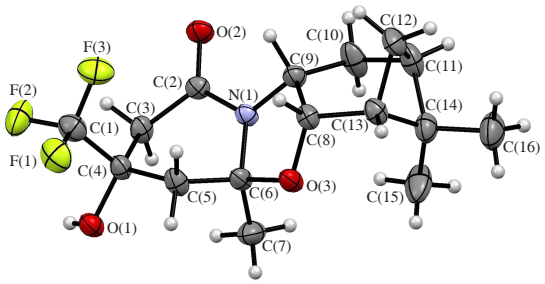


Figure 1 General view of the *trans*-**5** molecule. Ellipsoids are shown at the 50% probability level.

† *Crystal data for trans*-**5**. $C_{16}H_{22}F_3NO_3$ (M = 333.35), monoclinic, space group $P2_1$, a = 12.6750(9), b = 10.1414(6) and c = 13.6473(11) Å, β = 107.810(8)°, V = 1670.2(2) Å^3, μ(MoKα) = 0.112 mm^{-1}. Analysis was performed at 295(2) K on an Xcalibur 3 diffractometer by standard procedure (graphite monochromated MoKα radiation, ω-scanning). On the angles 5.1 < θ < 60.98° total of 8155 reflections were measured, 6366 unique reflections (R_{int} = 0.0450), 3032 reflections with $I > 2\sigma(I)$. The structure was solved and refined using the SHELXTL program package.[28] The structure was defined by direct statistical methods and refined by full-matrix anisotropic approximation for F^2 for all non-hydrogen atoms with ShelXL program.[29,30] The hydrogen atoms were localized by direct method and refined in the isotropic approximation. GOOF = 1.006, S = 1.006; final R values: R_1 = 0.0686, wR_2 = 0.1573 [$I > 2\sigma(I)$]; R_1 = 0.1414, wR_2 = 0.2183 (all data). Residual electronic density max/min was 0.51/–0.47 eÅ^{-3}

CCDC 2406848 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* https://www.ccdc.cam.ac.uk.

generation, it is a monoamine. This difference is due to the influence of methyl groups on the reactivity of the hydroxy group. The synthesized new terpene derivatives can be of interest for biological testing.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.71267/mencom.7699.

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