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One-pot synthesis of pyrrolooxazoles from pyrrolyl acetylenic ketones and natural aldehydes

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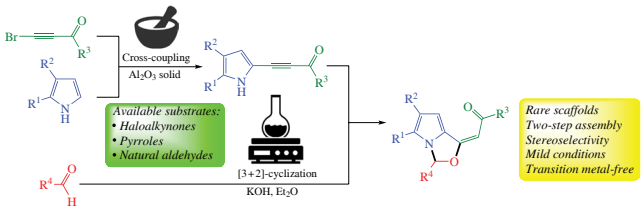
Natural aldehydes and some of their derivatives undergo base-catalyzed [3+2]-cyclization with pyrrolyl acetylenic ketones in a click-like manner (Et_2O, KOH, room temperature) to afford pyrrolo[1,2-*c*]oxazoles in up to 77% yield, a novel family of pharmaceutically prospective compounds.



Keywords: pyrrolyl acetylenic ketones, natural aldehydes, citral, cinnamaldehyde, vanillin, syringaldehyde, 3,4-di- and 3,4,5-trimethoxybenzaldehydes, pyrrolo[1,2-*c*]oxazoles, cyclization.

Natural aldehydes, abundant in environment, are considered to be attractive biosourced compounds. Many of nature-derived aromatic and unsaturated aldehydes are frequently used as efficient building blocks for design of heterocyclic systems and biologically active substances.

Typical representatives of natural aldehydes, such as cinnamaldehyde, vanillin, syringaldehyde and citral (and some of their derivatives) exhibit diverse pharmacological properties,[1–7] including anti-inflammatory,[8] anticancer,[9,10] antibacterial,[11] in particular bioactivity against drug-resistant pathogens and tumors.[5,12–15] They are used as building blocks in design of drugs and its candidates.[16–18]

The expected synergism of such important biologically active motifs as those of pyrroles, oxazoles and natural aldehydes, when incorporated into a single molecule, could lead to the creation of new compounds with increased biological activity, which can minimize the problem of multidrug resistance.

Among the suitable ways to combine these pharmacologically prospective subunits in one molecule might be our recently discovered click-like [3+2]-cyclization of pyrrolyl acetylenic ketones, readily available by the cross-coupling of pyrroles with acylhaloacetylenes in solid alumina,[19–21] with simple carbonyl compounds to give pyrrolo[1,2-*c*]oxazoles (Scheme 1).[22]

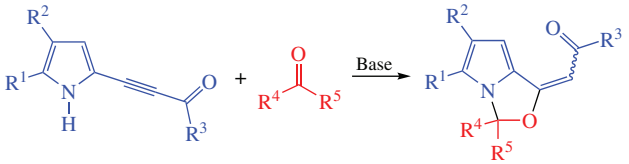
Although the cyclization described above had a wide substrate scope, the carbonyl components were mainly represented by ketones, the aldehydes class was covered by few representatives. Any natural biologically active aldehydes were not studied at all.

The aim of this work was to verify whether the above protocol is transferrable over natural aldehydes such as cinnamaldehyde, vanillin, syringaldehyde (and their methylated derivatives) and citral.

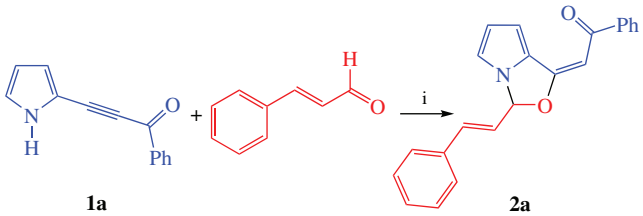
The experiments showed that the reaction of acetylenic ketone **1a** with cinnamaldehyde under the previously described conditions[22] (THF, 1 equiv. of KOH, 20–25 °C, 2 h) resulted in complex mixture of products, among which pyrrolo[1,2-*c*]-oxazole **2a** was identified and isolated in 18% yield only (Scheme 2). The reaction was accompanied by significant tarring, probably due to base-catalyzed oligomerization of cinnamaldehyde and the addition of the NH-pyrrole moiety to the double bond of this aldehyde.

Changing the solvent for diethyl ether (according to the previous screening results conditions[22]) allowed us to almost completely avoid the side processes and to obtain pyrrolo[1,2-*c*]-oxazole **2a** in 61% yield with complete conversion of starting reagents (Scheme 3).

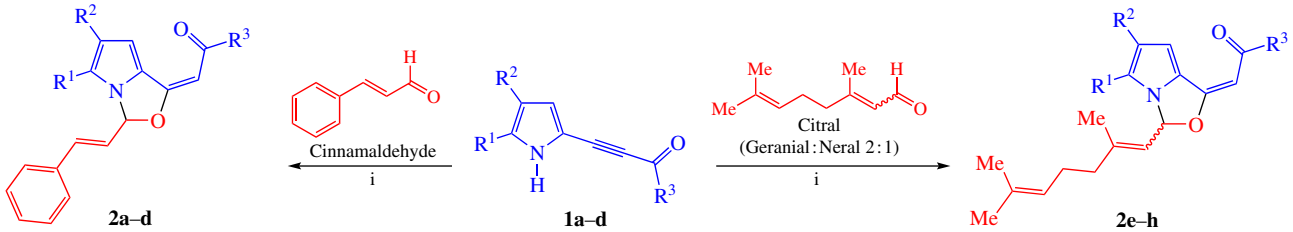
Reaction rate, effect of metal cation (Na^+ or K^+) in the base and base amount (0.5 or 1 equiv.) were evaluated by monitoring the syntheses directly in NMR tube. The reactants were mixed with NaOH or KOH in Et_2O and the NMR spectra were recorded during the reaction. With half amount (0.5 equiv.) of NaOH and KOH after 20 min the content of **2a** were 14 and 57%, respectively, indicating the much higher activity of the latter base in this process. After 40 min the content became 29 and



Scheme 1



Scheme 2 *Reagents and conditions*: i, KOH, THF, 20–25 °C, 2 h.



2a–d
E,*E*-isomer

1a–d

2e–h
E:*Z* = 2:1

2a $R^1 = R^2 = H$, R^3 = Ph, 61%
2b $R^1 = R^2 = H$, R^3 = thienyl, 66%
2c R^1 = Pr, $R^2 = Bu^n$, R^3 = Ph, 67%
2d $R^1 + R^2 = (CH_2)_4$, R^3 = 2-furyl, 51%

2e $R^1 = R^2 = H$, R^3 = Ph, 48%
2f $R^1 = R^2 = H$, R^3 = thienyl, 52%
2g R^1 = Pr, $R^2 = Bu^n$, R^3 = Ph, 49%
2h $R^1 + R^2 = (CH_2)_4$, R^3 = 2-furyl, 61%

Scheme 3 *Reagents and conditions*: i, KOH, Et_2O, 20–25 °C, 2 h.

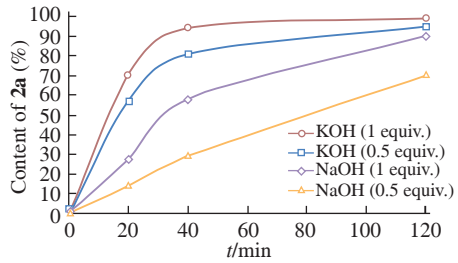


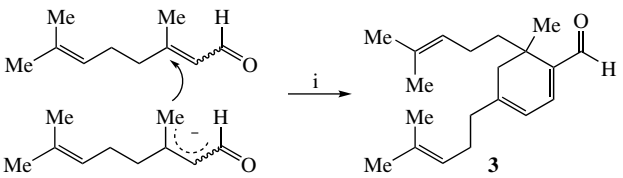
Figure 1 Effect of base and its amount on the formation of **2a**.

81%, respectively. The content of product **2a** reached 70% for NaOH after 120 min of reaction. For the same time with KOH about 5% of cinnamaldehyde and acetylene **1a** still remained. As expected, equimolar amount of NaOH and KOH lead to higher reaction rate: **1a** content were 28 and 70% after 20 min, 58 and 94% after 40 min, and 90 and 99% after 120 min (Figure 1).

Thus, the best isolated yield (61%) of target pyrrolo[1,2-*c*]-oxazole **2a** was reached with equimolar amount of KOH when the reaction was lasted for 2 h at room temperature (see Scheme 3).† These conditions were further applied as arbitrarily optimal for extension of this reaction over acetylenic ketones **1b–d** (see Scheme 3). The yields of the corresponding pyrrolo[1,2-*c*]oxazoles **2b–d** were within 51–67%.

Next, we have investigated the merging of acetylenic ketones **1a–d** with citral, an important widespread natural aldehyde. The latter commonly represent a 2:1 mixture of *E*-(geranial) and *Z*-(neral) isomers. The reaction under the above optimal conditions also proceeds smoothly, to deliver corresponding pyrrolo[1,2-*c*]-oxazoles **2e–h** in 48–61% yields, the *E*:*Z*-isomers ratio (2:1) being retained in the products in all the cases (see Scheme 3).

This reaction is accompanied by formation of a number of by-products as a result of base-catalyzed aldol condensation of citral. The major isolated side product was substituted cyclohexadiene **3** in up to 10% yield (Scheme 4).



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Scheme 4 *Reagents and conditions*: i, KOH, Et_2O, 20–25 °C, 2 h.

† *General procedure for the synthesis of pyrrolo[1,2-c]oxazoles* **2a–p**. Pyrrolyl acetylenic ketone **1a–d** (1 mmol) and aldehyde (1 mmol) were dissolved in diethyl ether (5 ml), then KOH·0.5H_2O (65 mg, 1 mmol) was added. Reaction mixture was stirred at room temperature for 2 h for citral, cinnamaldehyde, aldehydes **4c**,**d** and for 12 h for veratraldehyde **4a** and TMBA **4b** (TLC silica gel control, *n*-hexane–diethyl ether, 1:1). Then reaction mixture was filtered, solvent was removed and the residue was purified by column chromatography (SiO_2, *n*-hexane–diethyl ether from 10:1 to 2:1) to give pure pyrrolo[1,2-*c*]oxazole **2a–p**.

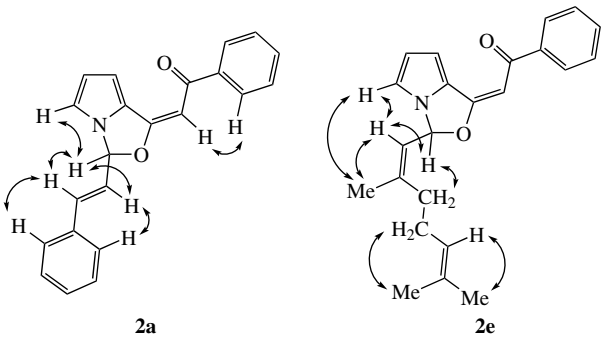
The same condensation, yielding a number of products with predominance of compound **3**, have been reported previously, spectral data (^{1}H NMR) of **3** are in coincidence with published ones.[23]

As to the stereochemistry of the reaction, all the products have *E*-configuration of acylmethylidene moiety, *i.e.* this [3+2]-cyclization is strictly stereoselective. Apparently, the process is kinetically controlled because while NMR monitoring no formation of *Z*-isomer was observed. The cause of this is likely intramolecular H-bonding between the proton at the position 3 of pyrrole ring and carbonyl group, that is supported by the strong downfield shift of the above proton (*ca.* 1 ppm) compared to the starting acetylenic ketone. This stereochemical behavior is in contrast with the previous work with simpler carbonyl compounds,[22] where the formation of both *Z*- and *E*-isomers was observed.

Structures of compounds **2** were confirmed by ^{1}H and ^{13}C NMR spectroscopy using also 2D COSY, NOESY, HMBC, HSQC techniques. Main NOESY (↔) correlations in **2a** and **2e** are presented in Figure 2.

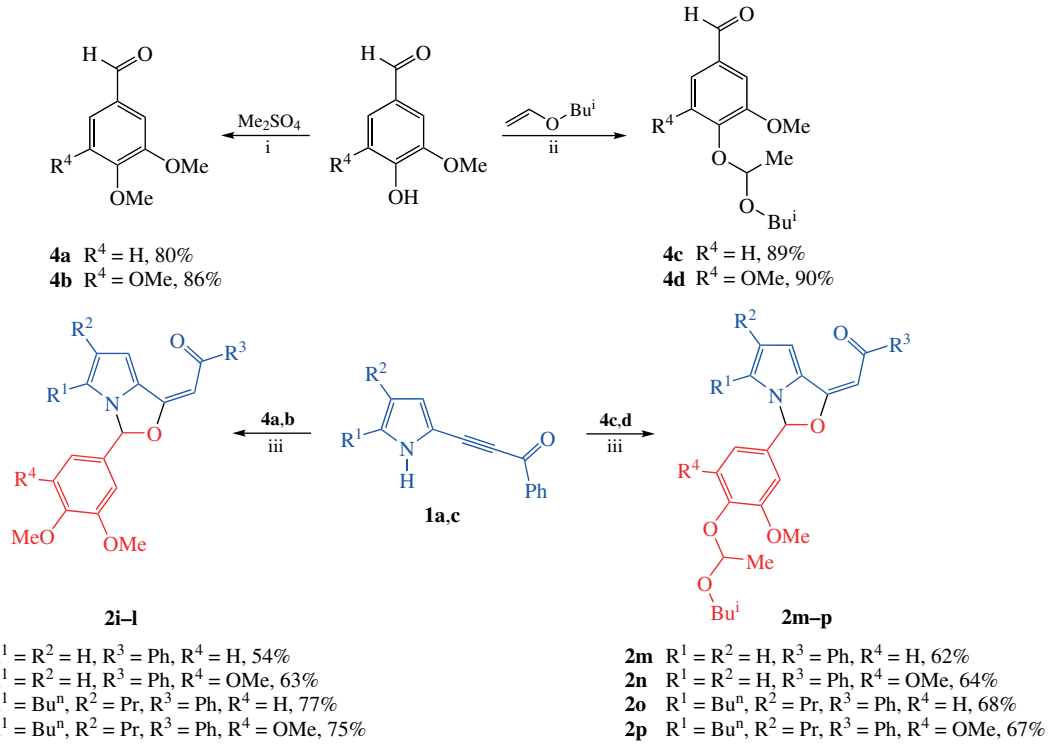
Other aldehydes of aromatic series, such as vanillin and syringaldehyde, under the same conditions turned out to be inactive and were isolated unchanged from the reaction mixture. The expected condensation did not take place even when KOH content was two-times higher and process was carried out at reflux of the solvent (Et_2O, 2 h). This result is predictable having in mind the interference of acidic phenol hydroxide in the process. One cannot exclude the influence of non-aromatic quinoid form of these aldehydes, which could present along with main benzoic tautomer.[24]

The hurdle was overcome by methylation of the phenol hydroxide groups. The methylated derivatives of vanillin (veratraldehyde, **4a**) and syringaldehyde (TMBA, **4b**) became capable of merging with pyrrolyl acetylenic ketones **1a**,**c**, albeit much slower (12 h), to provide the corresponding pyrrolo-[1,2-*c*]oxazoles **2i–l** in 54–77% yields (Scheme 5). Note, that with the methylated derivative **4b** of syringaldehyde the condensation proceeded more facile and cleaner, compared to



2a **2e**

Figure 2 Main NOESY (↔) correlations for **2a** and **2e**.



4a R^4 = H, 80%
4b R^4 = OMe, 86%
4c R^4 = H, 89%
4d R^4 = OMe, 90%

2i $R^1 = R^2$ = H, R^3 = Ph, R^4 = H, 54%
2j $R^1 = R^2$ = H, R^3 = Ph, R^4 = OMe, 63%
2k R^1 = Bu^n, R^2 = Pr, R^3 = Ph, R^4 = H, 77%
2l R^1 = Bu^n, R^2 = Pr, R^3 = Ph, R^4 = OMe, 75%

2m $R^1 = R^2$ = H, R^3 = Ph, R^4 = H, 62%
2n $R^1 = R^2$ = H, R^3 = Ph, R^4 = OMe, 64%
2o R^1 = Bu^n, R^2 = Pr, R^3 = Ph, R^4 = H, 68%
2p R^1 = Bu^n, R^2 = Pr, R^3 = Ph, R^4 = OMe, 67%

Scheme 5 *Reagents and conditions*: i, K_2CO_3, DMSO, 20–25 °C, 16 h; ii, TFA (0.6 mol%), no solvent, 50 °C, 24 h; iii, KOH, Et_2O, 20–25 °C, 2 h (for **2m**–**p**) and 12 h (for **2i**–**l**).

methylated derivative **4a** of vanillin. This is likely associated with a more electrophilic nature of aldehyde group due to electron accepting effect of two *meta*-MeO-groups. Although, the observed general deceleration of the condensation is probably resulted from the steric hindrance for the attack of pyrrolate anion at the aldehyde group.

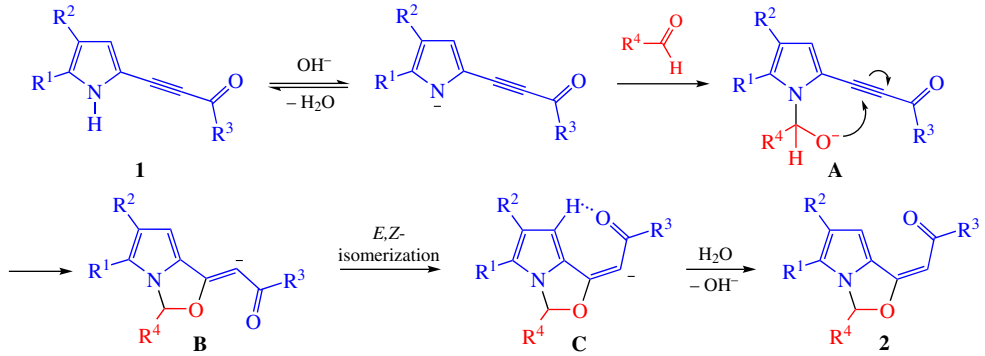
Another vanillin and syringaldehyde derivatives have been synthesized by reaction of both aldehydes with isobutyl vinyl ether (VIBE). Acetals formation was carried out in the VIBE medium without solvent to provide derivatives **4c**,**d** with protected OH-group in yield up to 90% (Scheme 5).

Cyclization of aldehydes **4c**,**d** with pyrrolyl acetylenic ketones **1a**,**c** to corresponding pyrrolo[1,2-*c*]oxazoles **2m**–**p** proceeds smoothly at room temperature with complete conversion for 2 h. Pyrrolo[1,2-*c*]oxazoles are formed as *E*-isomers (see Scheme 5).

An attention should be paid to dissimilarity of the reaction mechanism compared to that of the previous work. Essentially, the cyclization studied represents an intramolecular nucleophilic attack of the pyrrolate/carbonyl compound anionic adduct **A** to the triple bond (Scheme 6).

Commonly, such reactions proceed as concerted *trans*-addition,[25] when emerging *trans*-carbanion is simultaneously neutralized by a proton-transfer agent, that secures the kinetically controlled stereoselectivity. The *E*-stereoselectivity experimentally fixed here (^{1}H NMR) needs understanding. Assumingly, the key intermediate, *trans*-carbanion **B**, cannot be neutralized with proton rapidly enough due to lack of water in Et_2O. This allows *trans–cis* isomerization of the carbanion to occur, which should be facilitated with the formation of hydrogen bonding between pyrrole proton and carbonyl group (see above description of NMR spectra). Thus, the *E*-configuration of the adducts is predetermined already in the transition state **C**. Under the reaction conditions employed in the former work, the realization of such transition state however did not take place because in THF used there as a solvent the content of water (a proton-transfer agent) was much higher than in diethyl ether and, hence, the expected *trans*-addition occurred.

In conclusions, we have developed an efficient approach to new derivatives of pyrrolo[1,2-*c*]oxazoles based on smooth one-pot and atom-economy stereoselective [3+2]-cyclization of pyrrolyl acetylenic ketones with natural aldehydes and their derivatives, such as cinnamaldehyde, *O*-methylated derivatives of vanillin and syringaldehyde, citral. All molecular counterparts, natural aldehydes, pyrroles and oxazoles, possess wide spectrum of biological activities, and when being merged in one molecule provide new pharmaceutically prospective compounds. This work substantially expands the frontiers of the recently found



Scheme 6

[3+2]-cyclization of available pyrrolyl acetylenic ketones with carbonyl compounds, that previously tolerated only ketones and just few simple aldehydes. Thus, the results obtained demonstrate a general character of the strategy, which opens new opportunities for medicinal chemistry and the F&F industry.

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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.7571.

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