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Potassium phosphate catalyzed synthesis of substituted o-propargylsalicylaldehydes

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Abstract

We have explored the catalytic efficiency of anhydrous K_3PO_4 for the synthesis of o-propargylsalicylaldehydes by the reaction of substituted salicylaldehydes with propargyl bromide in S_N2 manner in DMF at room temperature. Operational simplicity, atom economy, easy work-up with high purity of products, and commercially available reagents are key features of the present method which adopts most of the principles of green chemistry.

Keywords: Salicylaldehyde, o-propargylation, potassium phosphate, propargyl bromide

Introduction

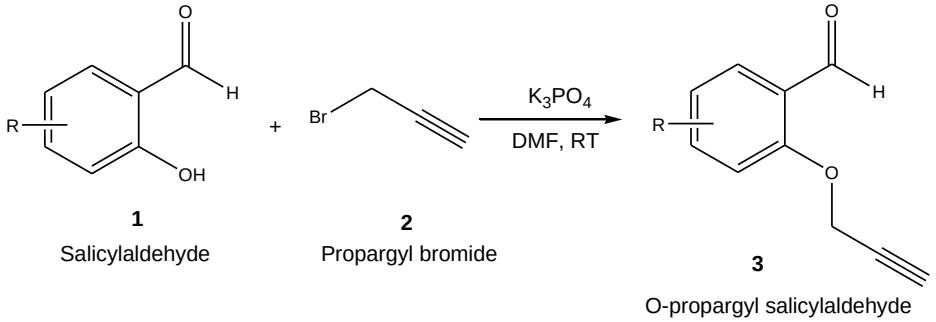
One of the prime objectives of organic synthesis is the development of highly efficient synthetic protocols for complex molecules used as precursors in useful organic transformations. Propargylation is one of the most important fundamental reactions in organic synthesis. It features mild reaction conditions, a tolerance of a diverse range of functional groups, and easy construction of carbon-carbon and carbon-heteroatom bonds. [1] The high density of functional groups of the resulting products renders them exceptionally versatile complex synthetic intermediates. This involves the propargyl as an equivalent for either a nucleophile or an electrophile .

o-Propargylsalicylaldehydes represent structural complex as precursors for important organic transformations namely synthesis of allylic amide functionalized 2*H*-chromenes and coumarins[2], click approach for the synthesis of 1,4-disubstituted 1,2,3-triazoles [3], benzopyran-fused tetra and pentacyclic framework synthesis by the domino Knoevenagel hetero Diels–Alder (DKHDA)[4] and 1-methyl-2-(2-(prop-2-yn-1-yloxy)benzylidene)hydrazine analogues[5], etc. They have commonly been prepared by a reaction of salicylaldehydes using propargyl bromide [6-12] /chloride [13]/ tosylate [14] employing K_2CO_3 [6-11], [13-14] or NaH[12] as a base in DMF solvent.

Anhydrous K_3PO_4 as a base has attracted the attention of scientists working in organic transformations due to its plethora of applications.[15-21] Catalytic efficiency of K_3PO_4 has been explored in Knoevenagel condensation resulting in alkylated Meldrum's acid [15], thia-Michael addition [17], tetrahydrobenzo[*b*]pyran[18], phosphonic acid diethyl esters [19], nitroaldol condensation[20], synthesis of 3-carboxycoumarins[21] and chalcones [22] encouraged us to explore its efficiency in the synthesis of *o*-propargyl salicylaldehyde. K_3PO_4 is low-cost, non-toxic, and could be an effective catalyst in the O-propargylation reaction. This is due to potassium phosphate possessing a potent electron-withdrawing counter anion, specifically PO_4^{3-}, which enhances the oxophilicity of the K^+ ion enough to establish a strong coordinate bond with the oxygen atom of OH in salicylaldehyde, facilitating the reaction efficiently. This manuscript reports anhydrous potassium phosphate-mediated synthesis of o-propargyl salicylaldehyde from salicylaldehyde and propargyl bromide in DMF at room temperature. (Scheme 1)

Results and Discussion

Scheme 1: Synthesis of o-propargyl salicylaldehydes



1 Salicylaldehyde + **2** Propargyl bromide → **3** O-propargyl salicylaldehyde

In an initial study, catalyst optimization was carried out for a model reaction of salicylaldehyde and propargyl bromide in dimethyl formamide (DMF) at room temperature. A model reaction was performed under catalyst-free conditions in DMF to explore the role of the catalyst. However, the reaction failed to give the desired product even after a prolonged time. **(Table 1, Entry 1)** Therefore, screening of catalyst was carried out by

employing various organic and inorganic bases *viz*. K_2CO_3, K_3PO_4, Et_3N, Et_2NH, and L-proline for model reaction. **(Table 1, Entries 2-6)** The best result was obtained in the presence of K_3PO_4 in terms of yield and reaction time. **(Table 1, Entry 3)** Conversely, poor yield was observed with Et_3N, Et_2NH, and L-proline. **(Table 1, Entries 4-6)**

Table 1. Screening of catalysts

Entry	Catalyst	Time (h)	Yield[b] (%)
1	-	48	-
2	K_2CO_3	24	90
3	K_3PO_4	22	94
4	Et_3N	30	58
5	Et_2NH	30	40
6	L^- Proline	30	45

[a]Reaction conditions: Salicylaldehyde (1 mmol), Propargyl bromide (1.2mmol), Base (1.1mmol), DMF (5 mL), RT; [b]Isolated yield

Optimization of solvent was carried out by performing model reaction in various solvents such as, acetone, ethanol (EtOH), dimethyl formamide (DMF), and acetonitrile (ACN). **(Table 2, Entries 1-4)**. Screening study revealed that, DMF was the best solvent for present transformation in terms of time and yield.

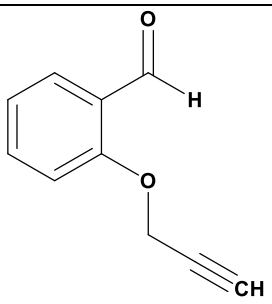
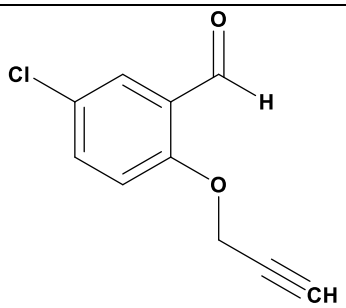
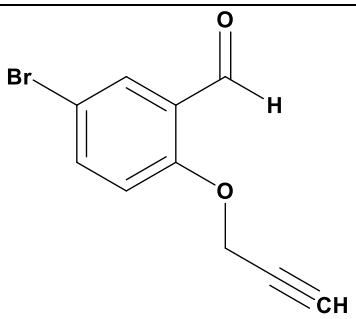
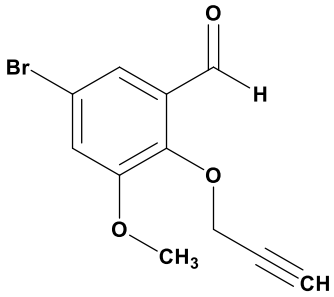
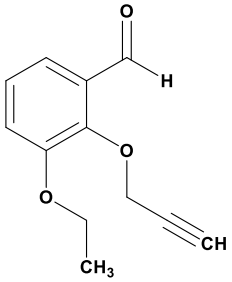
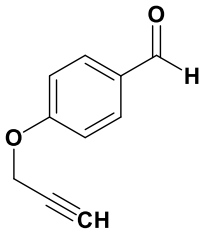
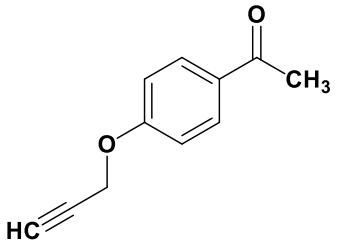
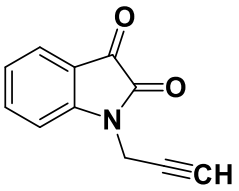
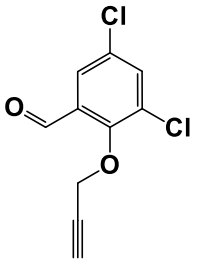
Table 2. Screening of solvents

Entry	Solvents	Time (h)	Yield (%)
1	DMF	22	94
2	Acetone	24	80
3	EtOH	24	60
4	Acetonitrile	24	89

[a]Reaction conditions: Salicylaldehyde (1 mmol), Propargyl bromide (1.2mmol), Potassium phosphate (1.1mmol), Solvent (5 mL), RT; [b]Isolated yield

After optimization of reaction conditions, we turned our attention towards assessing generality of the protocol by reaction of variety of substituted salicylaldehydes and propargyl bromide in the presence of K_3PO_4 in DMF as solvent. **(Table 3)** All the reaction proceeded smoothly affording the corresponding o-propargylated salicylaldehydes with good yields. The method was found to be suitable for both electron donating and withdrawing substituents present on the salicylaldehydes **(Table 3, entries 1-5)**. It is noteworthy to mention that isatin also undergo smooth propargylation under optimized reaction conditions affording desired product in good yield. **(Table 3, entries 6-8)**

Table 3. Library of synthesized substituted o-propargylsalicylaldehydes, acetophenone, benzaldehyde and *N*-propargyl isatin

 **3a, 20 h, 96%** 70-71°C [69-72 °C(CAS No. 29978-83-4)]	 **3b, 22 h, 92%** 74-75 [75-76 °C (CAS No. 224317-64-0)]	 **3c, 21 h, 94%** 93-95 [94-96 °C(CAS No. 122835-14-7)]
 **3d, 24 h, 90%** 151-152°C [153-154 °C(CAS No. 1432437-11-0)]	 **3e, 23 h, 90%** 113-115 °C [112-114 °C(CAS No. 1099639-68-5)]	 **3f, 24 h, 88%** 83-85 [80-84 °C (CAS No. 5651-86-5)]
 **3g, 24 h, 89%** 78-80 °C [81-83 °C (CAS No. 34264-14-7)]	 **3h, 23 h, 87%** 154-156 °C [156-158 °C(CAS No. 4290-87-3)]	 **3i, 23 h, 87%** 83-84 °C [84-86 °C (CAS No. 1126527-53-4)]

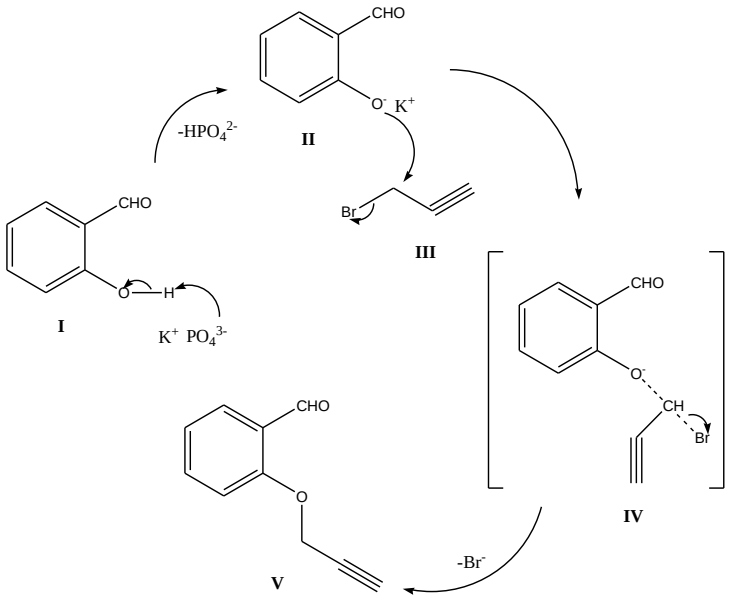
[a]**Reaction conditions:** Aldehyde/ Isatin/Acetophenone (1 mmol), Propargyl bromide (1.2 mmol), Potassium phosphate (1.1 mmol), DMF (5 mL), RT; [b]Isolated yield

The formation of the desired product was confirmed by various spectroscopic techniques such as IR, ^{1}H, and ^{13}C NMR which are in good agreement with the structure of synthesized derivatives. IR spectrum **(Fig. 1)** of *o*-propargylsalicylaldehyde**(Entry 1, Table 3)** shows the absorption band of carbonyl of aldehyde at 1678 cm^{-1}, whereas sharp absorption band observed around 2108 cm^{-1} due to terminal alkyne group by vanishing broad –OH stretching band around 3190 cm^{-1} confirms the o-propargylation of salicylaldehyde. ^{1}H NMR spectrum **(Fig. 2)** of the same moiety exhibits two sharp singlets and one doublet at δ 2.57, 10.48 and 4.83

ppm corresponding to alkynyl -CH, -CHO, and -OCH_2 protons, respectively. Three multiplets observed in the range of 7.07-7.87 display aromatic protons. In ^{13}C NMR **(Fig. 3)** the signal detected at δ 56.36 due to the presence of methylene carbon of O-CH_2- that was confirmed by the inverted signal observed in DEPT 135 at same δ value. Characteristic signal for -C=O of aldehyde functionality observed at 189.57 ppm. Aromatic carbons were observed in the range of δ 113.16-159.74 ppm.

o-Propargylsalicylaldehydes were prepared from the corresponding substituted salicylaldehyde by applying Williamsons ether synthesis via S_N2 pathway. The proposed mechanism is depicted in **Scheme 2**. Initially, the reaction of salicylaldehyde (I) with base potassium phosphate produces phenoxide ion (II) i.e. conjugate base, potassium phenoxide which attacks the propargyl bromide (III) at more electrophilic methylene site resulting in the displacement of bromine atom by the formation of a new carbon-oxygen bond furnished o-propargyl salicylaldehyde (V) *via* intermediate IV.

Scheme 2. Proposed mechanism for o-propargylation of salicylaldehydes



Conclusions

In the present manuscript, we have synthesized substituted o-propargylsalicylaldehydes by propargylation reaction of substituted salicylaldehydes and propargyl bromide in S_N2 manner using anhydrous K_3PO_4 as a base in DMF solvent. Ambient temperature, simple procedure, high yield and easy workup, high purity of products, and wide substrate scope are the green aspects of the present transformation. These o-propargylsalicylaldehydes can be used as precursors for many heterocycles and hence the present method will open the window of variety of heterocycles.

Experimental Section

General. All the reagents were commercially available (Sigma Aldrich) and used without further purification. Melting points were determined by open capillary method and are uncorrected.IR spectra were recorded on

FTIR-7600 spectrometer.^{1}H and ^{13}C NMR spectra were measured on a Bruker400 spectrometer operating at 400 and 100 MHz, respectively, using $CDCl_3$ as a solvent and TMS as the internal standard.

General procedure for synthesis of o-propargylsalicylaldehydes. In 25 mL round bottom flask, salicylaldehyde / aldehydes / ketones (1mmol), propargyl bromide (1.2 mmol) in DMF (5mL) was added anhydrous K_3PO_4 (1.1 mmol), and stirring was carried out till completion of reaction. Progress of reaction was monitored by TLC. Then ice was added to reaction mixture. Precipitated product formed was filtered and washed with water and dried.

Spectral data of representative o-propargylsalicylaldehyde derivatives

Entry 3a (Table 3). 2-(prop-2-ynyloxy)benzaldehyde. Brownish solid; Obs. mp 70 °C, Lit. mp 69.0-72.0 °C (CAS No.- 29978-83-4), IR **(Fig. 1)**: 3269, 2928, 2871, 2108, 1678, 1597, 1458, 1296, 1215, 1003, 744, 679 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) **(Fig. 2)**: δ 10.48 (s, 1H, -CHO), 2.57 (s, 1H, Propargyl-CH), 4.83 (d, 2H, -OCH_2), 7.07-7.13 (m, Ar-2H), 7.54-7.59 (m, Ar-1H), 7.84-7.87 (dd, Ar-1H, *J* 8 Hz, 1.6 Hz) ppm [25]; ^{13}C NMR (400 MHz, $CDCl_3$) **(Fig. 3, 4)**: δ 56.36, 113.16, 121.68, 125.46, 128.58, 135.72, 159.74, 189.57 ppm

Entry 3i (Table 3). 3,5-dichloro-2-(prop-2-ynyloxy)benzaldehyde. White solid; Obs. m.p. 82-84 °C, Lit. m.p. 84-86 °C (CAS No.-1126527-53-4); IR **(Fig. 5)**: 3268, 2975, 2869, 2113, 1683, 1598, 1479, 1457, 1400, 1286, 1218, 1193, 1103, 1043, 1012, 923, 831, 757, 698 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) **(Fig. 6):** δ 10.39 (s, 1H, -CHO) ,2.55 (s, 1H, Propargyl-CH), 4.90 (d, 2H, -OCH_2), 7.64-7.65 (d, Ar-1H, *J* 2.4 Hz), 7.77-7.78 (d, Ar-1H, *J* 2.4 Hz) ppm [25]; ^{13}C NMR (400 MHz, $CDCl_3$) **(Fig. 7, 8)**: δ 61.84, 70.25, 77.21, 126.41, 129.75, 131.33, 132.79, 135.58, 188.18 ppm

Supplementary Material

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