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Experimental and mechanistic insights into copper(II)–dioxygen catalyzed oxidative *N*-dealkylation of *N*-(2-pyridylmethyl)phenylamine and its derivatives†

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A di-(2-pyridylmethyl)phenylamine ($(PyCH_2)_2NPh$) supported $Cu(II)/O_2$ catalytic system was explored with the synthesis of pyridylmethyl-based compounds of carboxylate (PyCOOH), amide (PyC(O)NHPh), and imine (PyCH═NPh) from the oxidative *N*-dealkylation of *N*-(2-pyridylmethyl)phenylamine ($PyCH_2NHPh$) and its derivatives, by means of controlling the addition of a base and/or water to the reaction system under a dioxygen atmosphere at room temperature. Experimental studies showed that the imine and amide species could be precursors in succession in the way to the final oxidation state of carboxylates. A cyclic catalytic mechanism was proposed including the base triggered C–H bond activation of the 2-pyridylmethyl group ($PyCH_2$–) and the intermolecular Cu–OOH α-hydrogen atom abstraction from the coordinated imine substrate (PyCH═NPh).

Introduction

Enzymatic copper–dioxygen reactive species[1] play an important role as oxidative intermediates in many biological oxidation processes such as those of dopamine β-monooxygenase, hemocyanin and peptidylglycine α-amidating monooxygenase,[2] concerning aliphatic C–H bond deprotonation and thereafter hydroxylations.[3] Recently, the study of *N*-dealkylation has been of interest to chemists with the development of drug synthesis for the treatment of HIV, cardiovascular diseases, hypertension and high blood pressure.[4] However, the application of enzymatic copper–dioxygen adducts for the catalytic *N*-dealkylation of amines is still rarely reported,[5] and the oxidation of alkyl amines to the corresponding amides[6] was limited to the use of rigorous reaction conditions such as $Ru(OH)_x/Al_2O_3$ at high temperature and high pressure,[7] or the strong oxidant *t*-BuOOH[8] and/or RuO_4.[9] Efficient molecular catalytic methods are required for the progress of oxidative *N*-dealkylation including reactions that are both chemo-selective and economical in the availability of raw materials. Directed by these motivations, we have undertaken investigations into a copper(II)-mediated amino *N*-dealkylation reaction *via* the catalytic oxidation process, and report herein the synthesis of 2-picolinic acid (PyCOOH), *N*-phenylpicolinamide (PyC(O)NHPh) and *N*-(pyridin-2-yl-methylene)phenylimine (PyC═NPh) from the same starting material *N*-(2-pyridylmethyl)phenylamine ($PyCH_2NHPh$), by controlling the addition of different bases and/or water to the catalytic molecular systems at room temperature.

Results and discussion

Complex $[Cu^{II}(L_N)(H_2O)(OTf)](OTf)$ **1a** (L_N = $(PyCH_2)_2NPh$) was readily prepared by the stirring of L_N and $Cu(OTf)_2$ in a moist MeCN solution followed by the diffusion of Et_2O into the filtrate over 3 days. The reaction of the complex **1a**, $PyCH_2NHPh$, Et_3N and trace of water in MeCN under a dioxygen atmosphere generated a thermodynamic air-stable complex $\{[Cu^{II}(L_N)(PyCOO)](OTf)\}_n$ **1b** in 53% yield (Scheme 1), which has been structurally characterized by X-ray crystallography (Fig. 1). Treatment of **1b** with concentrated hydrochloric acid (37%) followed by the extraction of organic species in CH_2Cl_2 afforded a carboxylate product (PyCOOH) as a white solid. Modification of the experimental conditions by the absence of copper salt, ligand (L_N), base, dioxygen or water confirmed that all these species were necessary for a successful transformation from $PyCH_2NHPh$ to PyCOOH. The study showed that the formation of the $[Cu^{II}(L_N)]$ moiety was crucial for the

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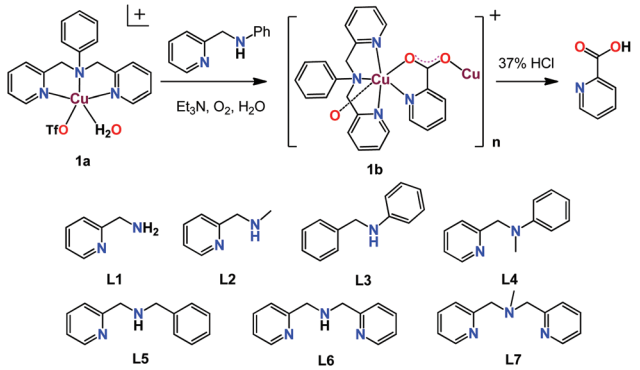
‡These authors contributed equally to this work and should be considered co-first authors.



Scheme 1 Routine and examination of substrates for the synthesis of 2-picolinic acid in the presence of O_2 and water.

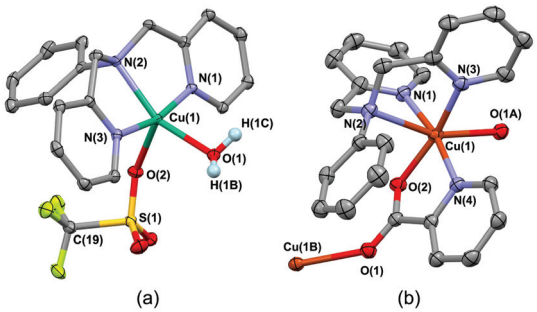
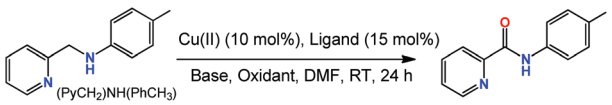


Fig. 1 Crystal structures of the complexes **1a** (a) (CCDC 1560832†) and **1b** (b) (CCDC 1560849†) showing a 50% probability ellipsoid.

process of highly efficient oxidative catalysis accompanied by the addition of dioxygen as an oxidant. Other copper sources such as $Cu(BF_4)_2{\cdot}6H_2O$ and $Cu(ClO_4)_2{\cdot}6H_2O$ provided the same product in similar yields. For the purpose of exploring the scope of substrates acceptable for our reaction, seven likely analogues **L1–L7** were chosen as substrates on trial (Scheme 1), but no sign of **1b** was found from the experiments. In contrast, the bis-ligand coordinated complexes **1c** and **1d** (Fig. S1†) were obtained instead of **1b** when tridentate substrates di-(2-pyridylmethyl)amine (**L6**) and *N*-methyl-*N*,*N*-di(2-pyridylmethyl)amine (**L7**) were used as substrates for the reactions. It is shown that the phenyl, pyridyl and the aromatic secondary amine groups are indispensable for the selection of reactive substrates suitable for this copper-mediated oxidative *N*-dealkylation activation.

In order to better understand the formation and reactivity of copper–dioxygen adducts, we successfully repeated this oxidation reaction by means of organometallic catalysis methodology and isolated the product as amides analogously. We commenced the investigation by choosing 4-methyl-*N*-(2-pyridylmethyl)phenylamine $(PyCH_2)NH(PhCH_3)$ as a model substrate and explored the reaction by changing different ingredients including the copper(II) salt, ligand, oxidant, base, solvent and the reaction temperature to find out the most suitable condition (Table 1). Based on the amount of experimental data

Table 1 Optimization studies for the formation of amide



En	Cu(II)	Base	Oxi	*T*	Ligand	Solv	Yield
1	**$Cu(OTf)_2$**	*t*-BuOK	O_2	RT	L_N	DMF	92%
2	**$Cu(OAc)_2$**	*t*-BuOK	O_2	RT	L_N	DMF	56%
3	**$CuCl_2$**	*t*-BuOK	O_2	RT	L_N	DMF	81%
4	**None**	*t*-BuOK	O_2	RT	L_N	DMF	0
5	$Cu(OTf)_2$	***t*-BuONa**	O_2	RT	L_N	DMF	76%
6	$Cu(OTf)_2$	**K_2CO_3**	O_2	RT	L_N	DMF	0
7	$Cu(OTf)_2$	**NaOH**	O_2	RT	L_N	DMF	0
8	$Cu(OTf)_2$	**None**	O_2	RT	L_N	DMF	0
9	$Cu(OTf)_2$	*t*-BuOK	**N_2**	RT	L_N	DMF	0
10	$Cu(OTf)_2$	*t*-BuOK	**Air**	RT	L_N	DMF	62%
11	$Cu(OTf)_2$	*t*-BuOK	O_2	**60 °C**	L_N	DMF	88%
12	$Cu(OTf)_2$	*t*-BuOK	O_2	**80 °C**	L_N	DMF	86%
13	$Cu(OTf)_2$	*t*-BuOK	O_2	RT	**None**	DMF	0
14	$Cu(OTf)_2$	*t*-BuOK	O_2	RT	L_N	**MeCN**	60%
15	$Cu(OTf)_2$	*t*-BuOK	O_2	RT	L_N	**THF**	0
16	$Cu(OTf)_2$	*t*-BuOK	O_2	RT	L_N	**CH_2Cl_2**	0

Reaction conditions: amine (0.1 mmol), Cu(II) salts (10 mol%), ligand (15 mol%), base (0.2 mmol), O_2 (1 atm), solvent (1 mL). En = entry; Oxi = oxidant; Solv = solvent.

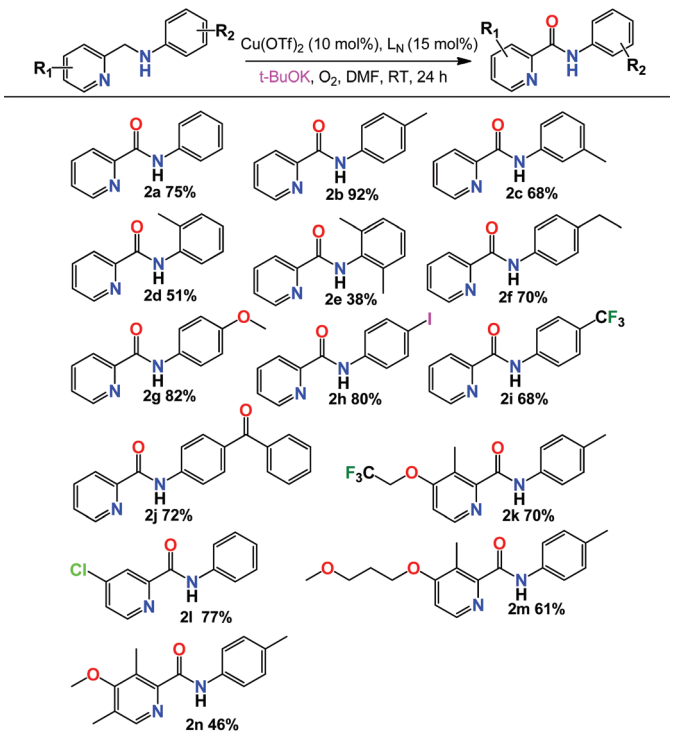
obtained, it was shown that the reaction of $(PyCH_2)NH(PhCH_3)$ with $Cu(OTf)_2$ (10 mol%), L_N (15 mol%) as the supported ligand, dioxygen as the oxidant, and *t*-BuOK as the base in DMF solution at room temperature gave the best result to yield the product, 4-methyl-*N*-phenylpicolinamide in a 92% yield. Modification of the experimental conditions by the absence of catalyst, base, oxidizing agent, or supported ligand (L_N), respectively, confirmed that these species played critical roles in this *N*-dealkylation reaction (entries 4, 8, 9 and 13). The presented results also indicated that the OTf^- anion coordinated $[Cu^{II}(L_N)]$ moiety worked as a highly efficient molecular catalyst in the process of oxidation of *N*-(2-pyridylmethyl)phenylamine derivatives to amides together with dioxygen. The coordination of the OTf^- anion and/or H_2O as the terminal groups led to a relatively weak ligand field at the central copper atom and the attendant tendency to form a $\{Cu^{II}(L_N)[(PyCH_2)NH(PhCH_3)]\}$ (Fig. S2†) intermediate heading for the oxidative molecular catalytic reaction. Other copper sources such as $Cu(OAc)_2$ (entry 2) and $CuCl_2$ (entry 3) provided the product in much lower yields, probably due to the presence of the strong ligand field of the OAc^- and Cl^- anions, respectively. Different solvents of DMF, MeCN, THF and CH_2Cl_2 were tried for the reaction (entries 1 and 14–16). It appeared that the polarity of the solvents would have a large effect on the reaction with yields of 92% in DMF down to 60% in MeCN and 0% in THF and CH_2Cl_2. Meanwhile, it was found that higher temperature had a negative effect on the formation of the amide products (entries 1, 11 and 12). Finally, the reaction time was explored at the points of 8 h, 16 h, 24 h and 36 h under the reaction condition of entry 1 in Table 1. The reactions yielded the product of $(PyC(O))NH(PhCH_3)$ in 87% (8 h), 91% (16 h), 92% (24 h) and 92% (36 h) after isolation. A suitable reaction time

of 24 h was determined with the consideration of other bulky substrates for a unified reaction condition, since bulky groups on the phenyl and pyridyl rings of substrates might slow down the reaction rates dynamically.

Encouraged by the above results, we started to examine the scope of the reaction as to other amine substrates for the catalytic reaction (Table 2). Firstly, alkyl substituted phenylamine derivatives (**2b–2f**) were employed for the study of the steric effect on the reaction, and the experimental results showed that 4-toluidine, 3-toluidine and 2-toluidine substituted phenylamine reactants yielded the desired amide products in 92% (**2b**), 68% (**2c**) and 51% (**2d**), respectively, with the 2,6-dimethylaniline substituted reactant giving only a 38% yield (**2e**). Obviously, the steric effect would reduce the yield drastically from the *para*-position to the *meta*- and/or *ortho*-position. The slightly larger ethyl group in the *para*-position (**2f**) could also lead to the decrease of yield over 20% by comparison of the methyl group at the same site (**2b**). Secondly, the electronic effect of substituents on the phenyl group was examined by employing variable substituents (**2g–2j**) in the *para*-position. The results indicated that the electron-donating groups (**2g2h**) showed positive effects on the reaction, but the use of electron-withdrawing groups on the phenyl group only gave products at around 60–70% yield (**2i2j**). Finally, the investigation of the steric effect on the pyridine site of the substrates demonstrated that the bulky groups on the pyridine ring would inhibit the reactions with yields down to 70% (**2k**), 61% (**2m**), and 46% (**2n**), in contrast to the pyridine-only substrate which afforded a yield of 92% (**2b**). In addition, no product species was detected when the 2-pyridylmethylamine derivatives of **L1–L7** (Scheme 1) were used as reaction substrates for the catalytic reaction, which was consistent with the result deduced from the inorganic section presented in Scheme 1.

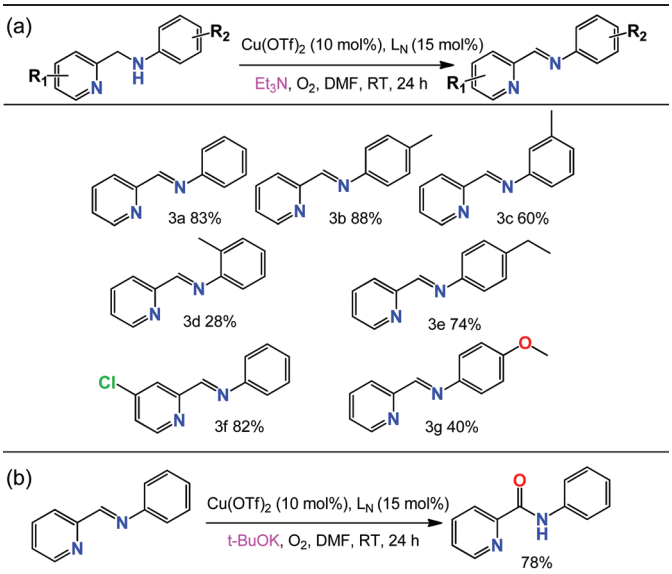
Interestingly, the catalytic products were found as imine species rather than amides when the base of Et_3N was used for the deprotonation of substrates instead of *t*-BuOK (Table 3(a)). Traces of amides were also isolated as by-products with the yield as low as 3–5% based on the amount of substrates used for the reaction. The exploration of suitable substrates for the generation of the imine products was carried out from the viewpoints of steric effect and electronic effect as well, and it was found that the imine generation reaction was very sensitive to the steric effect with the products yielding in 88% (**3b**), 60% (**3c**) and 28% (**3d**) for methyl substituted phenylamine substrates in the *para*-, *meta*- and *ortho*-positions, respectively. However, the study of the electronic effect failed due to unsuccessful attempts to isolate the corresponding imine products from major substrates, except for one sample that held an electron-donating group of methoxyl in the *ortho*-position of the phenyl ring and produced the imine in low yield (40%, **3g**). Perhaps the generated imine species were too reactive to be isolated for those ineffective reactions, since it has been reported that the oxidation of imine to amides was possible in the presence of strong oxidants $KMnO_4$[10] and $NaBO_3$/TFA[11] or by cyanide-mediated aerobic oxidation.[12] Moreover, the obtained imine was found in our lab able to be catalytically

Table 2 Scope of the reactions with respect to amides



All the reactions were performed on a 0.1 mmol scale under O_2 (1 atm): $Cu(OTf)_2$ (0.01 mmol), L_N (0.015 mmol), amines (0.1 mmol), *t*-BuOK (0.2 mmol), DMF (1 mL), RT, 24 h. Isolated yields were indicated.

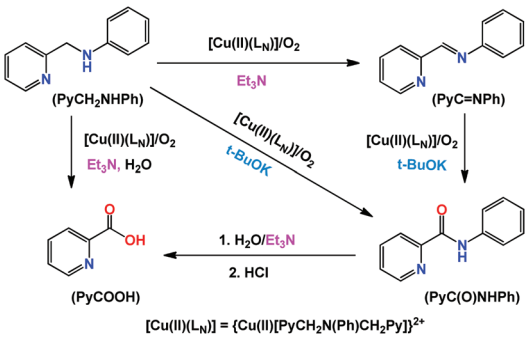
Table 3 Scope of the reactions with respect to imines



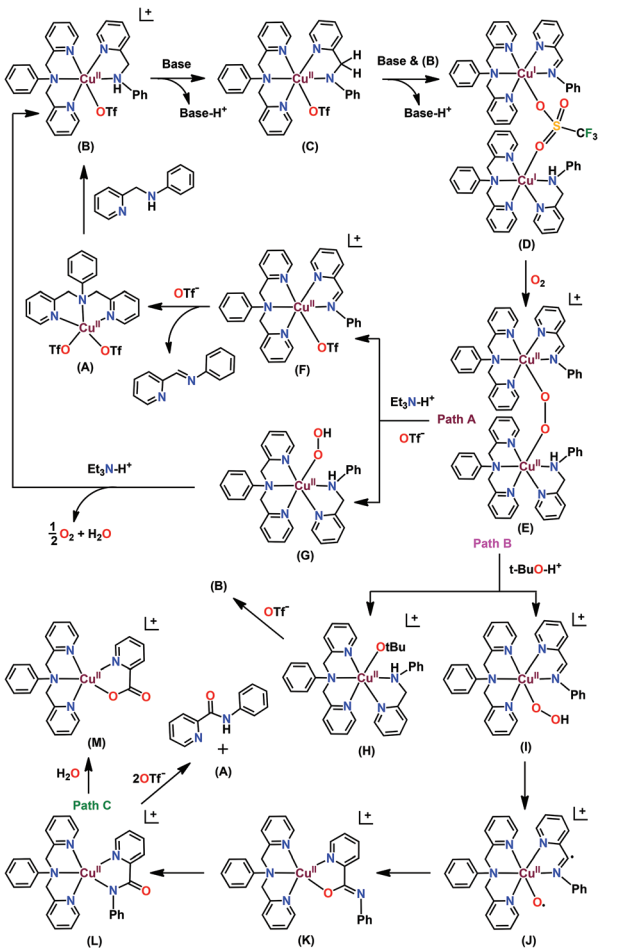
All the reactions were performed on a 0.1 mmol scale under O_2 (1 atm): $Cu(OTf)_2$ (0.01 mmol), L_N (0.015 mmol), Et_3N (0.1 mL), amine derivatives (0.1 mmol), DMF (1 mL), RT, 24 h. Isolated yields were indicated.

oxidized to amide in the presence of the copper(II) catalyst, the base of *t*-BuOK and dioxygen as well (Table 3(b)). This work indicated that the imine could be the intermediate in the oxidation reaction of *N*-(2-pyridylmethyl)phenylamine to the corresponding amide.

On the basis of the above results, a catalytic mechanism is proposed in Scheme 2. Mixing of the tridentate ligand L_N with $Cu(OTf)_2$ generates the complex (**A**), which reacts with the chelate ligand of $PyCH_2NHPh$ to produce the complex (**B**). In the presence of a base, the proton of the secondary amine of (**B**) is attacked to leave *via* the N–H bond cleavage to form an intermediate (**C**). The species of (**C**) executes an intermolecular two-electron reduction together with a joint (**B**) molecule to afford the dicopper(I) species (**D**), which turns into a μ-peroxo dicopper(II) intermediate (**E**) under two-electron oxidation in a dioxygen atmosphere. In path A, the intermediate (**E**) receives a proton from the base H^+ (Et_3N-H^+) and divides into two species of (**F**) and (**G**). The HOO^- group prefers to stay at the amine coordinated copper(II) side rather than the imine side possibly due to less electron donation from the amine donor than the imine donor. Thus, the imine product is released from (**F**) by the substrate of a triflate anion together with the regeneration of the starting catalyst (**A**). Meanwhile, the complex (**G**) can be protonated by a second portion of Et_3N-H^+ followed by the release of O_2 and H_2O to afford the complex (**B**). In path B, the intermediate (**E**) may undergo nucleophilic attack by the *t*-BuO^- group at the amine coordinated copper(II) side to form two species of (**H**) and (**I**), since the Cu(II) species at the amine side shows stronger electrophilicity to the strong electron donating group *t*-BuO^- compared to the imine side. The complex (**H**) may transfer to the species (**B**) after a substitution reaction with the triflate anion. The copper(II) moiety [Cu(II)–OOH] (**I**)[13] shows high reactivity towards the elimination of water *via* hydrogen atom transfer (**I** → **J**) and oxygen rebound to the carbon atom of the imine group (**J** → **K**) leads to the formation of the intermediate (**K**),[13,14] which accepts a proton from the solution and performs an intramolecular rearrangement reaction to produce the intermediate (**L**). Pyridyl amide is released as the second catalytic product. In path C, the species of (**L**) undergoes a hydrolysis reaction to afford the coordination complex (**M**) when a trace of water is present in the activation reaction (Scheme 1).



Scheme 3 Summary of the controlled *N*-dealkylation of $PyCH_2NHPh$ in the $Cu(II)/O_2$ molecular system under mild conditions.



Scheme 2 Proposed catalytic process for the oxidative *N*-dealkylation of *N*-(2-pyridylmethyl)phenylamine to imine, amide and carboxylate.

Conclusions

In summary, we have developed a simple and safe Cu(II)/O_2-catalytic molecular system for the oxidative *N*-dealkylation of *N*-(2-pyridylmethyl)phenylamine ($PyCH_2NHPh$) and its derivatives to synthesize pyridylmethyl-based analogous compounds of carboxylate (PyCOOH), amide (PyC(O)NHPh), and imine (PyCH=NPh), by controlling the addition of bases and/or water to the solution (Scheme 3). Experimental and mechanistic studies showed that the imine and amide species could be precursors in succession in the way to the final oxidation state of carboxylate. This work shows a successful example regarding the study of small molecule activation from the view of bioinorganic chemistry, coordination chemistry and catalytic chemistry, and offers an economic and efficient method for the catalytic oxidation of the methylene groups of amines by using an environmentally friendly catalyst, and a green oxidant under mild reaction conditions, and might provide a chance

to access the enzymatic copper–dioxygen system that could originate useful substrate hydroxylation reactions in the bio-inorganic and/or catalytic research area.

Experimental section

$Cu(OTf)_2$ (3.6 mg, 0.01 mmol), *N*,*N*-bis(pyridin-2-ylmethyl) phenylamine (L_N) (4.1 mg, 0.015 mmol), *t*-BuOK (22.4 mg, 0.2 mmol) or (Et_3N, 0.1 mL) and *N*-(2-pyridylmethyl)phenylamine derivatives (0.1 mmol) were mixed in dried DMF (1 mL) in a 35 mL Teflon screw-cap sealed tube. The tube was charged with O_2 (1 atm) and the mixture was vigorously stirred at RT for 24 h. After the reaction was completed, the reaction mixture was diluted with dichloromethane (20 mL), filtered through a pad of silica gel and concentrated under reduced pressure. The crude product was purified on a silica gel column.

Conflicts of interest

There are no conflicts of interest to declare.

Acknowledgements

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