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Mendeleev Commun., 2021, **31**, 856–858

Mendeleev Communications

Novel capto-dative (*Z*,*E*)-2-(alkylthio)alk-2-en-4-ynals: synthesis and heterocyclization

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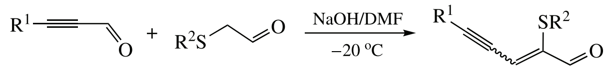
DOI: 10.1016/j.mencom.2021.11.029

An efficient synthesis of new (*Z*,*E*)-2-(alkylthio)alk-2-en-4-ynals by aldol condensation reaction of ynals with (alkylthio)-acetaldehydes using NaOH/DMF system has been developed. The reaction of these products with *N*,*N*′-diphenylethylenediamine and *p*-tosylmethyl isocyanide proceeds at the carbonyl group to form the corresponding imidazolidine and oxazole derivatives.



R^1 = Ph, Et_3Ge; R^2 = Bu, *n*-C_7H_{15}

- ¤ simple synthesis route
- ¤ gram scalability
- ¤ up to 76–81% yield
- ¤ good functional group tolerance
- ¤ synthetic applications

Keywords: α,β-enals, enynals, aldol condensation, heterocyclization, oxazoles, imidazolidines, organogermanium compounds.

The rich and rapidly developing chemistry of α,β-unsaturated aldehydes is covered in numerous articles and reviews.[1] In recent years, conjugated vinylacetylenic compounds containing double and triple carbon bonds in combination with an electron withdrawing group (aldehyde, keto, nitro groups) attract attention as useful and versatile building blocks.[2] However, the effective methods for the synthesis of highly functionalized alk-2-en-4-ynals still remain limited.[3–5]

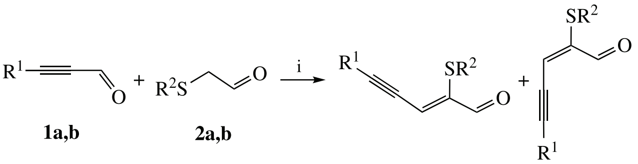
The aldol condensation is one of the most potent organic reactions for the design of complex molecules from smaller ones.[6] Interestingly, the base-catalyzed condensation has been successfully implemented to produce conjugated vinylacetylenic ketones.[7] However, this approach is still not employed for the synthesis of alk-2-en-4-ynals whose structure and chemical properties are rather intriguing.

Herein, we report the aldol condensation of propynals with (alkylthio)acetaldehydes using NaOH/DMF system to deliver 2-alkylthio-substituted (*Z*,*E*)-alk-2-en-4-ynals. It should be emphasized that sulfide substituent has been introduced into the position 2 of alk-2-en-4-ynals for the first time.

Previously, we described a synthesis of 2-alkoxy- and 2-alkylthio-3-(het)arylpropenals by the aldol condensation of (het)aryl-containing aldehydes with 2-alkoxy- and 2-(butylthio)acetaldehydes.[8] In the presence of NaOH (1–2 equiv.) at room temperature, the reaction stereoselectively proceeds in DMF. However, the disadvantages of this method include self-condensation reaction and decomposition of (butylthio)acetaldehyde to form BuSSBu. We commenced our study with optimization of the aldol reaction between α-butylthioacetaldehydes **2a** and 3-phenylpropynal **1a** in heterogeneous system solid NaOH–DMF (Scheme 1).

With 2 equiv. of NaOH, a strong resinification of the reaction mixture was observed, only 26% of the target product **3a** being isolated as a mixture of two isomers (Table 1, entry 1). At lower concentration of the alkali (1 equiv.), the total yield of the product was significantly increased, however the ^1H NMR spectrum showed signals of BuSSBu (entry 2). We found that 0.5 equiv. of NaOH provided 78% overall yield of (*Z*,*E*)-**3a** (entry 3). In the case of 0.1 equiv. of NaOH, acetaldehyde **2a** completely disappeared from the reaction mixture, while 3-phenylpropynal **1a** was retained in significant amounts (entry 4).

(Heptylthio)acetaldehyde **2b** was transformed into the corresponding enynal (*Z*,*E*)-**3b** as a 4 : 1 isomer mixture in 81% total yield (see Table 1, entry 5). In this case, the reaction was completed after 24 h. In compound **1b**, the triethylgermyl group does not undergo hydrolysis that ensures stability of the original propynal and its derivatives.[9] The reaction of 3-(triethylgermyl)-propynal **1b** with α-butylthioacetaldehyde **2a** proceeded similarly to form 5 : 1 mixture of isomers (*Z*,*E*)-**3c** (entry 6).



1a,b **2a,b**

a R^1 = Ph
b R^1 = Et_3Ge

a R^2 = Bu
b R^2 = *n*-C_7H_{15}

(*Z*)-**3a–c** (*E*)-**3a–c**

a R^1 = Ph, R^2 = Bu
b R^1 = Ph, R^2 = *n*-C_7H_{15}
c R^1 = Et_3Ge, R^2 = Bu

Scheme 1 *Reagents and conditions*: i, NaOH, DMF, room temperature.

Table 1 Optimization of the reaction conditions.[a]

Entry	Reactants	NaOH (equiv.)	Product	Yield[b] (%)	*Z*/*E* ratio
1	**1a** + **2a**	2	**3a**	26	8 : 3
2	**1a** + **2a**	1	**3a**	62	3 : 1
3	**1a** + **2a**	0.5	**3a**	78	3 : 1
4	**1a** + **2a**	0.1	**3a**	23[c]	3 : 1[c]
5[d]	**1a** + **2b**	0.5	**3b**	81	4 : 1
6	**1b** + **2a**	0.5	**3c**	76	5 : 1
7[e]	**1a** + **2a**	0.5	**3a**	73	3 : 1

[a] Reaction conditions: **1** (0.1 mmol), **2** (0.1 mmol), DMF (abs., 1.0 ml), 2 h. [b] Isolated yield after column chromatography. [c] From ^1H NMR of the crude mixture. [d] Reaction time 24 h. [e] 8 mmol scale synthesis.

Also, we have implemented the gram-scale (8 mmol) synthesis under optimized conditions when the reaction between **1a** and **2a** provided 1.43 g of 3 : 1 *Z*/*E* mixture of product **3a** (entry 7).

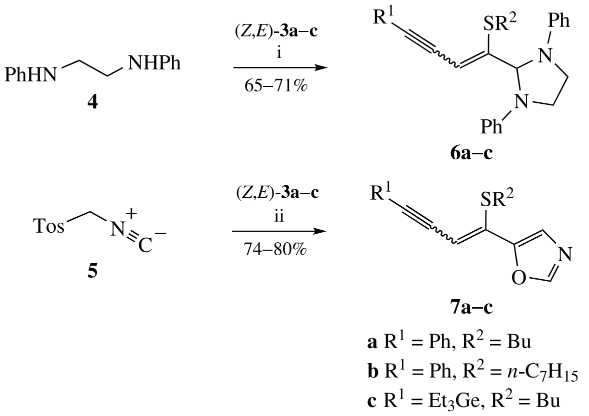
The structures of *Z*,*E*-isomers were confirmed by 2D NMR spectroscopy. The NOESY experiments revealed cross-peaks of the aldehyde and =CH protons for the major *Z*-isomer, as well as cross-peaks of the =CH and SCH$_2$ protons for the minor *E*-isomer (for details, see Online Supplementary Materials).

To estimate the relative energies of geometrical isomers of the formed enynals **3**, we carried out the quantum-chemical calculations at B3LYP 6-311++G** level of theory using Gaussian 09 software package.[10] The *Z*-isomers appeared to be more stable by 0.9–1.2 kcal mol^{-1} than *E*-isomers. At the same time, *s-trans* conformers were more preferable by 1.6–3.3 kcal mol^{-1} as compared to the *s-cis* ones. So, experimental and theoretical data are in good agreement with each other (see Online Supplementary Materials).

To evaluate the scope of the synthesis, we have carried out the reactions of the obtained compounds **3** with *N*,*N*′-diphenylethylenediamine **4** and *p*-tosylmethyl isocyanide **5** as nucleophiles (Scheme 2). In the synthesized polyfunctional captodative substrates **3**, electronic effects of carbonyl (–M) and alkylthio (+M) groups act in opposite directions. Consequently, regioselectivity of nucleophilic addition to the obtained systems is not obvious. The Parr functions could be useful tool to characterize electrophilic and nucleophilic centers in different molecules.[11] Analysis of the electrophilic Parr functions in the considered model substrates **A** and **B** predicts the presence of three electrophilic centers with close indices, however giving slight preference to the C-5 carbon atom (Figure 1, for details, see Online Supplementary Materials).

Hence, it should be expected that the synthesized enynals could interact with nucleophiles involving carbon atoms of conjugated C–C bonds. However, the nucleophiles in question chemoselectively attacked compounds **3a**–**c** exclusively at the carbonyl group. The inconsistency of predicted and observed results may be due to the fact that the Parr functions do not take into account the nature of nucleophile and steric effects. Anyway, new imidazolidines **6a**–**c** and oxazoles **7a**–**c** having an original combination of the substituents were obtained in high yields (see Scheme 2). The five-membered nitrogen-containing heterocycles such as oxazole and imidazolidine are often found in natural products, drugs, and synthetic compounds with diverse bioactivity.[12,13]

To our knowledge, the data on the reactions of nucleophiles with alk-2-en-4-ynals are lacking in literature. Heterocyclic amines (morpholine, piperidine) are known to add to the conjugated enyne ketones across the double or triple bond, depending on the kinetic and thermodynamic factors, while the addition of hydrazine hydrate occurs selectively at the C=O and C=C bonds.[14]



a R^1 = Ph, R^2 = Bu
b R^1 = Ph, R^2 = *n*-C$_7$H$_{15}$
c R^1 = Et$_3$Ge, R^2 = Bu

Scheme 2 *Reagents and conditions*: i, CHCl$_3$, 60 °C, 10–21 h; ii, K$_2$CO$_3$, MeOH, reflux, 2 h.

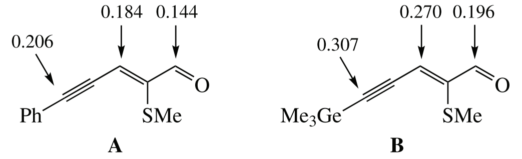


Figure 1 Electrophilic Parr functions for most stable *Z-s-trans* isomers of model compounds, calculated at B3LYP 6-311++G** level of theory.

In the obtained compounds **6**,**7**, the *Z*/*E* ratio remains the same as in the starting aldehydes. Their structures were established by NMR spectroscopy (^{1}H, ^{13}C, ^{15}N) including 2D (NOESY, COSY, HSQC, HMBC) techniques (for details, see Online Supplementary Materials). The quantum-chemical calculations showed that *Z*-isomers of oxazoles **7** are more thermodynamically favorable (by 0.7–1.1 kcal mol^{-1}), like to initial aldehydes, while in the case of imidazolidines **6** the *E*-isomers should be more stable by 0.4–2.3 kcal mol^{-1}.

In summary, we have performed the aldol reaction of ynals with (alkylthio)acetaldehydes using heterogeneous system NaOH/DMF to form 2-alkylthio-substituted (*Z*,*E*)-alk-2-en-4-ynals. These compounds reacted at the aldehyde group with certain binucleophiles to afford imidazolidine and oxazole derivatives. The course of the reactions was tracked by calculation methods. More extensive study of the reactivity of the enynals is underway in our laboratory now.

The main results were obtained using the equipment of Baikal Analytical Center of Collective Use of A. E. Favorsky Irkutsk Institute of Chemistry SB RAS. The reported study was funded by RFBR according to the research project no. 20-33-90022.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2021.11.029.

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Received: 7th June 2021; Com. 21/6578