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# Sodium tertiary-pentoxide: A mild and efficient base to make C-C bond between acetylenes and aldehydes (or) ketones producing propargyl alcohols

This report confirms that sodium tertiary-pentoxide is a very effective base for the nucleophilic addition of acetylenes to aldehydes and ketones in 1,4-dioxane at room temperature. These mild and operationally simple procedures have been working well with a variety of aromatic and heteroaromatic aldehydes and also equally working well with aliphatic, aromatic and heteroaromatic ketones. A very clean product of secondary and tertiary propargylic alcohols were obtained from 71-94% yield. This process has been explored in bulk scale synthesis on selected molecules and also adapted the column free purification for most of the substrates.

**Keywords:** C–C bond formation / Propargyl alcohol/ Alkynes / Aldehydes / Ketones

## Introduction

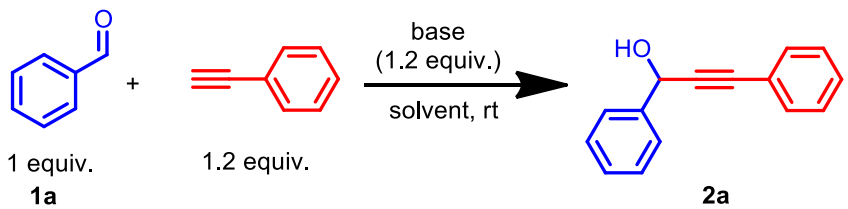
Development of straightforward and flexible synthetic routes for the constructions of C-C triple bond[1] is of great interest in organic synthesis due to their presence in a wide variety of natural products and pharmaceutical compounds,[2] among them alkynylation of carbonyl compounds to generate internal propargylic alcohol is a method[3] which produce internal secondary and tertiary propargyl alcohols, respectively. These propargyl alcohols are versatile intermediates for many transformations to make advance molecules.[4]

Several methods are being published for making propargyl alcohol using pyrophoric metal-bases; methyl magnesium bromide, butyl-lithium and sodium amide[5] to generate strong enough acetylide anions from terminal acetylene at very low temperature (-70°C) and subsequent nucleophilic addition to aldehydes or ketones.[6] Similarly, the transition-metal complexes (e.g., Ti, Cr, Cu, Zn, Ru, Rh, Pd, Ag, or In)[7] were also utilized in the past for enantioselective/non-enantioselective syntheses. However, these methods have critical drawbacks, such as moisture sensitivity, tedious workup, toxicity, high catalyst loadings, long reaction times and constrains on using aryl/alkyl halides, which lowers the overall feasibility

of these approaches for large-scale applications.[8] Apart from the pyrophoric and metal catalytic reagents; reactions using alkoxide and hydroxide bases, for example $Bu_4NBr$/NaOH,[9] $CsOH.H_2O$/THF,[10] KOH/DMSO,[11] *t*BuOK,[12] $CaC_2/Cs_2CO_3$/DMSO,[13] have been widely investigated to circumvent these drawbacks, however the reported methods possess poor yields[14] due to the decomposition of reaction mass and retro-Favorskii decomposition.[15] In addition, using *t*BuOK only converted aliphatic ketones into the corresponding tertiary ynols; attempted alkynylation of aldehydes were also unsuccessful at many conditions. A syringe pump technique adopted for handling $CsOH.H_2O$/THF[16] also failed to achieve the alkynylation of aromatic carbonyl compounds.

Furthermore, the reported methods for the synthesis of propargyl alcohols using strong metal bases, metal catalysts and alkoxide (or) hydroxide bases accounts complex operational procedures and economically restrictive. This prompted us to broaden our investigation on different sodium alkoxide bases and define a simple and economically viable route to synthesis propargyl alcohols. With the aim of achieving this, Sodium tertiary-pentoxide (NaO*t*P) is employed in the reactions as it is cheap, easily accessible and not yet explored on C-C bond forming reactions. This resulted; mild and highly efficient sodium tertiary-pentoxide mediated C-C bond formation between aldehyde/ketone with aryl acetylene producing internal propargyl alcohols. The added advantage of this scalable process is an easy purification without the aid of traditional column chromatography for most of the compounds.

**Table 1: Study of optimum reaction conditions[a]**



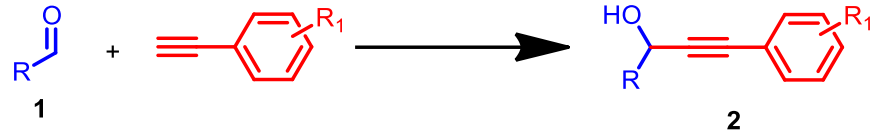
| Entry | Solvent | Base | t (h) | % yield of 2a |
|---|---|---|---|---|
| 1 | DMF | KOH | 15 | 5 |
| 2 | DMF | LiOH | 15 | 0 |
| 3 | DMF | NaOH | 15 | 15 |
| 4 | DMF | NaOMe | 15 | 0 |
| 5 | DMF | NaOEt | 15 | 0 |
| 6 | DMF | NaO*t*Bu | 15 | 10 |
| 7 | DMF | KO*t*Bu | 1 | 15 |
| 8 | DMF | LiO*t*Bu | 1 | 5 |
| 9 | THF | KO*t*Bu | 1 | 20 |
| 10 | THF | NaO*t*Bu | 1 | 40 |
| 11 | THF | LiO*t*Bu | 1 | 20 |
| 12 | THF | NaO*t*Pen | 1 | 50 |
| 13 | THF | LiHMDS (1M in THF) | 1 | 0 |
| 14 | THF | KHMDS (1M in THF) | 1 | 0 |
| 15 | THF | NaHMDS (1M in THF) | 1 | 0 |
| 16 | THF | KO*t*Bu (1M in THF) | 1 | 25 |
| 17 | THF | NaO*t*Bu (1M in THF) | 1 | 55 |
| 18 | THF | NaO*t*P (30% in THF) | 10 | 65 |
| 19 | 1,4-Dioxane | NaO*t*P (30% in THF) | 0.5 | 94 |
| 20 | Acetonitrile | NaO*t*P (30% in THF) | 1 | 5 |
| 21 | DMF | NaO*t*P (30% in THF) | 1 | 0 |

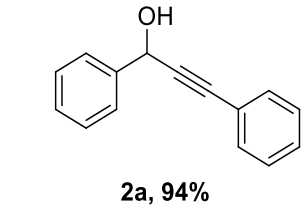
| | | | | |
|---|---|---|---|---|
| 22 | DMSO | NaO*t*P (30% in THF) | 1 | 0 |

**Results and discussion**

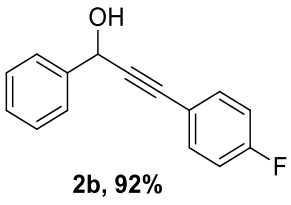
In order to optimize the alkynylation, we have chosen benzaldehyde and phenyl acetylene as model substrate (Table 1). The reaction was initially carried out with solid hydroxide and alkoxide bases separately in N,N Dimethylformamide (DMF) at room temperature. This leads to the reaction masses completely charring in all bases; only trace amount of product **2a** was isolated in sodium and potassium tertiary butoxides (Table 1, entry: 1-8). The next trials were made with the solid KO*t*Bu and LiO*t*Bu bases in the solvent tetrahydrofuran (THF), that yielded 20% of **2a** (Table 1, entry: 9, 11), still the reactions were incomplete and decomposes over a period, whereas the sodium alkoxides were giving average yield of **2a** (Table 1, entry: 10, 12). The further reactions with solutions of lithium bis(trimethylsilyl)acetamide, potassium bis(trimethylsilyl)acetamide and sodium bis(trimethylsilyl)acetamide[17] in THF were conducted to achieve strong acetylide anion for nucleophilic addition, however there was no desired compound observed (Table 1: entry: 13-15). Solutions of metal alkoxides in THF were next selected instead of solids to ease the reactions, to avoid solubility issues and enhance safety and the rate of reactions. These reactions enforced separately with KO*t*Bu (1M in THF) and NaO*t*Bu (1M in THF) in THF solvent at room temperature yielded 25% and 55% of **2a**, and the yield was improved by using NaO*t*P (30% in THF) (Table 1, entry: 18). At the end, the effect of solvent was tested with NaO*t*P (30% in THF); except THF and 1,4-dioxane, the remaining solvents acetonitrile, DMF and DMSO have not produced the desired propargyl alcohols (Table 1, entry: 19-21). Hence, concluded that the entry 19 of Table 1, 94% yield of **2a**, as optimised reaction condition.

**Table 2: Scope of the synthesis of secondary propargyl alcohols[a]**

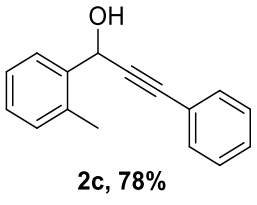


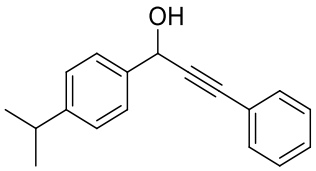

**2a, 94%**



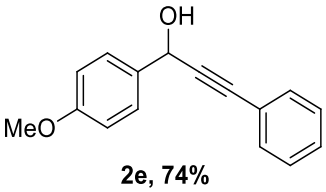

**2b, 92%**



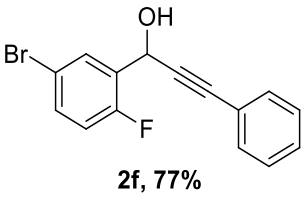

**2c, 78%**



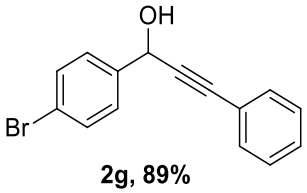

**2d, 93%**



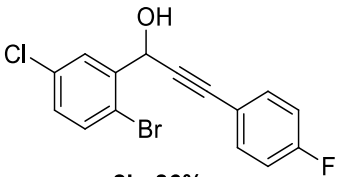

**2e, 74%**



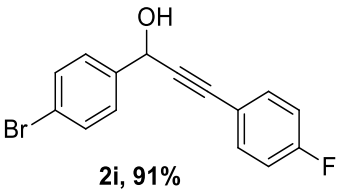

**2f, 77%**



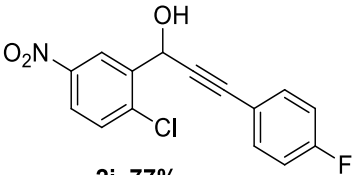

**2g, 89%**



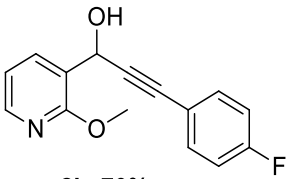

**2h, 86%**



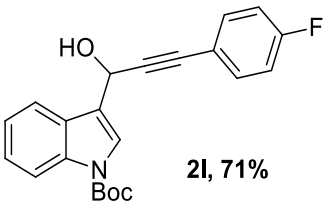

**2i, 91%**




**2j, 77%**




**2k, 70%**



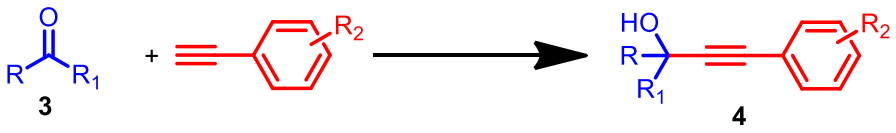

**2l, 71%**

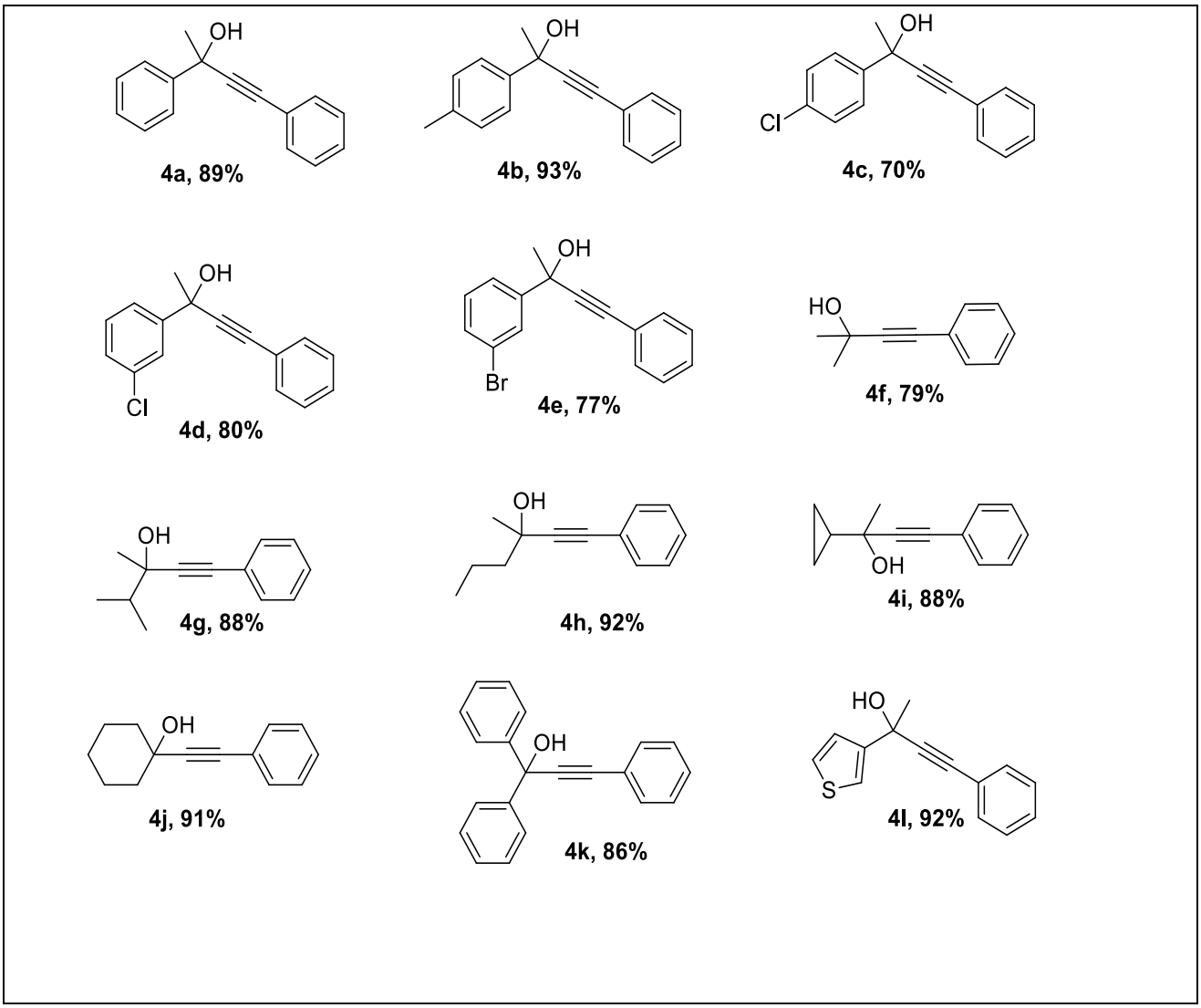
[a]A solution of acetylene (1.2 equiv.) in 1,4-dioxane (10 volume) in round bottom flash (RBF) under nitrogen atmosphere, was added Sodium tertiary pentoxide (NaO*t*P) (30% in THF) (1.2 equiv.) at room temperature for 5 min., and stirred for 10 minutes. A solution of ketone (**1**) (1.0 equiv.) in 1,4-dioxane (5 volume) added into the mass for 5 min. and stirred for 15-30 minutes

With the optimal reaction conditions in hand, we set about evaluating the scope for making secondary propargyl alcohols, when benzaldehyde was treated with phenyl acetylene and 4-fluorophenyl acetylene produced excellent yields of **2a** and **2b,** respectively. Similarly, electron donating substituents at ortho-position of benzaldehyde has given relatively less yield, 78%, of **2c** and there was an excellent yield when the reaction was carried out on 4-isopropylbenzaldehyde (**2d),** whereas relatively less yield (74%) was obtained when the

reaction was carried out between 4-methoxybenzaldehyde and aryl alkyne (**2e**). Following the very good to excellent yields of electron rich benzaldehyde derivatives, the focus was shifted towards the electron deficient carbonyls; the 5-bromo-2-fluorobenzaldehyde and 4-bromobenzaldehyde were successfully coupled with phenyl acetylene and offered 77% of **2f** and 86% of **2g**, respectively. 4-Fluorobenzaldehyde was separately treated with 2-bromo-5-chlorobenzaldehyde, 4-bromobenzaldehyde and 2-chloro-5-nitrobenzaldehydes, and yielded the respective propargyl alcohols, 86% of **2h**, 82% of **2i** and 73% of **2j**. Here, the –bromo or –chloro carrying propargyl alcohols are potential starting material for Sonogashira and Suzuki coupling reactions.[18] Furthermore, the heterocyclic carbonyl compounds, such as substituted pyridine and NBoc Indole also well accommodated the optimized condition and produced good yield of **2k** and **2l**.

**Table 3: Scope of the synthesis of tertiary propargyl alcohols[a]**






[a]A solution of acetylene ( (1.2 equiv.) in 1,4-dioxane (10 volume) in RBF under nitrogen atmosphere, was added Sodium tertiary pentoxide (NaO*t*P) (30% in THF) (1.2 equiv.) at room temperature for 5 min., and stirred for 10 minutes. A solution of ketone (**3**) (1.0 equiv.) in 1,4-dioxane (5 volume) added into the mass for 5 min. and stirred for 1-3h.

To further expand the scope of this methodology, the feasibility of synthesising tertiary propargyl alcohol was investigated under the same optimal conditions. However, the reactions have taken 1-3h for completion, possibly due to the mild electrophilic nature. In general, acetophenone derivatives will undergo Aldol condensation in metal alkoxide basic conditions,[19] nevertheless no Aldol product is resulted in NaO*t*P, which is unexpected. The details are captured in Scheme 2, at first acetophenone and *p*-methyl acetophenone were successfully coupled with phenyl acetylene yielded 89% of **4a** and 93% of **4b,** respectively. The position of chloro substituent has minor effect on yield, for example 4-

chloroacetophenone has offered relatively less yield of **4c** compared to 3-chloroacetophenone which was giving 80% of **4d**. Substituting from chloro to bromo substituent on acetophenone have no effect on the yield of desired tertiary propargyl alcohols (**4e**). Similar reactions with aliphatic ketone were also tested using ethynyl benzene as a nucleophile, where acetone was successfully reacting with their counter part produced 79% of **4f.** The phenyl acetylene was separately treated with 3-methylbutan-2-one, 2-pentanone and cyclopropyl methyl ketone achieved an excellent yield of **4g, 4h** and **4i**, respectively. In addition, cyclohexanone also offered an excellent yield of 1-(phenylethynyl)cyclohexanol (**4j**) without the Aldol side product. This reaction was also compatible with substrates containing diphenyl ketone and afforded good yields of the corresponding C-C products (**4k**). Impressively, the thiophene-3-carboxaldehyde was also well tolerated with the optimized condition, yielded 92% of **4l**. Following the attainment of successful synthetic procedures for secondary and tertiary propargyl alcohols, the scalability of this C-C bond forming reaction was tested on gram scale in eight moieties and the results are presented in Table 4.

**Table 4**: Scalability of this process was tested in six compounds

| Entry | Substrate / Quantity (g) | Product / Quantity (g) | Yield (%) |
|---|---|---|---|
| 1 | 1a / 5.0 | 2a / 9.22 | 94 |
| 2 | 1c / 1.5 | 2d / 2.35 | 93 |
| 3 | 1f / 2.2 | 2g / 3.0 | 89 |
| 4 | 1f / 3.5 | 2i/ 5.26 | 91 |
| 5 | 3c / 1.8 | 4c / 2.09 | 70 |
| 6 | 3h / 3.3 | 4h / 6.63 | 92 |
| 7 | 3j / 1.2 | 4j / 2.22 | 91 |
| 8 | 3k/ 2.4 | 4k / 3.22 | 86 |

## Conclusions

We demonstrated that the NaO*t*P promotes the facile reaction of alkynes with variety of aldehydes and ketone under mild reaction conditions leading to the production of functionalized secondary and tertiary propargylic alcohols in good to excellent yields. The procedure tolerates aromatic, aliphatic and heteroaromatic aldehydes and ketones, as well as aromatic alkynes. As the proposed method is simple, inexpensive, and environmentally benign, it may have vast applications in both academia and the chemical industries.

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