

Tracking the Progress and Mechanism Study of a Solvothermal in Situ Domino N-Alkylation Reaction of Triethylamine and Ammonia Assisted by Ferrous Sulfate

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Supporting Information

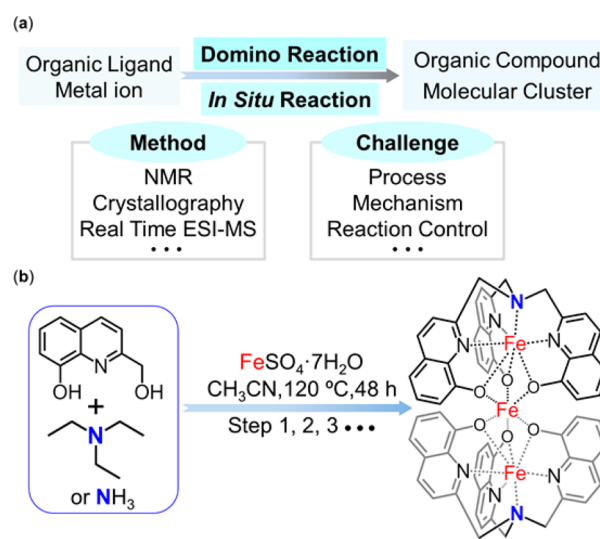
ABSTRACT: Atom economic in situ domino N-alkylation reactions of triethylamine/ammonia with 2-(hydroxymethyl)quinolin-8-ol (HL-OH) assisted by $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$ were realized under mild solvothermal conditions at 120 °C in acetonitrile. The resulting tripodal 2,2',2''-[nitrilotris(methylene)]tris(quinolin-8-ol) ($\text{H}_3\text{L}_3\text{-N}$) forms a linear trimer $[\text{Fe}_3(\text{L}_3\text{-N})_2]$ (**1**). Electrospray ionization mass spectrometry of the reaction solution provides evidence for the intermediates of three steps, while crystallography and X-ray photoelectron spectroscopy characterize the trimer. Shortening the time of the reaction allowed for the organic intermediates to be isolated, which led to a proposed mechanism. The method provides a facile way to produce symmetric tertiary amine from widely used NEt_3 and NH_3 . The results represent an example of the in situ Fe^{2+} -catalyzed domino reaction in which Fe^{2+} is coordinated by the generated ligands and is involved in each step until the final cluster **1**.

One of the primary goals in chemistry is to understand how reactions progress while identifying the intermediates so that schemes and mechanisms can be drawn.^{1–3} Observing and tracking these reactions using the appropriate methods are prerequisites to attaining these goals.^{2,3} Choosing a reaction procedure is an important basis for direct synthesis and for further reactions.^{3,4} The solvothermal and hydrothermal techniques are becoming important synthetic tools and have generated otherwise unattainable organic molecules, coordination polymers (or metal–organic frameworks), and clusters.^{3–5} Often in situ metal/ligand reactions take place when a solvothermal technique is employed in which the starting ligands undergo reactions assisted by the metals to produce oligomeric ligands that are difficult to synthesize or even inaccessible using traditional organic synthetic approaches.⁴ In addition, the in situ produced ligands could further participate in the assembly of transition metals to give functional coordination complexes with

novel structures and physical properties.^{3,4} The investigation of the mechanism of such in situ metal/ligand reactions is helpful in understanding the processes that can lead to the rational design of target molecules.⁴

Rarely have domino reactions, where simple starting materials undergo a series of step-by-step reactions in one pot, been reported using the solvothermal method.⁶ Domino reactions are desirable for the construction of complicated compounds because it is atom, step, and time economic (Scheme 1a).^{6,7} Fe-catalyzed domino reactions are appealing for their cheapness and hypotoxicity (Table S1). However, in situ metal/ligand

Scheme 1. (a) General Scheme of Domino Reactions and (b) in Situ Multistep N-Alkylation of NEt_3 or Ammonia Assisted by $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$ To Produce the Cluster **1**



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domino reactions are rare, and mechanistic study is still in its infancy.

2-(Hydroxymethyl)quinolin-8-ol (HL-OH) is known to undergo an in situ C–C coupling reaction in the presence of ethanol, $\text{Co}(\text{H}_2\text{O})_6(\text{NO}_3)_2$, and triethylamine under solvothermal conditions to give 1,2-bis(8-hydroxyquinolin-2-yl)ethane-1,2-diol, which resulted in the formation of red crystals of the single-molecule magnet $[\text{Co}^{\text{II}}_7(\text{bhqe})_3(\text{OH})_2(\text{H}_2\text{O})_6] \cdot 2\text{C}_2\text{H}_5\text{OH} \cdot \text{H}_2\text{O}$.⁸ In contrast, 1,2-bis(benzo[*d*]imidazol-2-yl)-1,2-ethanediol undergoes in situ dehydration under solvothermal conditions in the presence of water, methanol, $\text{Zn}(\text{H}_2\text{O})_6(\text{NO}_3)_2$, and triethylamine to form 1,2-bis(benzo[*d*]imidazol-2-yl)-1,2-ethanol (H_3L^n) and crystallizes in the highly luminescent $[\text{Zn}_3(\text{H}_2\text{L}^n)_6](\text{NO}_3)_4 \cdot 8\text{H}_2\text{O} \cdot 2\text{CH}_3\text{OH}$, which is a nontoxic bioimaging marker for tumor cells.^{3b} The importance of in situ oligomerization of ligands in a solvothermal reaction thus prompted us to explore a low-redox-potential metal such as Fe^{2+} in the reaction of HL-OH.

An unprecedented Fe^{2+} -catalyzed domino reaction of the widely used organic base NEt_3 with HL-OH, producing a linear trinuclear iron cluster $[\text{Fe}_3(\text{L}_3\text{-N})_2]$ (**1**; Scheme 1b and Figure S1), has been observed. Crystal data for **1** and selected bond lengths and angles are summarized in Table S2. 2,2',2''-[Nitrilotris(methylene)]tris(quinolin-8-ol) ($\text{H}_3\text{L}_3\text{-N}$) is potentially expected to lose three protons of its alcohols, giving six negative charges for a pair to obtain the neutral trimeric complex (Figure S2); therefore, each Fe atom has to be divalent. This was confirmed by X-ray photoelectron spectroscopy (XPS; Figure S3c). The two peripheral Fe atoms are seven-coordinated by four N and three O atoms of each $\text{L}_3\text{-N}$, and the central Fe atom bridges the two through coordination to the six O atoms (Figure S4a). The coordination sphere around the seven-coordinated Fe^{II} is a capped flattened octahedron, which is suggested by calculation of the continuous-shape measurement value (Table S3). The molecular ion peak ($[\text{Fe}_3(\text{L}_3\text{-N})_2]^+$; m/z 1138.12) of cluster **1** was recorded by electrospray ionization mass spectrometry (ESI-MS; Figure S5 and Table S4).

It is clear from the crystal structure of compound **1** that the in situ metal/ligand reaction of HL-OH and NEt_3 in the presence of $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$ generated the coordinating tripod amine ligand. Quite surprising was the involvement of the commonly used organic base NEt_3 as the nitrogen source. When the reaction was performed without NEt_3 , neither crystals of cluster **1** nor the ESI-MS signal related to the $\text{Fe}_3(\text{L}_3\text{-N})_2$ fragment was observed in the reaction solution and precipitate. The mild conditions and the use of the most abundant metal are very encouraging as potential commercially economic terms for industrial application.⁹ Consequently, we set out to unravel the reaction pathway in order to provide a mechanism.

ESI-MS of the reaction solutions as a function of time (1, 5, 24, and 48 h) of the solvothermal treatment was used to search for information on the reaction process (Figures 1a and S7). The spectrum after 1 h shows four main sets of peaks at m/z 342.03, 432.00, 518.06, and 543.11, which were assigned to the respective species $[\text{Fe}^{\text{III}}(\text{L-O})(\text{H}_2\text{O})_4(\text{CH}_3\text{CN})]^+$ (**F1**, m/z 342.05), $[\text{Fe}^{\text{II}}(\text{L-NEt}_2)\text{K}_2(\text{OH})_3(\text{H}_2\text{O})]^+$ (**F2**, m/z 432.02), $[\text{Fe}^{\text{II}}(\text{L}_2\text{-NEt})(\text{CH}_3\text{OH})(\text{OH})]^+$ (**F3**, m/z 518.05), and $[\text{Fe}^{\text{II}}(\text{L}_3\text{-N}) + 2\text{H}]^+$ (**F4**, m/z 543.11). These fragments contain the deprotonated starting ligand (L-O) and the monosubstituted (L-NEt₂), disubstituted (L₂-NEt), and trisubstituted (L₃-N) amine intermediates, suggesting a possible step-by-step reaction. After 5 h, the main **F1**–**F4** peaks are still present and their intensities have changed marginally. By 24 h, **F1** has disappeared

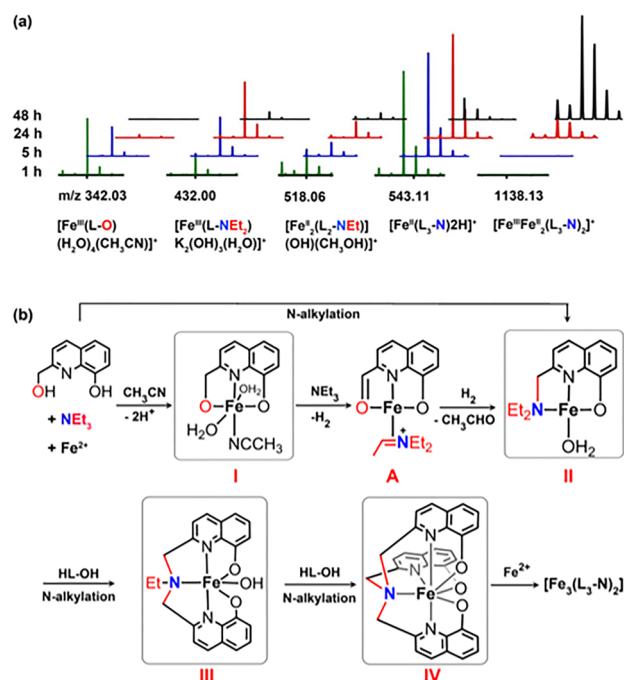


Figure 1. (a) Selected peaks of the time-dependent ESI-MS spectra of the reaction of NEt_3 with HL-OH in the presence of $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$. (b) Proposed mechanism (the intermediates in squares have the core structures of the detected fragments in part a).

and a new species has appeared at m/z 1138.13, which is assigned to the molecular ion of cluster $[\text{Fe}_2^{\text{II}}\text{Fe}^{\text{III}}(\text{L}_3\text{-N})_2]^+$ (**F5**, 1138.13). After 48 h, the intensities of **F2**–**F4** have become very weak and that of **F5** is the most prominent peak. The change of the intensities of the peaks of **F1**–**F4** indicates their intermediate nature and that NEt_3 undergoes stepwise N-alkylation. The time-dependent ESI-MS spectra of the reaction precipitates (Figure S7b) are similar to those of the reaction solutions, confirming that domino N-alkylation produces cluster **1**. To our knowledge, this is the first time that the N-alkylation reaction of amine with alcohol was monitored by ESI-MS and the key intermediates were successfully detected.

The amount of reaction precipitate increases with time. The XRD pattern of the reaction precipitate resembles more and more that simulated for the crystal (Figure S6), also suggesting that the amount of cluster **1** increases. This is also confirmed by the increase of the peak intensity of **1** in the time-dependent ESI-MS of the reaction precipitate (Figure S7 and Table S5).

Through variation of reaction time, the N-alkylated organic intermediates HL-NEt₂ and $\text{H}_2\text{L}_2\text{-NEt}$ and the product $\text{H}_3\text{L}_3\text{-N}$ could be obtained postsynthetically through acidification of the reaction solution and precipitate, followed by extraction and thin-layer chromatography (Figures S7d, S8, and Table S6).

From the results of the above analyses, a plausible mechanism is proposed (Figure 1b and Table S7). First, coordination of HL-OH with Fe^{2+} in the presence of NEt_3 produces pincer-type intermediate **I** ($[\text{Fe}^{\text{III}}(\text{L-O})(\text{H}_2\text{O})_4(\text{CH}_3\text{CN})]^+$, m/z 342.03). It is known that the manganese pincer complexes (Mn-PNP) are efficient catalysts for N-alkylation of primary and secondary amines with alcohol via a hydrogen-borrowing (BH) pathway.¹⁰ Although it can also undergo a nucleophilic substitution pathway (Table S8), the alkaline environment is not suitable for it. Then the coordinated CH_2O group transforms to the CHO group, as proposed via the BH mechanism.¹¹ It is known that the tertiary

amine could undergo N–C bond cleavage via an iminium ion intermediate catalyzed by an iron complex.¹² Furthermore, the reductive amination of tertiary amine and aldehyde has been reported via the iminium cation intermediate.¹³ Then, coordination of NEt₃ with the central Fe atom leads to α -CH activation to give the coordinated iminium ion intermediate **A**. The reaction between the iminium ion and aldehyde results in intermediate **II** ([Fe^{III}(L-NEt₂)(OH)₃]⁺) and acetaldehyde, which has so far been elusive possibly because of its low boiling point and high reactivity. **II** is also a tertiary amine reacting with another molecule of HL-OH via N-alkylation to give intermediate **III** ([Fe^{II}(L₂-NEt)(OH)]⁺; *m/z* 518.06). In **III**, the L₂-NEt ligand will also coordinate with Fe²⁺. This could preserve the Fe²⁺ cation from dissociation and then facilitate the third step N-alkylation to give intermediate **IV** ([Fe^{II}(L₃-N)]⁺). In **IV**, Fe²⁺ is trapped by ligand L₃-N and hinders coordination of the other ligand to Fe²⁺. Finally, two **IV** intermediates are easily linked by one Fe²⁺ atom through the O atoms of L₃-N to produce the final product **1**. The key intermediates (**I–IV**) are the cores of the fragments **F1–F4** observed by ESI-MS. The Fe ion is indispensable for this transformation because without FeSO₄·7H₂O or when using other sulfate, no related fragments were detected by MS (Figure S12). Furthermore, the ligand HL-OH could provide suitable electronic and steric environments for Fe²⁺, which is helpful for coordination of NEt₃ followed by a further reaction with the in situ generated aldehyde group. HL-OH is also helpful in stabilizing the N-alkylation intermediates, assisting further reaction of the intermediates with another two HL-OH ligands, from which triple N-alkylation is achieved. However, other alcohols [(1-methyl-1H-benzo[d]imidazol-2-yl)methanol and (1H-benzo[d]imidazol-2-yl)methanol] do not undergo this transformation, as judged by the absence of any crystals or crystalline products as well as the intermediates and molecular fragments corresponding to **1** in the MS of the solutions. Fe²⁺ is preserved in the final [Fe₃(L₃-N)₂]⁺ cluster. This could explain why the amount of FeSO₄·7H₂O is slightly more than HL-OH, different from the commonly used catalyst loading. In contrast to N-alkylation reactions of low-weight amines in the literature that always end after two steps,^{14,15} the present procedure goes to the third step leading to the symmetrical tertiary amine.

Direct N-alkylation of amine with alcohol constitutes an attractive environmentally friendly process because water is generated as the main byproduct.^{10,14–17} N-alkylation of tertiary amine with alcohol has rarely been reported (Table S9).¹⁸ The products are usually formed from single or double N-alkylation of tertiary amine catalyzed by RuCl₃·3H₂O^{18a} or under harsh conditions.^{18b,c} To our knowledge, this is the first example of a triple domino N-alkylation of NEt₃ assisted by iron catalyst under solvothermal conditions. Furthermore, these results show that the time-dependent ESI-MS is a valuable tool for monitoring the domino reaction, from which the reaction could be controlled to gain the desired intermediates.

As a cheap and readily available nitrogen source, ammonia has been applied in N-alkylation with alcohol.¹⁹ The N-alkylation of NH₃ was realized at the same reaction condition, producing the same cluster **1** with improved yield (Figures S9, S10, and Table S10). A possible mechanism involving triple BH pathways is proposed (Figure S10). In effect, NH₃ is a good enough nitrogen source to give complex **1**.

In summary, we found a rare in situ domino N-alkylation reaction of triethylamine assisted by FeSO₄·7H₂O in the solvothermal reaction at moderate pressure and lower temper-

ature resulting in a trimeric cluster. For the first time, the stepwise intermediates are identified by ESI-MS. Estimation of their quantities at different reaction times followed by their isolation reveals three consecutive N-alkylation steps that allowed for a mechanism to be established. The selective synthesis of organic ligands HL-NEt₂, H₂L₂-NEt, and H₃L₃-N is realized by controlling the reaction time. It is also less hazardous and more economic than those in the literature. Application of the procedure for the reaction of ammonia was also successfully performed with improved yield. Because Fe²⁺ is present in all of the intermediates and products, it is reasonable to conclude that the chelating ligands HL-OH, L-NEt₂/L-NH₂, and L₂-NEt/L₂-NH could provide suitable electronic and steric environments for Fe²⁺, which could promote multiple N-alkylations and the stepwise assembly. This could give some insight of the coordination catalysis and self-catalysis. The results represent a vivid example of the metal-catalyzed in situ domino reaction. The synthesis of other multidentate ligands via this strategy is ongoing.

■ ASSOCIATED CONTENT

📄 Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.inorgchem.7b01190.

Experimental details, crystal data, mass spectrometry, XRD, XPS, and NMR (PDF)

Accession Codes

CCDC 1540483–1540484 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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