

A comparative study of Cu(II)-assisted vs Cu(II)-free chalcogenation on benzyl and 2°/3°-cycloalkyl moieties

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Abstract. A relative synthetic strategy toward intermolecular oxidative C–Chalcogen bond formation of alkanes has been illustrated using both Cu(II) assisted vs Cu(II) free conditions. This led to construction of a comparative study of hydrocarbon benzylic and 2°/3°-cycloalkyl moieties bond sulfenylation and selenation protocol by the chalcogen sources, particularly sulfur and selenium, respectively. In addition, this protocol disclosed the auspicious formation of sp^3C-S coupling products over leading the sp^3C-N coupling products by using 2-mercaptobenzothiazole (MBT) substrates.

Keywords. C-H functionalization; C-Chalcogen bond formation; metal vs. metal free condition

1. Introduction

Chalcogen containing molecules are important motifs found in organic synthesis,¹ biological chemistry,² and materials science.³ However, the direct C–H functionalization of simple hydrocarbons has emerged as a research topic of great interest in recent years due to the potential opportunity of developing novel methodologies in synthesis and chemical processes.⁴ The selective activation of benzylic C–H bonds in toluene derivatives is significant since the catalytic functionalization of toluene can yield industrially important chemicals such as benzyl alcohols, benzaldehydes, and benzoic acids. However, it is more difficult to achieve the benzylic C–H bond functionalization⁵ because of the existence of both sp^2 as well as sp^3 C–H bonds. Notably, copper salts have been used as a catalyst for the oxidation of certain types of hydrocarbons to give alcohols, ketones, or carboxylic acids.⁶ Further, intermolecular heteroatom-based functionalization is very rare.⁷

In the area of C–H bond functionalization, much attention has been paid to C–C, C–O, and C–N bond-forming reactions.⁸ In contrast, only a few methods for C–H bond sulfenylation and selenation have been published recently.⁹ Therefore, the development of a general alkyl C–H thio and seleno etherification reaction that enables the selective preparation of valuable alkyl thioethers, and is compatible with a broad

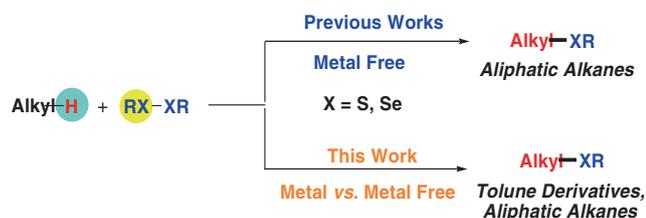
scope of substrates and tolerant to a wide range of functional groups, would be of prime synthetic value. To the best of knowledge, in literature till now, there are very few examples of benzylic and 2°/3°-cycloalkyl moieties have been reported.^{9c,d,e} It is worthy to note that in literature,^{9e} the toluene derivatives are over oxidized to give carbonyl derivative benzylic sp^2 C-S coupling products, however herein only benzylic sp^3 C-S coupling products are exclusively observed.

From earlier observations, the reaction was believed to undergo via a radical alkyl species, which then reacted with chalcogen to afford the desired products. The fact that alkanes could be easily converted into the corresponding alkyl radicals in the presence of peroxides¹⁰ was a motivation to try the direct coupling of alkanes with chalcogens in a novel C–H chalcogenation reaction. However, very few reactions are reported recently using DTBP (di-tertiary butyl peroxide) under metal free condition. The earlier report was also completely silent about toluene derivative moiety (benzyl radical). Keeping this observation in view, a comparative investigation is disclosed herein for thio- and seleno-ether formation via both metal-assisted and metal-free conditions, which also envisaged that chalcogen source is utilized as a stoichiometric reactant for the chalcogenation of alkanes.

2. Experimental

Working hypothesis is given in scheme 1.

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Scheme 1. Reactions of chalcogens with alkyl halides or alkanes.

3. Results and Discussion

3.1 Reactions and Yields

To test our hypothesis on the intermolecular *S*-alkylation of simple alkanes, 2-mercaptobenzothiazole (MBT, **2a**) was initially employed to react with *p*-xylene using catalytic amount of various Cu salts and ditertiary butyl peroxide (DTBP) oxidant under various conditions (table 1). Gratifyingly, the desired product (**4aa**) formed with a complete conversion was obtained at 120°C using 10% of Cu(OAc)₂.H₂O salt and 3 equiv. of DTBP (entry 5). The loading of reduced amounts of oxidant resulted in lower conversion (entry 7). However, it is interesting to see that, in the absence of metal catalyst the oxidant also afford the expected product in moderate yield. With initial observations in hand, the protocol was treated with various solvents sources (CH₃CN, DCE, DMSO, DMF, EtOH, benzene) and found that the solvent is ineffective for this reaction. The other oxidant candidates (TBHP, T-HYDRO, DCP)

Table 1. Selected list for the Optimized Conditions^a.

| Entry | Metal Salt | Oxidant | NMR Yield% |
|-----------|---|-----------------|---------------------------|
| 1 | CuI | DTBP (3) | 33 |
| 2 | CuBr | DTBP (3) | 36 |
| 3 | CuBr ₂ | DTBP (3) | 44 |
| 4 | Cu(OAc) ₂ | DTBP (3) | 74 |
| 5 | Cu(OAc)₂.H₂O | DTBP (3) | 85 |
| 6 | Cu(OAc) ₂ .H ₂ O | DTBP (4) | 82 |
| 7 | Cu(OAc) ₂ .H ₂ O | DTBP (2) | 65 |
| 8 | Cu(OAc) ₂ .H ₂ O | TBHP(3) | 12 |
| 9 | Cu(OAc) ₂ .H ₂ O | T-HYDRO (3) | 21 |
| 10 | Cu(OAc) ₂ .H ₂ O | DCP (3) | 45 |
| 11 | - | DTBP(2) | 22 |
| 12 | - | DTBP(3) | 69(65)^b |
| 13 | - | DTBP(4) | 64 |
| 14 | - | - | N.D |

^a *p*-Xylene 10 mmol, metal salt 10% compared to MBT, MBT 0.3 mmol, Temp. 120°C, Time 18 h. C₂H₂Cl₄ (TCE) used as an internal standard. N.D. = Not detected. ^bIn bracket isolated yield.

Table 2. Scope of thiol/diaryldisulfides for sulfenylation of sp³ C-H bond.^a

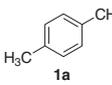
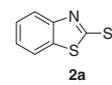
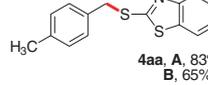
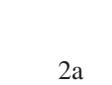
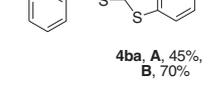
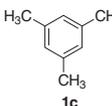
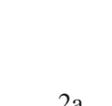
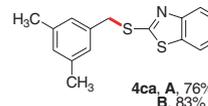
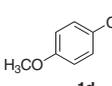
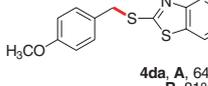
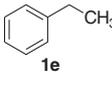
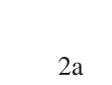
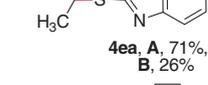
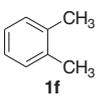
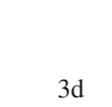
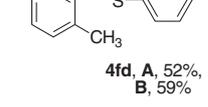
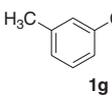
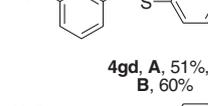
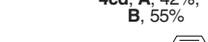
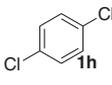
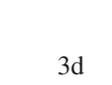
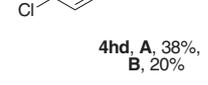
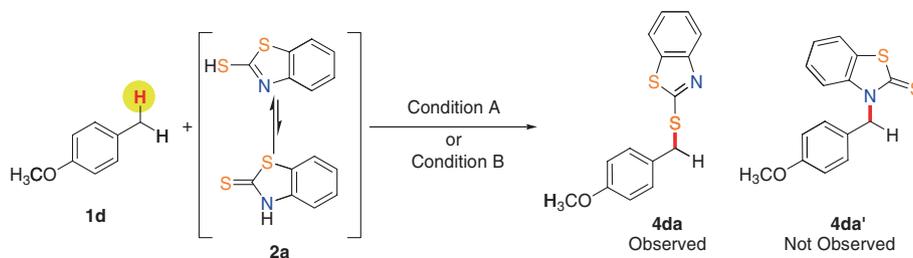
| Alkyl-H (1a-1o) | ArS-SAr (2a-3f) | Condition A Condition B | Alkyl-SAr (4aa-4od) |
|---|---|----------------------------|---|
|  |  | |  4aa, A, 83%, B, 65% |
|  |  | |  4ba, A, 45%, B, 70% |
|  |  | |  4ca, A, 76%, B, 83% |
|  |  | |  4da, A, 64%, B, 81% |
|  |  | |  4ea, A, 71%, B, 26% |
|  |  | |  4fd, A, 52%, B, 59% |
|  |  | |  4gd, A, 51%, B, 60% |
|  |  | |  4cd, A, 42%, B, 55% |
|  |  | |  4hd, A, 38%, B, 20% |

Table 2. (continued)

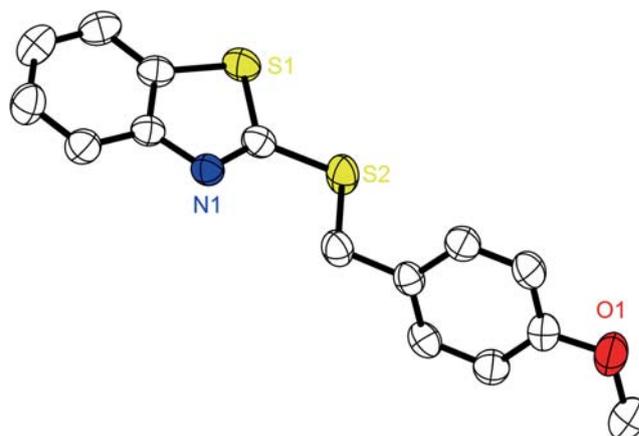
| Alkyl-H (1a-1o) | | + | ArS-SAr (2a-3f) | | Condition A | → | Alkyl-SAr (4aa-4od) | |
|-----------------|----|---|-----------------|--|-------------|---|------------------------|--|
| | | | | | Condition B | | | |
| | 3d | | | | | | 4id, A, 48%, B, 61% | |
| | 3d | | | | | | 4jd, A, 65%, B, 86% | |
| | 3d | | | | | | 4kd, A, 68%, B, 89% | |
| | 3d | | | | | | 4ld, A, 61%, B, 95% | |
| | 3d | | | | | | 4md, A, 53%, B, 88% | |
| | 3d | | | | | | 4nd, A, 57%, B, 75% | |
| | 3d | | | | | | 4od, A, 62%, B, 52% | |

Condition A: Alkane 10 mmol, (ArS)₂ 0.15 mmol or RSH 0.3 mmol, Cu(OAc)₂·H₂O 10 mol%, DTBP 0.9 mmol. Condition B: Alkane 10 mmol, (ArS)₂ 0.15 mmol or RSH 0.3 mmol, DTBP 0.9 mmol. ^aIsolated yield. ^bAdamantane (**1o**) 2.5 equiv. used compared to (PhS)₂ and benzene 1 mL used as solvent. ^cTemp. 120 °C, Time 18 h.

were also found to be ineffective for this transformation. However, 18 h is the optimum reaction time to afford good yield of the desired product. It is worthy to observe that 120 °C is optimum temperature for this protocol for both metal free and Cu(II) catalyzed reaction.



Scheme 2. A comparative observation for C-S bond formation.

Figure 1. ORTEP diagram of compound **4da**.

With the newly developed protocol of intermolecular C-H sulfenylation, a variety of thiol sources were next subjected to the optimized conditions (table 2). Mercapto thiol derivatives such as (**2a**, **2b**, **2c**) were still facile reactants albeit with moderate to good yield. In these cases, Cu(II) catalyst was ineffective to promote the reaction to get good yield compared to metal free condition. A good yield of product was observed as well from the diaryldisulfide moieties with alkane derivatives (**4aa**, **4ba**, **4ca**). The toluene derivatives such as toluene (**1b**), mesitylene (**1c**), *p*-methylanisole (**1d**) also provided corresponding their C-S coupling product (**4ba**, **4ca**, **4da**) in good to excellent yields. However, metal free condition provided better chemical yield compared to metal free condition for these moieties. Although for MBT moiety there is a chance also to couple on nitrogen site to form **4da'** product, interestingly that it regioselectively was giving single C-S coupled isomer (scheme 2) which is further confirmed by X-ray crystallographic analysis (depicted in figure 1, H atom omitted for clarity). Surprisingly, ethylbenzene (**1e**) gave a poor yield (**4ea**) in the absence of Cu(II) salt. Perhaps, it is due to presence of methyl group at the alpha position which makes it difficult to form free radical in the absence of metal salt.

The optimized imitation procedure was subsequently applied to a range of simple alkanes like mesitylene (**1c**), *o*-xylene (**1f**), *m*-xylene (**1g**), using a phenyl disulfide source under both metal and metal free conditions (table 2). Stimulatingly, metal free condition gave better yield (**4cd**, **4fd**, **4gd**) compared to Cu(II) assisted reaction. However, in the case of *p*-Cl toluene (**1h**) poor yield (**4hd**) was obtained in metal free condition. Polycyclic aromatic ring like 1-methyl naphthalene (**1i**) also provided corresponding C–S coupling product (**4id**) in good yield in metal free condition. After seeing these observations, the reaction condition was shifted to aliphatic alkane derivatives like cyclopentane (**1j**), cyclohexane (**1k**), cycloheptane (**1l**), cyclooctane (**1m**), cyclododecane (**1n**) and adamantane (**1o**) yielding good to excellent yield of corresponding C–S coupled products (**4jd**–**4od**) under metal free condition. It was also observed that, adamantane (**1o**) tertiary carbon is more favorable to form free radical compared to secondary

carbon to give exclusively C–S coupled product, which was further confirmed by X-ray crystallographic analysis (**4od**, depicted in figure 2, H atom omitted for clarity). From this observation, it is clear that particularly aliphatic alkanes in presence of Cu(II) salts poison the formation of C–S coupling product and metal free condition is more facile.

From the mentioned observations, aim was to find out the reactivity of same family chalcogen derivative selenide substrates (table 3). Likewise, C–S bond formation of *p*-xylene (**1a**), mesitylene (**1c**) afforded their corresponding sp^3 C–Se coupling product in better yield under metal free condition. Further, 1-methyl naphthalene (**1i**) reacted with diphenylselenide (**3g**) moderately to provide (**4ig**) product. However, from the

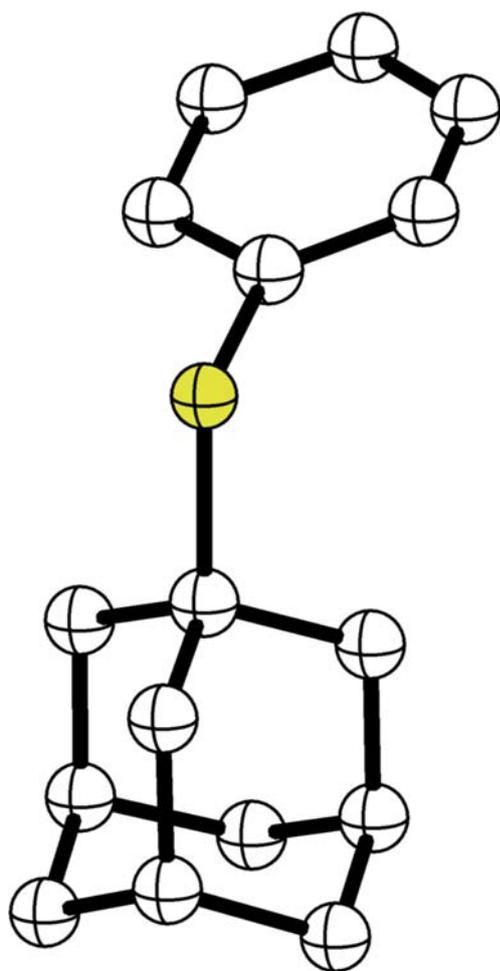
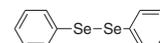
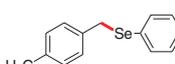
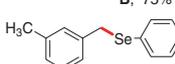
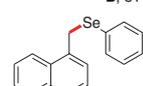
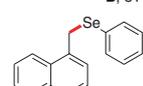
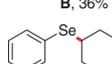
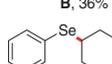
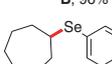
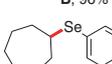
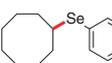
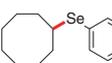
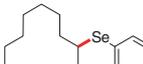
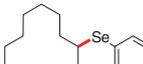


Figure 2. ORTEP diagram of compound **4od**.

Table 3. Scope of various alkanes for selenation of sp^3 C–H bond.^a

| | Alkyl-H + PhSe-SePh (1a,1c,1i, 1k-1n) 3g | Condition A Condition B | Alkyl-SePh (4ag-4ng) |
|----|---|----------------------------|---|
| 1a |  | |  4ag, A, 66%, B, 75% |
| 1c |  | |  4cg, A, 59%, B, 81% |
| 1i |  | |  4ig, A, 46%, B, 36% |
| 1k |  | |  4kg, A, 71%, B, 96% |
| 1l |  | |  4lg, A, 69%, B, 89% |
| 1m |  | |  4mg, A, 90%, B, 79% |
| 1n |  | |  4ng, A, 63%, B, 78% |

Condition A: Alkane 10 mmol, (PhSe)₂ 0.15 mmol, Cu(OAc)₂·H₂O 10 mol%, DTBP 1.2 mmol.

Condition B: Alkane 10 mmol, (ArSe)₂ 0.15 mmol, DTBP 1.2 mmol. ^aIsolated yield. ^bTemp. 120°C, Time 18 h.

Table 4. Effect of Radical Inhibitors on the Reaction Efficiency^a.

| Entry | Radical Scavenger | Condition A % | Condition B % |
|-------|-------------------|---------------|---------------|
| 1 | None | 85 | 65 |
| 2 | TEMPO | 27 | 15 |
| 3 | BHT | 05 | 02 |
| | DPE | 35 | 08 |

Condition: 1 equiv. radical scavenger was added compared to MBT (both in condition A and B).

experimental observation it was found that in the presence of metal salt (**4ig**) gave good yield whereas (**4id**) gave poor yield. Notably, aliphatic cycloalkanes like cyclohexane (**1k**), cycloheptane (**1l**), cyclooctane (**1m**) and cyclododecane (**1n**) provided their corresponding C–Se coupling products (**4kg**, **4lg**, **4mg**, **4ng**) in excellent yields under metal free condition. From this observation, it seems to be that Cu(II) salts poison the yield of aliphatic alkane derived substrates.

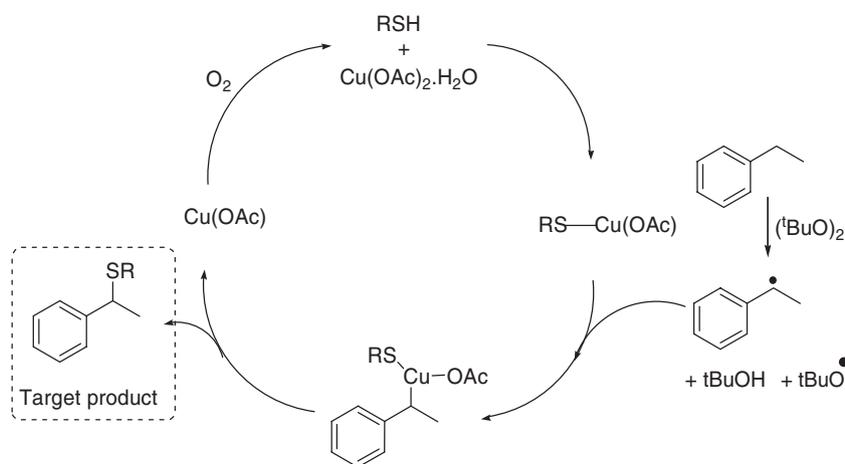
A radical inhibition test was next carried out in order to get insight into whether the reaction proceeds via radical intermediates. When TEMPO, 2,6-di-tert-butyl-4-methylphenol (BHT) or 1,1-diphenylethylene (DPE), which are well known to be active radical scavengers, was added to the reaction mixture, the reaction progress was significantly decreased under either the Cu-assisted or Cu-free conditions. Poor product yields were obtained, suggesting that present intermolecular sp³ C–S bond-forming reaction involves radical intermediates (table 4).

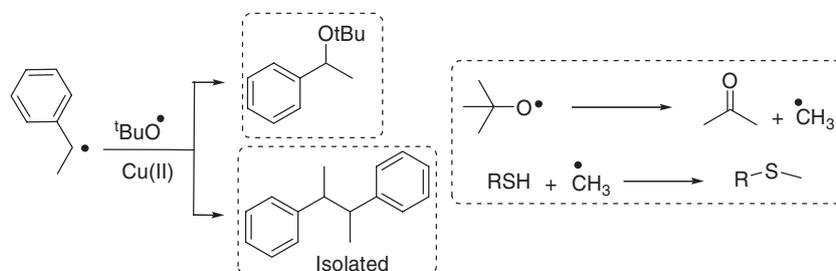
3.2 Mechanism

Based on the above experimental data, a plausible pathway for the formation of sulfenylated product is proposed in scheme 3. Our proposed mechanism begins with the thio-Cu(II) complexation. Subsequently, decomposition of (tBuO)₂ to produce a tert-butoxy radical which supports to abstract a hydrogen atom from an alkane to form an alkyl radical, followed by a potential intermediate containing a Cu(III) complex species. The next step plausibly, undergoing reductive elimination route to generate the desired sulfenylated product.

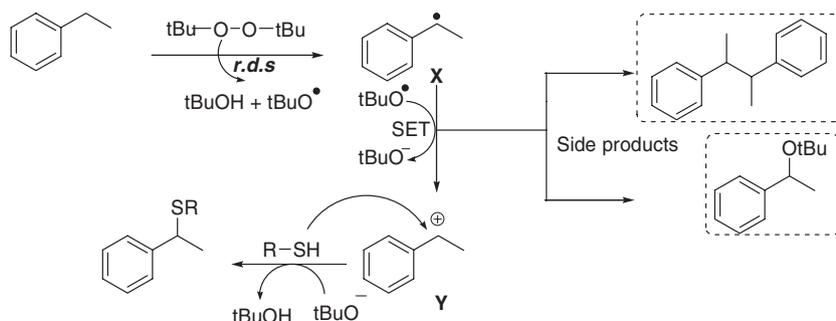
Perhaps, the reaction of thiol with tBuOOTBu in the presence of Cu leads to rapid oxidation of thiol to exclusive formation of thioanisole derived product, in which the methyl radical is derived from tert-butoxy radical by β-Me scission.^{10b} Second, copper participates in the event after the turnover-limiting step of C–H functionalization by tert-butoxy radical to form the S-alkyl product. However, it is possible that the formation of O-alkylated product as a side derivative via the insertion of t-butoxy radical to the Cu salt, followed by reductive elimination of Cu(III) species. Further, the oxidative dimerised product of alkane substituents has also been isolated as a side product which is generated during the course of reaction and fully characterized (scheme 4).^{9,10}

From the observed reaction conditions, it is clear that in the absence of metal salt also the product is formed and in most cases with a better yield compared to Cu(II) assisted protocol. These results led us to propose that a single electron transfer oxidation pathway might be engaged in the generation of an alkyl radical X, which is further oxidized to a cationic species Y, and

**Scheme 3.** Proposed mechanistic pathway.



Scheme 4. Possible formation of side product.



Scheme 5. Proposed mechanistic pathway in the absence of metal catalyst.

then subsequent nucleophilic attack of thiol moiety provides the product, being sulfenylated at the alkyl site (scheme 5).^{9,10}

4. Conclusions

In summary, a highly efficient intermolecular oxidative C–H chalcogenation of alkanes with thiol and selenide derivatives using peroxide (DTBP) as oxidant as well as reagent in the presence of both Cu(II) free and Cu(II)-assisted conditions have been developed. A broad range of substrates are selectively chalcogenated at the benzyl or alkyl position. Although detailed mechanistic descriptions and development of milder reaction conditions are still desirable, it is believed that in forthcoming period this new protocol will be offering a new avenue for a more practical and selective construction of C–chalcogen bond from the unactivated sp^3 C–H bonds.

Supplementary Information

CCDC 1058940, 1058941 contain the supplementary crystallographic data for the compound **4da** and **4od**. These data can be obtained free of charge via www.ccdc.cam.ac.uk/datarequest/cif. The NMR spectra and figures (^1H and ^{13}C), are available at www.ias.ac.in/chemsci.

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