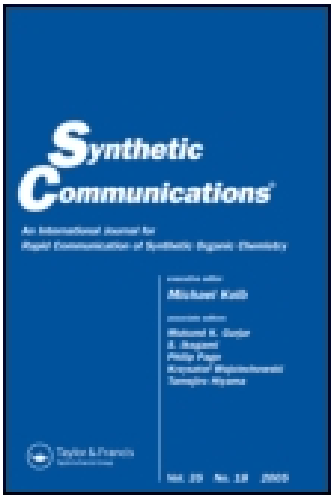

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# Potassium Carbonate-Mediated Efficient and Convenient Synthesis of 3-Methyl-1-phenylchromeno[4,3-c]pyrazol-4(1H)-ones

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# POTASSIUM CARBONATE–MEDIATED EFFICIENT AND CONVENIENT SYNTHESIS OF 3-METHYL-1-PHENYLCHROMENO[4,3-*c*]PYRAZOL-4(1*H*)-ONES

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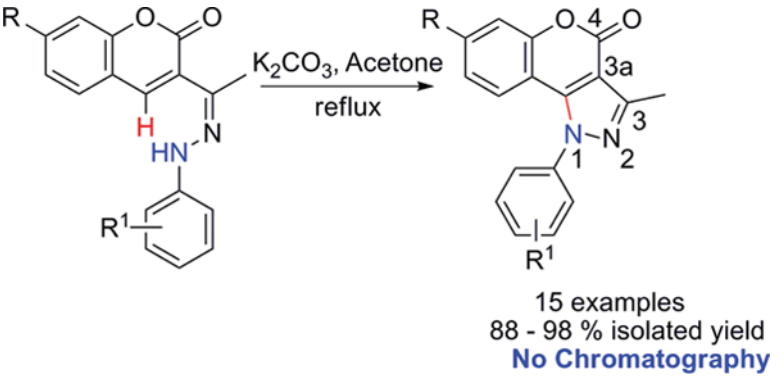
## GRAPHICAL ABSTRACT




**Abstract** *Unprecedented cyclization was observed during N-sulfonylation of 3-[1-(phenylhydrazono)-ethyl]-chromen-2-one in pyridine, affording 3-methyl-1-phenylchromeno[4,3-c]pyrazol-4(1H)-ones. To avoid use of noxious pyridine, reaction was tried in different basic conditions and the best results were obtained with potassium carbonate in acetone. A wide range of substrates bearing either electron-donating or electron-withdrawing substituents on phenylhydrazine ring were compatible with the developed methodology. Rapid access of starting material, 3-acetylcoumarin, excellent yields of products, and use of environmentally benign base and solvent for the cyclization make this strategy an efficient and convenient method for synthesis of 3-methyl-1-phenylchromeno[4,3-c]pyrazol-4(1H)-ones.*

**Keywords** Acetone; 3-methyl-1-phenylchromeno[4,3-*c*]pyrazol-4(1*H*)-ones; potassium carbonate

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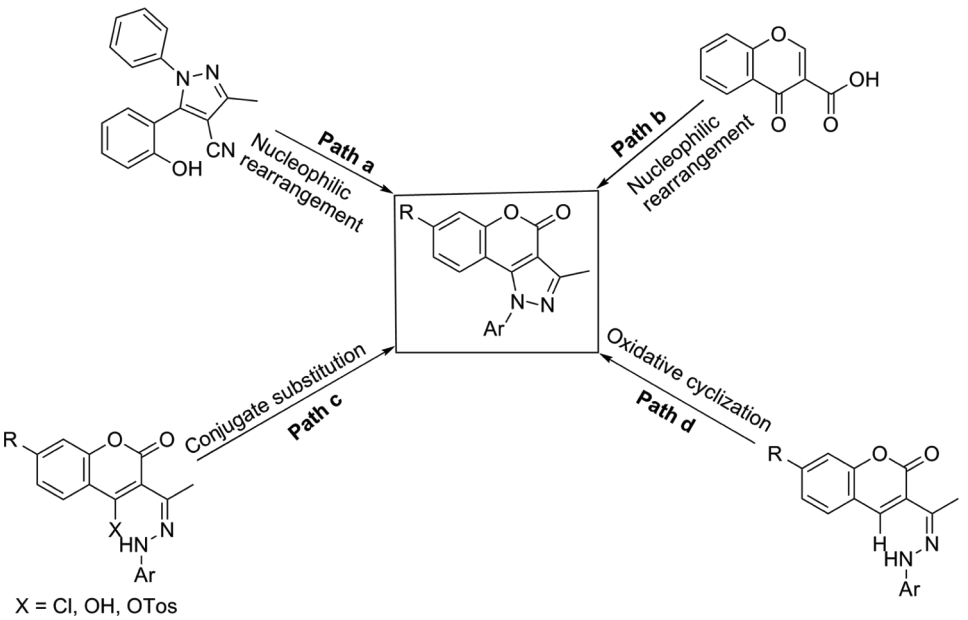
## INTRODUCTION

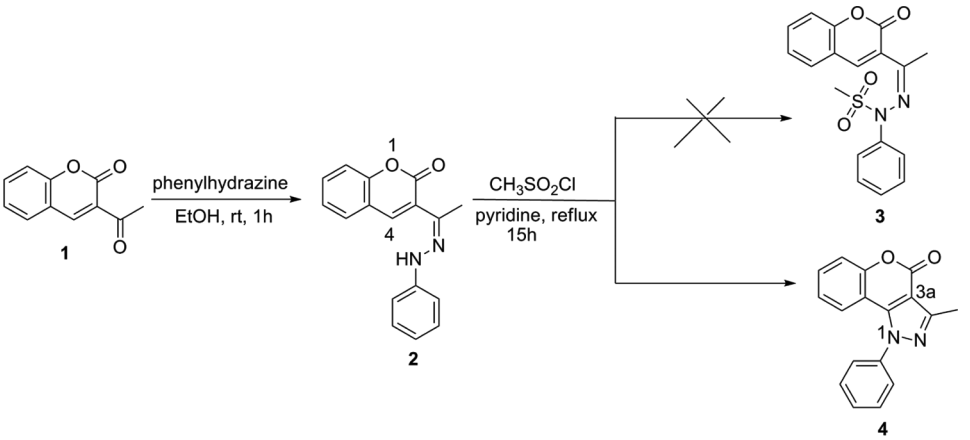
Pyrazole and its derivatives are well explored as anti-inflammatory,[1,2] antiviral,[3,4] antimalarial,[5,6] HIV-reverse transcriptase inhibitors,[7,8] antimicrobial,[9,10] and antitumor agents.[11,12] In particular, 3-methyl-1-phenylchromeno[4,3-*c*] pyrazol-4(1*H*)-ones are well known for their affinity toward benzodiazepine central receptor and are used as an intermediate to synthesize immunomodulatory drugs.[13] In the literature, several methods for the synthesis of chromenopyrazoles have been reported, such as reaction of arylidenechromones and hydrazine in basic media,[14] nucleophilic rearrangement of 3-cyano-4-[(*o*-hydroxy)phenyl]-1-phenyl-3-methylpyrazole (path a, Scheme 1),[15] and 3-chromonecarboxylic acids (path b, Scheme 1),[16] intramolecular conjugate substitution of coumarin hydrazones (path c, Scheme 1),[17] employing catalysts such as Zn[L-proline]$_2$.[18] However, most of these methods require the presence of a leaving group (chloro, hydroxyl, and *O*-tosyl) at C-4 position of 3-acetylcoumarin and use of high-boiling solvents, making access to starting material cumbersome. Other methods using 2-methylchromonecarbonitrile[15] and 3-chromonecarboxylic acids[16] as synthones suffer from the drawback that the preparation of these starting materials requires two to three steps. Recently, a few reports based on oxidative cyclization of coumarin hydrazones, utilizing catalyst such as copper acetate,[19] CuO/SBA-15,[20] and Cu $(SO_3)_2CF_3$[21] have been described in the literature (path d, Scheme 1). Yang et al. reported cyclization of coumarin hydrazones by air oxidation and catalytic oxidation under solvent-free conditions. However, the air oxidation and solvent-free conditions required long reaction time for 90–94% conversion (12–25 days, in case of air oxidation and 34 h under solvent-free




**Scheme 1.** Various methods of preparation of chromenopyrazoles.

conditions). In addition to long reaction time, elevated temperature up to 150 °C is required under solvent-free conditions that make the overall methodology inconvenient.[21] Although these methods rule out the requirement of leaving group at C-4 position of coumarin hydrazones, they suffer from certain drawbacks such as low to moderate yield of desired compounds, difficulty in separation, and recycling of homogeneous catalyst. Moreover, in the case of method employing CuO/SBA-15, special efforts are required for the preparation of catalyst. The approach utilizing copper catalysts is based on transmetallation followed by conjugate addition of organocopper reagent. A nucleophilic activation of secondary nitrogen of coumarin hydrazone to facilitate the cyclization could serve as an alternative approach. We observed an unexpected cyclization when N-sulfonylation of **2** was attempted in the presence of methanesulphonyl chloride using pyridine both as a base and a solvent. The reaction resulted in the formation of **4** instead of **3** (Scheme 2). The observed cyclization eliminates requirement of a leaving group at C-4 position of coumarin hydrazone and use of additional metal catalyst, making the overall synthesis of 3-methyl-1-phenylchromeno[4,3-*c*]pyrazol-4(1*H*)-ones simple and efficient. Also, the use of noxious agent such as $POCl_3$, which is required for the synthesis of starting material 3-acetyl-4-hydroxycoumarin, as an additional step could be avoided.[22]

One-pot easy access of starting material and formation of desired chromenopyrazole in good yield along with our desire to find a substitute of noxious pyridine encouraged us to study the cyclization of 3-[1-(phenylhydrazono)ethyl]chromen-2-ones. Inspired from the unexpected cyclization of coumarin hydrazones into their corresponding pyrazoles under basic conditions, herein we report an efficient and environmentally benign synthesis of chromenopyrazoles utilizing the simple and economic base potassium carbonate in a less hazardous solvent such as acetone. To the best of our knowledge, this is the first report on the development of a methodology based on base-induced nucleophilic activation–cyclization of 3-[1-(phenylhydrazono)ethyl]chromen-2-ones for the synthesis of chromenopyrazoles.

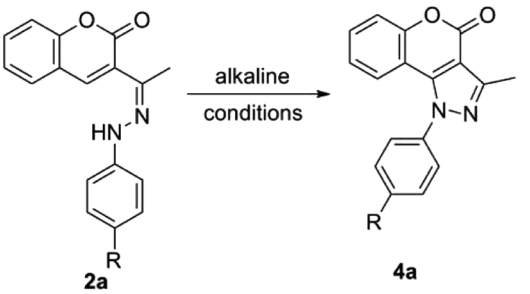



**Scheme 2.** Synthesis of 3-methyl-1-phenylchromeno[4,3-c]pyrazol-4(1*H*)-one.

## RESULTS AND DISCUSSION

3-Acetylcoumarin (**1**) was synthesized by Knoevenagel condensation of commercially available salicylaldehyde and ethyl acetoacetate.[2] It was then converted into 3-[1-(phenylhydrazono)-ethyl]-chromen-2-one (**2**) by treating it with phenylhydrazine, followed by reaction with methanesulfonyl chloride in pyridine to form its N-sulfonyl derivative (**3**). Unprecedently, it underwent cylization to afford **4** (Scheme 2). The cyclization of **2** in the absence of leaving group at C-4 position was surprising, as cyclization of this class of compounds is generally reported in the presence of a leaving group at the C-4 position. A similar experiment was repeated using pyridine in the absence of methanesulfonyl chloride and it again furnished compound **4**. While attempting these reactions, it was observed that **2a** cyclized to corresponding pyrazole compound **4a** (25–30% yield) under base-free conditions when kept in chloroform for 2 days at room temperature, which is also witnessed in the literature.[19,21] So, we hypothesize that rate of cyclization might increase under reflux conditions of solvent. To substantiate our hypothesis, we performed similar reaction under reflux conditions of acetone, chloroform, and ethanol. However, it was observed that reaction did not proceed to completion even after refluxing for 24 h (Table 1, entry 1). Based on the aforementioned finding, we anticipated that base could act as a driving force by enhancing the nucleophilicity of secondary nitrogen of coumarin hydrazone and facilitate aromatization. Thus, to gain more understanding of this reaction and obliterate the limitations of the earlier methods, different bases and solvents were explored to arrive at the best possible yield (Table 1). The reaction was attempted using triethylamine and piperidine in place of pyridine, but poor solubility of compound **2a** in these bases necessitates the use of solvent. Chloroform was selected as a one of the solvents as it facilitated cyclization under base-free conditions. In addition, other aprotic (acetone) and protic (ethanol) solvents were tried. It was observed that organic bases gave products in moderate to poor yields when ethanol was used as a solvent (Table 1, entries 2–7). The competitive proton abstraction by the base from ethanol and decrease in the nucleophilicity of secondary nitrogen due to hydrogen bonding with ethanol may account for the poor yield. Further, aprotic solvents such as chloroform and acetone were explored and the reaction worked quite well with acetone. This may be due to the fact that acetone is a more polar aprotic solvent as compared to chloroform. Similar results were obtained in the case of inorganic bases such as potassium carbonate and sodium carbonate (Table 1, entries 8 and 9). Strong bases such as NaOH and KOH were found to be ineffective under all solvent conditions, as substantial decomposition, multitude of side products, or poor yields were obtained (Table 1, entries 10 and 11). Competitive proton abstraction of olefinic and methyl proton by strong bases may account for formation of complex reaction mixtures. An excellent yield of desired product was obtained when the reaction was carried out with potassium carbonate in acetone. Further, to investigate the effect of amount of base on the reaction completion, different amounts of potassium carbonate were used. The use of stoichiometric amounts of potassium carbonate has little impact on reaction time and percentage yield (Table 2, entries 1 and 2). However, with catalytic amount, we obtained comparatively lower yield of **4a**, with concomitant longer reaction time (Table 2, entry 3). Therefore, we intended to use 1 equiv of potassium carbonate to examine the substrate scope under optimized

**Table 1.** Optimization of various alkaline and solvents conditions for the cyclization of 3-[1-(phenylhydrazono)ethyl]chromen-2-one (**2a**)[a]




| Entry | Base (1 equiv) | Solvent | Isolated yield (%) |
|---|---|---|---|
| 1 | None | $CHCl_3$ | 30 |
| | | EtOH | 20 |
| | | Acetone | 45 |
| 2 | Pyridine[b] | neat | 85 |
| 3 | Triethylamine | $CHCl_3$ | 40 |
| | | EtOH | 25 |
| | | Acetone | 65 |
| 4 | DMAP | $CHCl_3$ | 45 |
| | | EtOH | 28 |
| | | Acetone | 60 |
| 5 | Piperidine | $CHCl_3$ | 32 |
| | | EtOH | 18 |
| | | Acetone | 69 |
| 6 | DBU | $CHCl_3$ | 40 |
| | | EtOH | 30 |
| | | Acetone | 72 |
| 7 | DABCO | $CHCl_3$ | 42 |
| | | EtOH | 28 |
| | | Acetone | 75 |
| 8 | $K_2CO_3$ | $CHCl_3$ | 51 |
| | | EtOH | 32 |
| | | Acetone | 97 |
| 9 | $Na_2CO_3$ | $CHCl_3$ | 45 |
| | | EtOH | 22 |
| | | Acetone | 83 |
| 10 | NaOH | $CHCl_3$ | No reaction[c] |
| | | EtOH | No reaction[c] |
| | | Acetone | No reaction[c] |
| 11 | KOH | $CHCl_3$ | No reaction[c] |
| | | EtOH | No reaction[c] |
| | | Acetone | No reaction[c] |

[a]The reactions were carried out with **2a** (0.72 mmol) and base (0.72 mmol) at 50 °C for 24 h.
[b]2 equiv were used.
[c]Desired products were not formed.

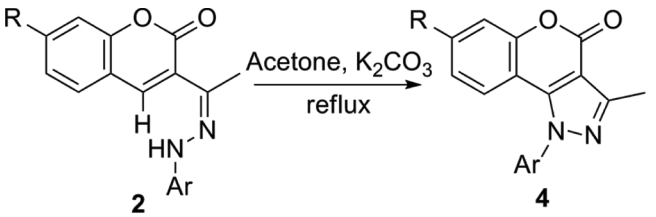
conditions. As potassium carbonate has gained recognition as favorable environmentally benign alternatives[23,24] and acetone represents class 3 solvent,[25] the present methodology adds to the development of sustainable chemistry.

**Table 2.** Effect of amounts of potassium carbonate on cyclization of **2a**

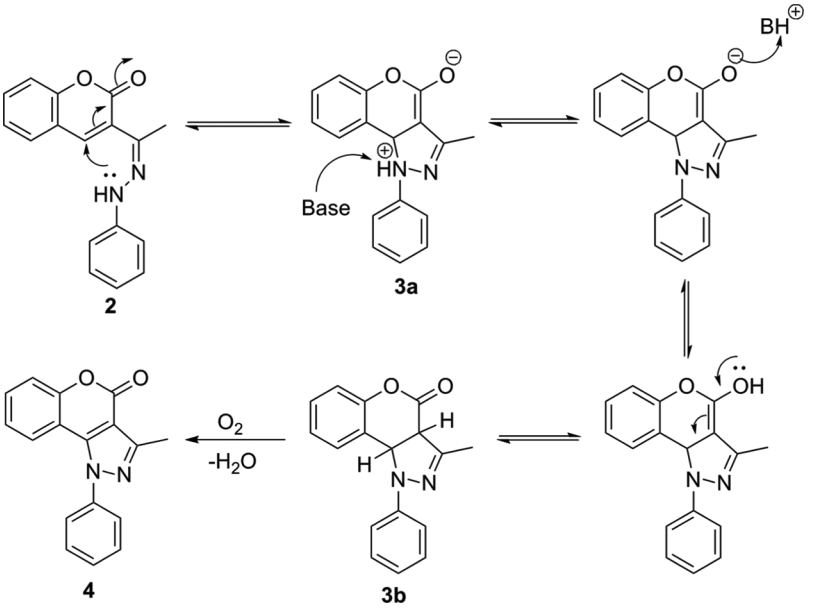
| Entry | Equiv | Time (h) | Isolated yield (%) |
|---|---|---|---|
| 1 | 1.5 | 16 | 92 |
| 2 | 2 | 12 | 88 |
| 3 | 0.5 | 28 | 85 |

To illustrate the versatility of developed methodology, a variety of phenylhydrazines were used as starting materials, and results are depicted in Table 3. Apart from 3-acetylcoumarin, the substrate scope of optimized conditions was also extended to 3-acetyl-7-methoxycoumarin as a starting material. The desired products were formed in excellent yields in all cases. Almost all substrates containing either electron-withdrawing or donating groups reacted at nearly the same time (15–18 h) except for compound **2b, 2e, 2f**, and **2o**. The short reaction time of **2b** and **2e** might be because of easy activation and enhanced nucleophilicity of the nitrogen center due to strong electron-withdrawing effect of halogen substituents, whereas **2f** and **2o** took longer time because of electron-donating substituents, which has a reverse effect. The observed effect of electronic nature of substituent on the rate of aza-Michael addition is supported by aza-Michael addition reactions of 4-nitrophthalimide with α,β-unsaturated ketones, which revealed that activation of Michael donor is enhanced when substituted with electron-withdrawing groups.[26] The products were isolated

**Table 3.** Synthesis of various chromenopyrazoles using optimized conditions




| Entry | Ar | R | Product | Time (h) | Isolated yield (%) |
|---|---|---|---|---|---|
| 1 | $C_6H_5$-(**2a**) | H | **4a** | 18 | 95 |
| 2 | 4-$CF_3$-$C_6H_4$-(**2b**) | H | **4b** | 10 | 90 |
| 3 | 4-Cl-$C_6H_4$-(**2c**) | H | **4c** | 15 | 93 |
| 4 | 4-Br-$C_6H_4$-(**2d**) | H | **4d** | 15 | 95 |
| 5 | 2,4-$(Cl)_2$-$C_6H_3$-(**2e**) | H | **4e** | 10 | 90 |
| 6 | 2,5-$(CH_3)_2C_6H_3$-(**2f**) | H | **4f** | 24 | 89 |
| 7 | 2-$CF_3$-$C_6H_4$-(**2g**) | H | **4g** | 15 | 91 |
| 8 | 4-F-$C_6H_4$ (**2h**) | H | **4h** | 14 | 92 |
| 9 | $C_6H_5$-(**2i**) | $OCH_3$ | **4i** | 17 | 98 |
| 10 | 2-$CF_3$-$C_6H_4$-(**2j**) | $OCH_3$ | **4j** | 17 | 92 |
| 11 | 4-$CF_3$-$C_6H_4$-(**2k**) | $OCH_3$ | **4k** | 15 | 96 |
| 12 | 4-Cl-$C_6H_4$-(**2l**) | $OCH_3$ | **4l** | 15 | 95 |
| 13 | 4-Br-$C_6H_4$-(**2m**) | $OCH_3$ | **4m** | 15 | 96 |
| 14 | 4-F-$C_6H_4$-(**2n**) | $OCH_3$ | **4n** | 15 | 90 |
| 15 | 2,5-$(CH_3)_2C_6H_3$ (**2o**) | $OCH_3$ | **4o** | 24 | 88 |




**Scheme 3.** Plausible mechanism of cyclization.

by employing simple workup such as filtration followed by recrystallization in methanol. The structural assignments of synthesized compounds were made on the basis of $^{1}$H NMR, $^{13}$C NMR, and high-resolution mass spectrometry (HRMS).

Keeping in view these observations and related literature,[19,22] a plausible mechanism of this reaction is depicted in Scheme 3. First, under a reversible mechanism, the substrate **2** undergoes intramolecular Michael addition to give intermediate **3a**. Base plays a catalytic role by deprotonating **3a** instead of **2**, because the NH proton of **2** is not acidic enough to be abstracted by weak or mild bases. Because of resonance stabilization, **2** require strong basic conditions to generate an anion, which is evidenced from the literature.[27,28] Subsequently, resonance stabilization of **3a** to afford dihydro-pyrazolone intermediate **3b** is followed by in situ irreversible oxidative dehydrogenation by oxygen in the air to furnish final compounds.

## EXPERIMENTAL

All the chemicals were procured from Sigma Aldrich (U.S.A.), S.D. Fine Chemicals, and Alfa Aesar (India). Thin-layer chromatography (TLC) was performed on precoated TLC silica-gel 60 $F_{254}$ plates (Merck, Germany). $^{1}$H NMR spectra were recorded on Bruker Avance III 400 spectrometer operating at a frequency of 400.13 MHz for protons, and tetramethylsilane (TMS) was used as an internal standard. Chemical shifts are reported as δ values and referenced to $CDCl_3$ (for $^{1}$H NMR 7.26 ppm and for $^{13}$C NMR 77.00 ppm). HRMS spectra were recorded on MaXis$^{TM}$ UHR-TOF (Bruker, Singapore). Melting points were determined on a digital melting-point apparatus (Perfit, India).

### General Procedure for Synthesis of 3-Methyl-1-phenylchromeno [4,3-c]pyrazol-4(1H)-ones (4)

The reaction mixture containing 3-acetylcoumarin (3.5 mmol) and various substituted phenylhydrazines (3.7 mmol) was refluxed in ethanol (10 mL) for 5 h, and reaction progress was monitored by thin-layer chromatography (TLC). On completion of the reaction, the solvent was removed from the reaction mixture under vacuum to afford the corresponding coumarin hydrazones, which were further used for cyclization without purification. For cyclization, a reaction mixture containing coumarin hydrazones (1.09 mmol) and potassium carbonate (1.09 mmol) was refluxed in acetone (5 mL) for 10–24 h. Reaction was monitored by TLC. On completion, the reaction mixture was filtered and the solvent was removed under reduced pressure. Finally crystallization was done in methanol to get pure compounds in excellent yield.

## CONCLUSION

In summary, an efficient and novel protocol for the cyclization of 3-[1-(phenylhydrazono)ethyl]-chromen-2-ones into corresponding pyrazoles using potassium carbonate as catalyst in acetone has been developed. The developed methodology eliminates the requirement of a leaving group at C-4 position of starting material 3-acetylcoumarin. The nonhazardous experimental conditions, rapid access of starting material, and good yields of desired products made this methodology simple and economical.

## FUNDING

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## SUPPLEMENTARY DATA

Full experimental detail, mp, $^{1}$H NMR, $^{13}$C NMR, and HRMS spectra for this article can be accessed on the publisher's website.

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