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A simple and efficient method for mild and selective oxidation of propargylic alcohols using TEMPO and calcium hypochlorite†

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Oxidation of propargylic alcohols to the corresponding aldehydes and ketones was achieved at room temperature using 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) and calcium hypochlorite ($Ca(OCl)_2$). Propargylic diols yielded corresponding dialdehydes as the product. This system was found to be very efficient for both the electron donating and electron withdrawing groups such as methoxy and nitro substituted alcohols, respectively. This method does not require any additives and demonstrates the controlled, selective oxidation of propargylic alcohols affording up to 97% isolated yield.

α,β-Acetylenic carbonyl compounds and ynones are important precursors in the preparation of a variety of heterocyclic compounds,[1a] such as α,β-unsaturated ketones,[1b] cyclopentanones,[1c] C-nucleosides[1d,e] and chiral pheromones,[1f,g] whisky lactones (found in wine and other alcoholic beverages), which are used as starting materials for various bioactive compounds.[2a] Such compounds act as core elements of many potentially useful natural products (Fig. 1(i)),[2b,c] such as β-lactams (structural fragments of natural antibiotic malyngolide, Fig. 1(ii))[3] and epoxydiynes, which are motifs of neocarzinostatin (antibacterial and antitumor, Fig. 1(iii)).[4]

α,β-Acetylenic dialdehydes and aldehydes are key intermediates for making compounds with high birefringence. Examples are acetylenes with long molecular size such as bis(phenyldiynyl)benzenes and diphenylhexatriynes (Fig. 2).[5] A crucial role is played by these high birefringence liquid crystals in the field of display technology and they have been used widely in spatial light modulators and in compensation films for viewing angle, reflectors and polarizers.[6]

Various methods for the oxidation of propargylic alcohols have been developed using stoichiometric oxidants such as MnO_2, chromium salts with a combination of dimethyl sulfoxide and oxalyl chloride (Swern oxidation), $TiCl_4/Et_3N$ system and Dess–Martin reagent.[7] Furthermore, Ishii and coworkers have used $Cu(acac)_2$–NHPI(*N*-hydroxyphthalimide) and Katsuki and coworkers have used (nitroso)(selene) ruthenium(II) chloride as catalysts.[8]

Oxidation of propargylic alcohols under aerobic condition with palladium(II) catalyst[9] failed to produce the corresponding carbonyl compounds due to the formation of inactive metallic palladium forming unidentified tarry compounds. The instability of the produced carbonyl compounds in the reaction system, catalyst deactivation by the formation of metallic polymers and the formation of stable complexes between metal salts and some electron donors on the starting alcohols (hetero atoms and unsaturated carbon-carbon bonds) are some of the limitations of the oxidation of these alcohols. Further vanadium and Fe^{3+}/TEMPO based catalysts were developed for the aerobic oxidation of propargylic alcohols.[10] Hypochlorites are useful reagents for many organic reactions,[11a] oxidation of propargylic alcohols to alkyne carboxylic acids using nitroxyl radical with hypohalites has

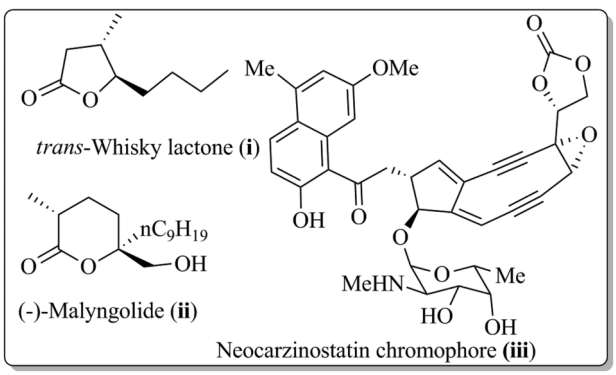

Fig. 1 Some biologically important compounds from α,β-acetylenic carbonyl compounds.

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† Electronic supplementary information (ESI) available: Full synthetic experimental and spectroscopic details of characterization data and ^1H and ^{13}C NMR spectra. See DOI: 10.1039/c3ra41721b

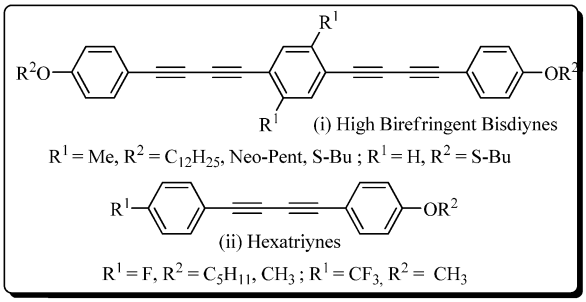
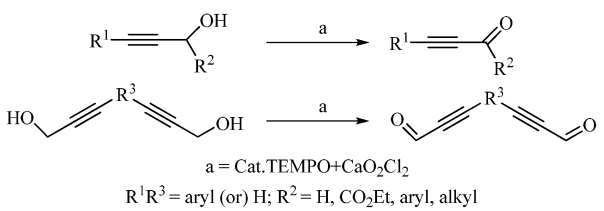


Fig. 2 High birefringent bisdiynes and hexatriynes from α,β-acetylenic dialdehydes and aldehydes.

been patented[11b] and reported using sodium hypochlorite (yield < 5%) and sodium chlorite[11c] with improved yields (90%) of the product acid. TEMPO (2,2,6,6-tetramethyl piperidine-1-oxyl) with various oxidants used stoichiometrically or catalytically is well known for the oxidation of alcohols to carbonyl compounds.[12,11b] Oxidant sodium hypochlorite (NaOCl) with TEMPO along with additives like phase transfer catalysts and base is well-liked for the oxidation of primary and secondary alcohols.[13] In contrast to sodium hypochlorite, calcium hypochlorite $Ca(OCl)_2$ is a readily available, stable, solid, inexpensive and an easy-to-use oxidizing agent in numerous organic tranformations.[14] Recently, we have noticed that TEMPO with oxidant $Ca(OCl)_2$ catalyzes the oxidation of benzylic alcohols to aldehydes and ketones without addition of acid or base and other additives like phase transfer catalysts under very mild reaction conditions.[15] Further, we have gone through the literature on oxidation of properglic alcohol to aldehydes and ketone, and we found that still there are limitations, like the use of high temperature, prolonged reaction time, inconvenient reaction conditions (additional usage of acids or bases, additives and usage of buffers to maintain the pH conditions) and toxic reagents for the same.[11]

In the present study, the oxidation of propargylic alcohols containing other functional groups, which are sensitive to oxidation and high temperatures, without addition of acid or base using catalytic amount of TEMPO in the presence of calcium hypochlorite in acetonitrile at room temperature (Scheme 1) has been pursued.‡ Initial experiments tried with primary propargylic alcohols attached to the phenyl moiety gave the corresponding aldehyde in 85% yield (Table 1, Entry 1). Next the primary propargylic alcohols connected to the groups such as bromo substituted pyridine, pyridine, methoxy substitued phenyl, nitro



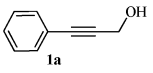
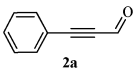
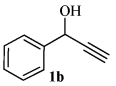
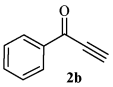
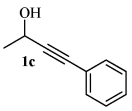
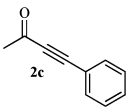
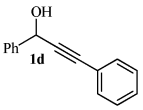
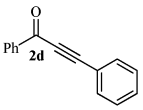
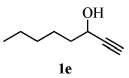
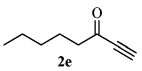
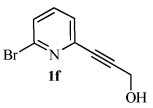
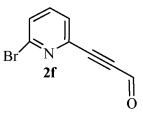
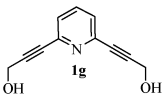
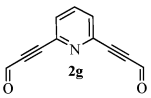
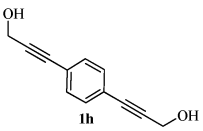
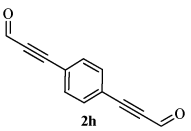
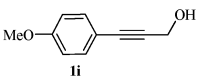
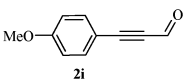
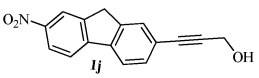
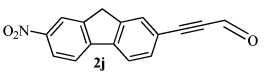
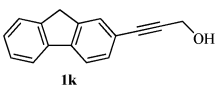
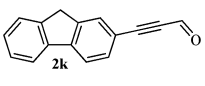
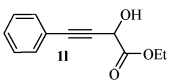
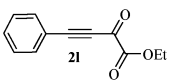
Scheme 1 Oxidation of propargylic alcohols to α,β-acetylenic carbonyl compounds.

subtituted fluorene and fluorene (Table 1, Entries 6–11) gave corresponding aldehydes in good to excellent yields (62 to >99%). Similarly, secondary alcohols having the phenyl and acetylene moiety gave the corresponding ketone in 90% yield (Table 1, Entry 2). Next the secondary alcohols attached to the groups such as methyl and phenyl acetylene, phenyl and phenyl acetylene, hexyl and acetylene (Table 1, Entries 3 to 5) provided the corresponding ketones in good to high yields (63 to 86%). In addition the secondary alcohol is attached to the phenyl acetylene group and the ester moiety (Table 1, Entry 12) is efficiently converted to the corresponding ketones in 85% yield. In the case of diols (Table 1, Entries 7 and 8), the reaction gave the corresponding dialdehydes in excellent yields (97 and >99%). The developed catalytic system was found to be a very efficient method for both electron donating and withdrawing groups such as methoxy and nitro substituted alcohols (Table 1, Entries 9 and 10). It is also important to note that this is the first ever report on oxidation of aryl heterocyclic propargylic diols (Table 1, Entries 6 and 7), fluorene and fluorene substituted propargylic alcohols (Table 1, Entries 10 and 11) to the corresponding aldehydes to the best of our knowledge. Here, the starting materials (Table 1, Entries 3 and 6–11) were prepared using the reported Sonogashira coupling reaction,[16a] and further the propargylic α-hydroxy ester (Table 1, Entry 12, **1l**) was prepared *via* cross-coupling reaction of terminal alkyne and monooxalyl chloride in the presence of copper catalyst.[16b]

In the oxidation of propargylic alcohols, nitrosonium ion ($TEMPO^+$ **I**), is the actual oxidant, while in the absence of TEMPO, no oxidation takes place. All the added substrate (>99% conversion, Table 1, Entry 7) is directly converted to dialdehyde upon addition of 1 mol% TEMPO. The mechanism can be formulated on the basis of similar cases as shown in Scheme 2.[17] Generated OCl^- from $Ca(OCl)_2$ should react with TEMPO to form intermediate **I**, which oxidizes the alcohol to the corresponding carbonyl compound giving the TEMPOH **II**, which shows the signal at *m*/*z* 158.2 (Fig. 3). Further intermediate **II** gets oxidized to the oxoammonium derivative **I** from OCl^- (Scheme 2) and the pH of the reaction remains almost neutral. The generated acid (H^+) [$Ca(OCl)_2$reacts with water to produce HOCl and ($Ca(OH)_2$) and the available chlorine (65%) in $Ca(OCl)_2$ reacts with water to produce HOCl and HCl] is neutralized by base $Ca(OH)_2$ (pK_b = 2.43).[18] In the case of NaOCl (the available chlorine is 10–15%) the pH of the reaction medium is 13, because of the caustic by-product NaOH (pK_b = 0.2) produced in the reaction. In order to control the pH of the reaction medium and improving the selectivity of the reaction, the addition of additives and buffers inside the reaction medium is necessary. Hence, when $Ca(OCl)_2$ is used as an oxidant the reaction does not required additives and buffers due to the neutral reaction conditions.

In conclusion, calcium hypochlorite with catalytic amount of TEMPO was found to be a versatile terminal oxidant to provide high yields of aldehydes, dialdehydes and ketones from a variety of propargylic alcohols at room temperature. The oxidation was carried out under atmospheric oxygen. The above catalytic system can be readily adjusted to suit various substrates under very mild conditions. Significantly, this protocol does not require any acid or base and does not give any side products and dialcohols selectively

Table 1 Oxidation of propargylic alcohols to α,β-acetylenic carbonyl compounds

Entry	Substrate	Product	Reported Yield %[g] (Time [h])	% Yield [this study] (Time [h])[c]
1	 1a	 2a	>98[19a](2)	85[b](3)
2	 1b	 2b	94[19b](30)	90[b](1)
3	 1c	 2c	33[10a](3)	63[b](2)
4	 1d	 2d	81[10a](3)	86[b](1.5)
5	 1e	 2e	65[10a](36)	66[b](4)
6	 1f	 2f	N.R.[a]	85[b](3.5)
7	 1g	 2g	N.R.[a]	>99[de](1)
8	 1h	 2h	N.D.[a]	97[d](3)
9	 1i	 2i	85[19c](48)	62[b](4)
10	 1j	 2j	N.R.[a]	>99[bef](4)
11	 1k	 2k	N.R.[a]	95[b](3.5)
12	 1l	 2l	50[19d]	85[b](1.5)

[a] N. R.: not reported; N.D.: yields not determined. [b] Conditions: 1 mmol substrate, 1.56 mg TEMPO (1 mol%). 142 mg, $Ca(OCl)_2$, acetonitrile (4 mL). [c] Isolated Yields. [d] Two equivalents of calcium hypochlorite was used along with TEMPO (1 mol%). [e] Conversion was measured by ^1H NMR. [f] Tetrahydrofuran was used as solvent. [g] Reference number.

gave corresponding dialdehydes in excellent yields, and sensitive groups like ester, alkynes and hetero atom were also stable under these conditions.

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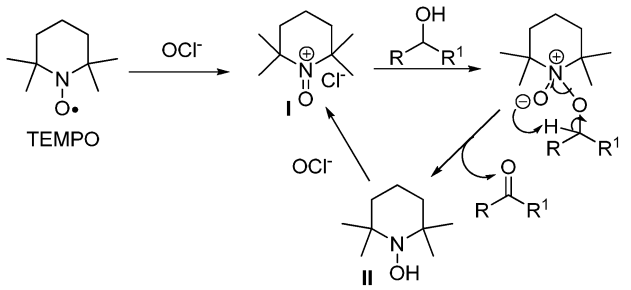

Scheme 2 Proposed mechanism for oxidation of propargylic alcohos with catalytic TEMPO with terminal oxidant calcium hypochlorite.

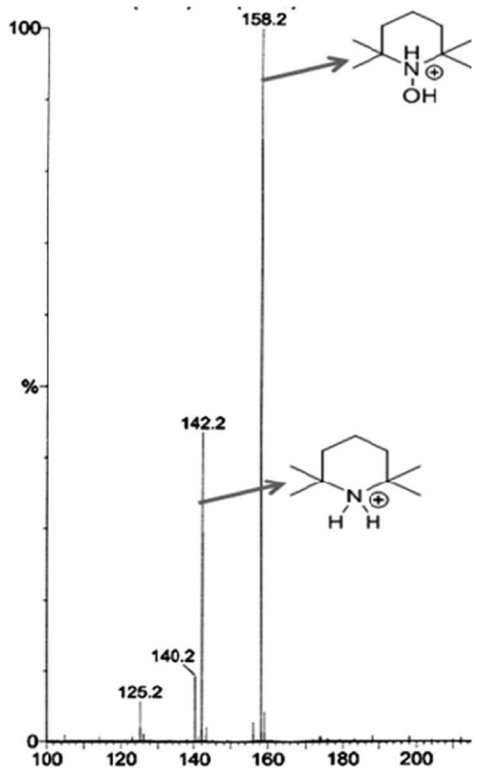

Fig. 3 Mass spectra ESI(+) obtained under standard conditions from samples taken from a reaction mixture.

University and IIT Madras) for providing the NMR and Mass analysis.

Notes and references

‡ *Experimental*. All commercially available alcohols and solvents were used as received without any further purification, non commercial alcohols were freshly prepared and characterised fully before use. **Typical procedure for oxidation of propargylic alcohols**. A mixture of TEMPO (1.56 mg, 1 mol%) and 3-(9*H*-fluoren-2-yl)prop-2-yn-1-ol (**1k**) (1 mmol) in acetonitrile (4 mL) was taken in 25 mL round bottom flask. Calcium hypochlorite (142 mg, 1 mmol) was added in portions over 10 min at 0 °C and the reaction mixture was allowed to room temperature until completion. The suspension was filtered, the organic phase was washed with saturated aq. $NaHCO_3$ (8 mL) followed by brine (8 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel, using hexane:ethylacetate (99 : 1) as the solvent to give 3-(9*H*-fluoren-2-yl)prop-2-yn-1-al (**2k**) as a white colour solid, mp: 110–112 °C ^{1}H NMR (400 MHz, $CDCl_3$,TMS) δ = 3.92 (s, 2H), 7.38–7.82 (m, 7H), 9.45 (s, 1H) ^{13}C NMR(400 MHz, $CDCl_3$,TMS): δ = 37.0, 89.2, 97.0, 117.3, 120.4, 121.0, 126.0, 127.5, 128.4, 130.2, 133.0, 141.0, 144.0, 144.3, 145.3, 177.0; I.R (KBr) ν = cm^{-1}: 700, 888, 1644, 1604, 2179, 2925, 3060 HRMS: Calc for $C_{16}H_{11}O$; 219.0810; Obs. 219.0811. Data for unreported compounds is given in the supplementary information.†

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