A Straightforward Method for the Synthesis of Functionalized Trisubstituted Alkenes through Na₂S/Al₂O₃ Catalyzed Knoevenagel Condensation

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 Na_2S/Al_2O_3 catalyzed the Knoevenagel condensation between an aldehyde and an active methylene compound to yield various trisubstituted alkenes.

Keywords: Knoevenagel condensation; Na₂S; Al₂O₃; Active methylene compound; Arylidenes; Trisubstituted alkenes.

The synthesis of arylidene derivatives has attracted considerable attention from organic chemists for many years because many of them have significant biological activity. Moreover, benzylidene malononitriles have been reported to be effective anti-fouling agents, fungicides and insecticides.¹ They are important intermediates for the synthesis of various organic compounds.¹

The Knoevenagel reaction is a venerable reaction and it is the most simple and straightforward method used to produce substituted alkenes. Classically, the process consists of the condensation of aldehydes with active methylene compounds in the presence of a variety of reagents and gives good yields of arylidenes or alkylidenes. Several weak bases²⁻⁴ or Lewis acid⁵⁻⁶ catalysts have been used in the Knoevenagel condensations. It can also be performed in heterogeneous media.⁷⁻¹⁰

The preparation of sodium sulfide adsorbed onto alumina (Na₂S/Al₂O₃) was first describes by Regen¹¹ who used it to prepare dialkyl sulfides from primary alkyl halides. Pagni and Kabala¹² later reported its use in the synthesis of cyclic sulfides from straight chain α,ω -dibromides. It is also used as a reagent for the facile synthesis of 2,11dithia[3,3]metacyclophanes.¹³

In continuation of our interest in catalytic¹⁴⁻²³ and Knoevenagel reactions,²⁴⁻²⁷ in the present study, we report the sodium sulfide adsorbed onto basic alumina (Na₂S/Al₂O₃) as a highly efficient catalyst for condensation of aldehydes with active methylene compounds such as malononitrile and ethylcyanoacetate under heterogeneous conditions. We first performed the Knoevenagel reaction of

3-nitronezaldehyde with malononitrile, in the presence of a catalytic amount of Na_2S (20 mol %) in refluxing dichloromethane. After 1.5 h, 99% yield of the product was obtained. In order to investigate the effect of the alumina on the reaction time, the reaction was repeated in the presence of Na_2S (20 mol %) and basic Al_2O_3 (0.05 g). Interestingly, we have obtained 99% yield of 1,1-dicyano-2-phenylethylene after only 5 min at room temperature.

After optimizing the reaction conditions, various aromatic aldehydes reacted very well with malononitrile and ethylcyanoacetate as active methylene compounds to give the corresponding arylidenes in good to excellent yields (Scheme I). More interestingly, the reaction is highly stereoselective affording alkenes in E-geometry.

Scheme I

$$R_{1} \xrightarrow{O}_{R_{2}} + \left\langle \begin{array}{c} CN \\ R_{3} \end{array} \xrightarrow{Na_{2}S (20 \text{ mol}\%)/Al_{2}O_{3}(0.05 \text{ g})} \\ CH_{2}Cl_{2} \end{array} \xrightarrow{R_{1}} \\ R_{2} \xrightarrow{CN}_{R_{3}} \\ R_{3} = CN, COOEt \end{array} \right\rangle$$

Knoevenagel condensation involving various aromatic carbonyl compounds with malononitrile and ethylcyanoacetate as the active methylene compounds was carried out with Na₂S/Al₂O₃ at room temperature and under reflux conditions. The aromatic aldehydes readily condensed with malononitrile, while with ethylcyanoacetate, the reaction is slightly slower. This may be attributed to the fact that abstraction of a proton from the active methylene group of ethylcyanoacetate is more difficult due to its lower activity.

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Entry	\mathbb{R}^1	R ²	R ³	Time (min)	Condition	$X_{1}^{2} = 1 + (0/)^{2}$	m.p. (°C)	
					Condition	Y leid (%)	Found	Reported
1	C ₆ H ₅ -	Н	CN	20	Reflux	90	83-84	83 ²⁸
2	$4-Cl-C_6H_4-$	Н	CN	30	Reflux	90	166-167	164^{31}
3	2-NO ₂ -C ₆ H ₄ -	Н	CN	10	room temperature	98	141-142	-
4	3-NO ₂ -C ₆ H ₄ -	Н	CN	5	room temperature	99	101-103	104-105 ²⁹
5	4-NO ₂ -C ₆ H ₄ -	Н	CN	5	room temperature	97	161-162	$159-160^{28}$
6	4-CH ₃ -C ₆ H ₄ -	Н	CN	55	Reflux	96	137-138	135^{32}
7	2-CH ₃ O-C ₆ H ₄ -	Н	CN	45	Reflux	97	80	78^{35}
8	4-CH ₃ O-C ₆ H ₄ -	Н	CN	10	Reflux	94	113-114	115^{28}
9	C ₆ H ₅ -HC=CH-	Н	CN	5	Reflux	98	122-123	128^{32}
10	C ₆ H ₅ -	C_6H_5	CN	24 hours	Reflux	No reaction	-	-
11	C ₆ H ₅ -	CH_3	CN	24 hours	Reflux	No reaction	-	-
12	C ₆ H ₅ -	Н	COOEt	25	Reflux	90	50-51	52^{28}
13	$4-Cl-C_6H_4-$	Н	COOEt	45	Reflux	90	87-89	87 ³⁴
14	2-NO ₂ -C ₆ H ₄ -	Н	COOEt	7	room temperature	96	102	96 ³⁵
15	3-NO ₂ -C ₆ H ₄ -	Н	COOEt	5	room temperature	95	130	128-132 ³³
16	4-NO ₂ -C ₆ H ₄ -	Н	COOEt	7	room temperature	95	169	170^{34}
17	4-CH ₃ -C ₆ H ₄ -	Н	COOEt	65	Reflux	94	93-94	92^{28}
18	2-CH ₃ O-C ₆ H ₄ -	Н	COOEt	60	Reflux	90	70	69 ³⁴
19	4-CH ₃ O-C ₆ H ₄ -	Н	COOEt	30	Reflux	86	85	$80-84^{28}$
20	HC=CH-C ₆ H ₅	Н	COOEt	5	Reflux	96	115	116^{30}
21	C ₆ H ₅ -	C_6H_5	COOEt	24 hours	Reflux	No reaction	-	-
22	C ₆ H ₅ -	CH_3	COOEt	24 hours	Reflux	No reaction	-	-

Table 1. Knoevenagel condensation catalyzed by Na₂S/Al₂O₃

^a Yields refer to the isolated pure products.

It can be seen from Table 1 that all reactions proceed selectively to the dehydrated products without any side reaction. No self-condensation, Cannizaro products or hydrated products of Knoevenagel adducts were obtained.

As shown in Table 1, aromatic aldehydes containing both electron donating or withdrawing groups gave the desired products in good to excellent yields in the reaction time ranging from 5 to 65 minutes. Deactivated aldehydes such as nitrobenzaldehyde isomers and 4-chlorobenzaldehyde required shorter reaction times due to the electron withdrawing groups (Table 1, entries 2-5, 13-16). Moreover, the steric hindrance seems to have significant effects on the reaction times and yields (Table 1, entries 7-8, 18-19). We also investigated Knoevenagel condensation of ketones with malononitrile and ethylcyanoacetate. No reactions occurred under the conditions in which aldehydes gave almost quantitative conversions.

The use of Na₂S/Al₂O₃ as catalyst in this reaction allowed us to perform the condensation under mild conditions. In this case, yields were excellent. The salient features of this reaction are the following: a) use of inexpensive and readily available catalyst b) and simplicity of performance and work-up. In order to show the merit of the present work in comparison with some reported procedures, we compared the results of the synthesis of olefinic compounds in the presence of HZSM-5,²⁴ Proline,³⁶ RE-NaY zeolite³⁷ and Na₂S/Al₂O₃ with respect to the reaction times and yield of products (Table 2). The results show that Na₂S/Al₂O₃ promotes the reaction more effectively than HZSM-5. Reaction in the presence of other catalysts in Table 2 required longer reaction times.

In summary, we have demonstrated the Na_2S/Al_2O_3 catalyzed condensation between various aldehydes and active methylene compounds in a heterogeneous system. This method offers some advantages in terms of simplicity of performance, easy work-up, use of inexpensive, available and easy to handle catalysts and high yields of products and

 Table 2. Comparison of the synthesis of trisubstituted alkenes using different catalysts

	<u> </u>			
Entry	Catalyst	Time	Yield (%)	Ref.
1	HZSM-5	5-12 (h)	60-80	24
2	Proline	Over night	66-100	36
3	RE-NaY Zeolite	8-18 (h)	78-100	37
4	Na ₂ S/Al ₂ O ₃	5-65 (min)	86-99	This work

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relatively short reaction times.

EXPERIMENTAL

Melting points were measured by using the capillary tube method with an electro thermal 9100 apparatus. ¹H NMR spectra were recorded on a Brucker DRX-90 AVANCE by using TMS as an internal standard (CDCl₃ solution). IR spectra were recorded as KBr disc on the FT-IR Brucker Tensor 27. All products were known compounds and identified by comparison of their spectral and physical data on the basis of literature descriptions.²⁸⁻³⁵

Reaction of aldehydes with active methylene compounds: General procedure

 $Na_2S.9H_2O$ (20 mol %) and basic alumina (0.05 g) were mixed thoroughly in a mortar. To this mixture CH_2Cl_2 (3 mL), aldehyde (1 mmol) and active methylene compound (1 mmol) were added. The mixture was stirred at room temperature or under reflux for the indicated time (Table 1). After completion of the reaction, as indicated by TLC, the mixture was filtered off. Upon the evaporation of solvent, the crude product was recrystallized from ethanol and identified by comparison of spectral and physical data with those described in the literature.

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