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A Column-Free and Aqueous Waste-Free Process for Thioamide Preparation with Lawesson's reagent

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Abstract

After completing thio-substitution with the Lawesson's reagent, ethanol was found to be able to efficiently decompose the inherent stoichiometric six-membered-ring by-product from the Lawesson's reagent to a highly polarized diethyl thiophosphate. This treatment could significantly simplify the following column purification of the desired thioamide in a small scale preparation. As scaling up the preparation of two pincer-type thioamides, we have successfully developed a convenient process with ethylene glycol to replace ethanol during the workup, including traditional phase-cut, extraction, and re-crystallization. The newly developed column-free procedure did not generate P-contained aqueous waste, and only organic effluents were discharged. It was believed that the optimized procedure can greatly provide opportunity of the application of the Lawesson's reagent for various thio-substituted reacions in scaling up preparation.

Keywords

Lawesson’s reagent; Column-free; Thionation; Thioamide; Scale-up

Introduction

The transformation of carbonyl into thiocarbonyl group is one of the most important reactions in organic synthetic chemistry [1]. The Lawesson’s reagent (LR) is widely applied in this transformation, as well as for the syntheses of various sulfur-contained heterocyclic compounds [2-4]. Although LR is a powerful, mild and versatile thionation reagent, the workup procedure has been received quite a few negative comments [5-9]. The reason is that an inherent six-member ring structure **A** (Figure 1) was formed as LR completing thio-substitution [10-12]. It was observed that the polarity of the compound **A** is generally similar to the desire products, and any purification effort of the desired products by extraction operations makes less efficiency because of its good solubility. Thus, the purification was rather difficult and usually a careful column separation was necessary because of both the polarit and the stoichiometric amount of the compound **A**. With regard to this, LR is always limited to a small-scale preparation [5,7].

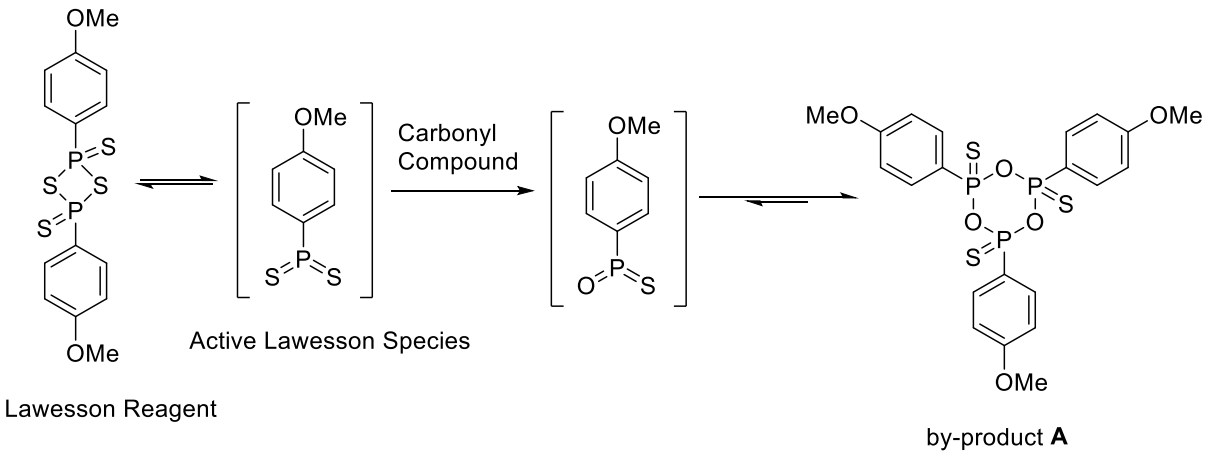


Figure 1. Generation of the six-membered by-product **A**

Other than the exploration of the potential surogates of LR for the thionations, considerable efforts have been devoted to the improvements of the workup of the LR reactions. For example, Soós and coworkers attached perfluorinated alkyl chains bonding to LR, which could simplify the product isolation via a fluorous reversed-phase solid extraction technique [8,9]. This method with long perfluorinated alkyl chains is attractive in parallel synthesis and also in high-throughput biological screening. However, both modified LRs and fluoro sources are rather high-cost and not practical for scaling up. Besides, basic aqueous solutions were utilized as well in the work-up process. It was believed that the compound **A** was converted to an aqueous soluble thio-phosphate (Figure 2) [13-15]. This operation indeed simplified the work-up procedure and the scaling up column-free purification, while generated quite a lot of P-contained aqueous waste. The P-contained aqueous waste was unfavorable during the scaling up because of the difficult treatment in the downstream and also one of the sources of eutrophication. Therefore, optimizing the work-up process of applying LR in thionation reaction is greatly appealing for the potential large-scale preparations.

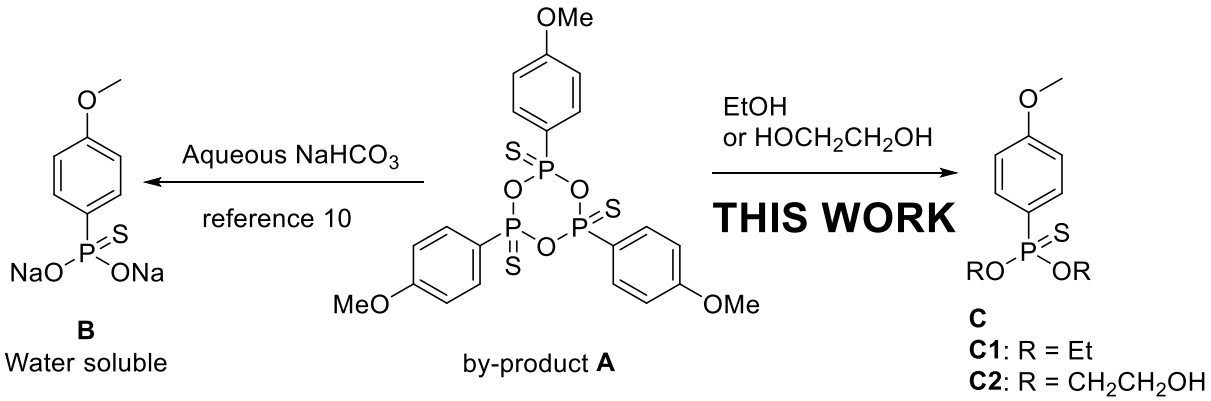


Figure 2. Work-up procedure for the reaction with LR

Thioamide compounds are one of the most attractive molecules in pharmaceuticals, agrochemicals, electronic chemicals and material sciences [16-22]. In coordination chemistry, pincer-type ligands containing thio-amide motif have already exhibited their

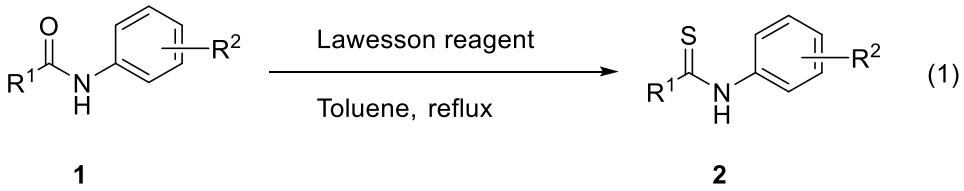
incomparable chelating ability to the selected transition-metals, and their corresponding complexes have been applied in various areas such as chemical-sensor materials, tunable redox-potential complexes, polymer hybrid luminescence materials, building blocks for multinuclear com- plexes, and catalysts for cross-coupling reactions [23-30]. The thio-substitution of amides with LR is an efficient and straightforward method, either the availability of amide substrates, LR, or the reaction condition [7,8,31-35]. With thio-substitution of amides as a model, we herein reported an efficient work-up procedure of applying LR by utilizing ethylene glycol to decompose the compound **A** (Figure 2). With a combination of some usual operations, such as, phase-cut, extraction and crystallization, the desired thioamide products were efficiently obtained in excellent yields.

Results and Discussion

Our initial exploration began with the thio-substitution of *N*-phenyl benzamide (**1a**) with LR in the reflux of toluene (Eqn 1). After completing the reaction, the splitting solutions were treated with different active additives under different temperature in order to find a reagent which can efficiently decompose the compound **A** [36]. MeOH or EtOH was initially tested. The experimental results showed that MeOH can't fully decompose the compound **A** between 40 ^{o}C to reflux, either stripping toluene or not. To our delight, EtOH worked well under refluxing temperature, a new spot with much higher polarity on TLC plate was observed. With a mixed solvent of ethyl acetate/petroleum ether (1:3) as the eluent, Rf of the compound **A** was around 0.5, while Rf of the new generated compound was around 0.05 either from MeOH or EtOH treatment. Later, the new generated compound by EtOH treatment was assigned as diethyl *p*-methoxyphenylthiophosphate (**C1**) via GC-MS and confirmed by GC-TOF [37]. The

polarity variation after MeOH or EtOH treatment indicated that the column separation can be greatly simplified in small-scale preparation. With this improvement, various thioamides were conveniently synthesized with the simplified column separation in good to excellent yields (Table 1).

Table 1: Synthesis of thioamides [a]



1 **2**

Entry	Substrate			Product (**2**)	Yield(%)[b]
	R^1	R^2	**1**		
1	Ph	H	**1a**	**2a**	85
2	4-MeC_6H_4	H	**1b**	**2b**	79
3	4-BrC_6H_4	H	**1c**	**2c**	79
4	4-*t*-BuC_6H_4	H	**1d**	**2d**	76
5	Ph	4-Me	**1e**	**2e**	82
6	Ph	4-Cl	**1f**	**2f**	92
7	Ph	4-Br	**1g**	**2g**	84
8	Ph	4-I	**1h**	**2h**	78
9	Ph	3-Cl	**1i**	**2i**	75
10	$PhCH_2$	H	**1j**	**2j**	70
11	*t*-Bu	H	**1k**	**2k**	76

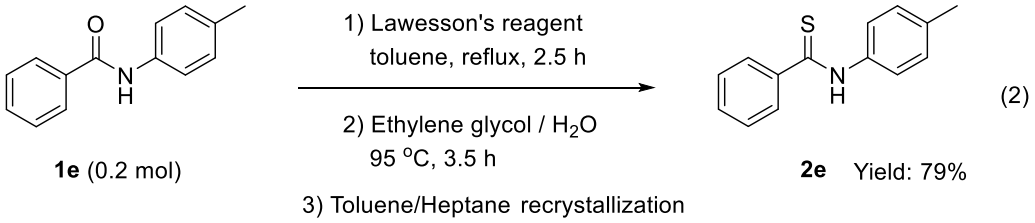
[a]Reaction conditions: **1** (1 mmol), LR (0.55 mmol), toluene (4 mL), reflux, 4 h, then added 2 mL of EtOH, reflux 2 h; [b]Isolated yields by column chromatography.

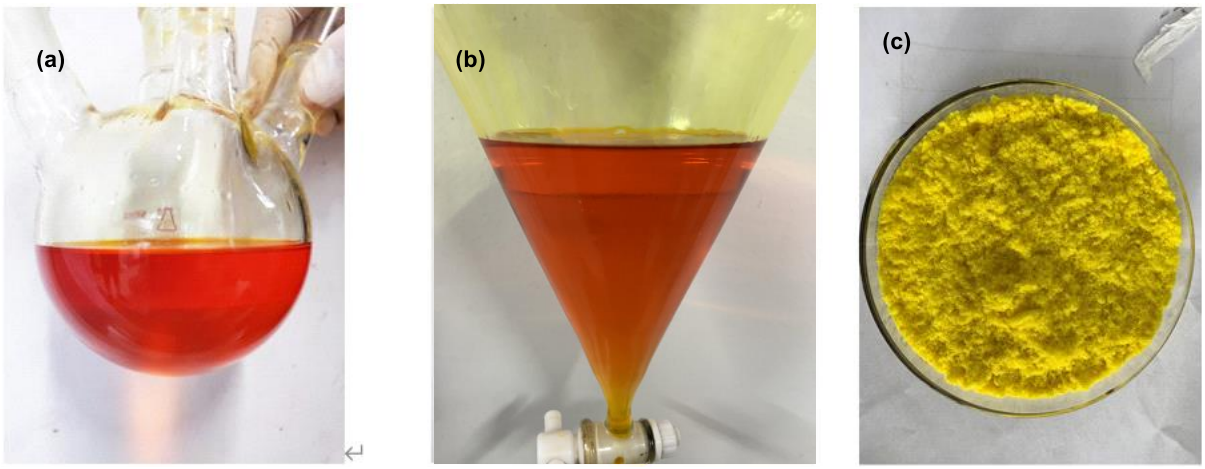
Although the small synthesis of thioamides was addressed, the column purification was extremely unfavorable during scaling-up preparations. After considerable efforts for the

reaction mixture with EtOH treatment, either solvent extraction/phase-cut with different polarity or even with aqueous workup, it was disappointedly found that the compound **C1** can be well distributed in most solvents and acted as a polar solvent component. Although less polar solvent, such as heptane, is able to reject part of the compound **C1**, it can't extract the desired thioamide. Water can partially extract the compound **C1** into aqueous phase, but the aqueous mixture pulled some products too. Moreover, aqueous workup after EtOH treatment is also problematic because of P-contained aqueous waste, and this two-step treatment procedure was not as good as the direct saturated aqueous $NaHCO_3$ procedure [14]. With the above observation, we reckoned that converting the compound **A** to a more polarized by-product can probably make a breakthrough. As a common knowledge, the more polarized alcohols over EtOH are those diols or polyols, while the simplest MeOH was previously ruled out. Ethylene glycol, a basic chemical and the simplest diol, can be slightly soluble in toluene and attracted our interests. Both its strong polarity and layering ability showed that ethylene glycol seemed to be an ideal choice.

After the completion of the thioamide reaction with **1e** (0.20 mol) and LR (0.102 mol) (Eqn 2) (Figure 3, d3&d4), excess ethylene glycol was added to decompose the compound **A**, following the previous EtOH treatment procedure. To our astonishment, the decomposition was much slower as expected by TLC monitoring (Figure 3, d5). It was assumed that the ring-opening could be interfered by water or accelerated by the *in-situ* generated thiophosphoric acid. Thus, 1.0 mL water was added into the mixture. We were pleased to find that the compound **A** can be smoothly decomposed by ethylene glycol at 95^{o}C in 3.5 h. With the decline of compound **A** in toluene layer, a new compound **C2** was observed (Figure 3, d7). It was also noticed that the pH of ethyl glycol layer came up to about 2-3. Thus, we reckoned that the assumed by-product **C2** was further decomposed to the thio-phosphoric acid which was well soluble in ethylene

glycol. After phase-cut around 50 ^{o}C (Figure 3, a), the ethylene glycol phase was back extracted with toluene (Figure 3, b). The cooled toluene layers were treated with activated carbon and filtered off. Toluene and the potential volatiles were stripped off, the residual was re-crystallized with mixed solvents of toluene and heptane to afford 36.0 g of the desired thioamide (**2e**) as a yellow crystalline (Figure 3, c).





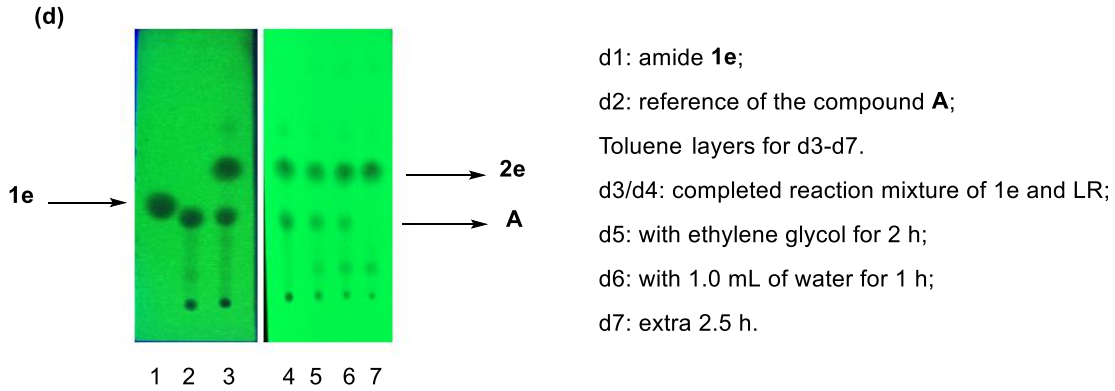
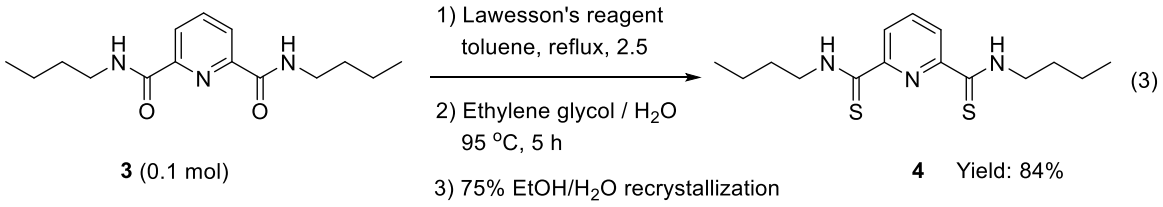


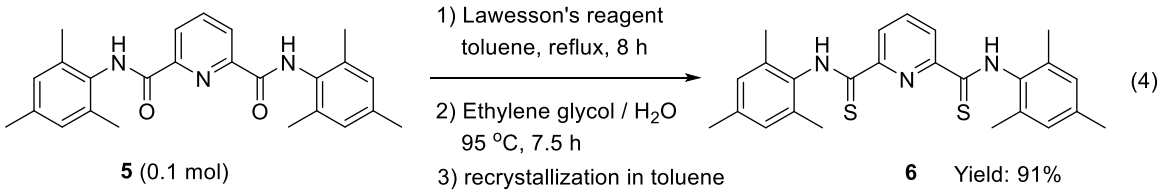
Figure 3. Phase-cut of reaction, recrystallization of product, and TLC monitoring the treatment of ethylene glycol. (a: Reaction complete (upper layer is toluene); b: Back extraction (upper layer is toluene); c: Product **2e** after re-crystallization; d: TLC monitoring of reaction mixture and reaction workup between amide **1e** and LR)

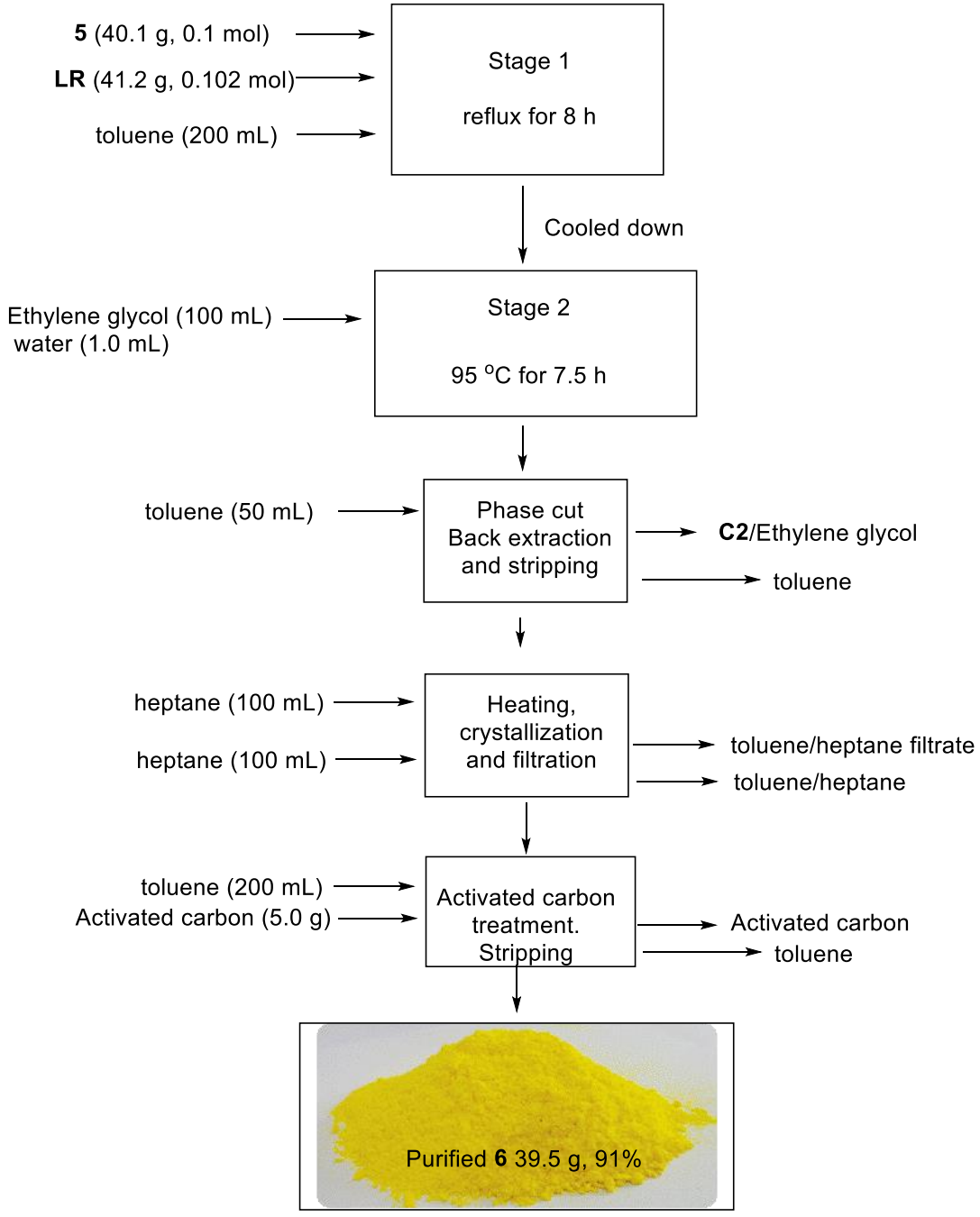
With the proof that ethylene glycol can efficiently decompose the compound **A** and simplify the work-up of reaction with LR, this newly developed method was extended to synthesize two pincer ligands, *N,N'*-di-*n*-butyl pyridine-2,6-dithiocarboxamide (**4**, Eqn 3) and *N,N'*-di(2,4,6-trimethylphenyl) pyridine-2,6-dithiocarboxamide (**6**, Eqn 4) [29,30,38,39]. With the slightly excess of LR, the diamide substrates **3** could be smoothly exchanged in reflux toluene for 2.5 h by TLC monitoring. Cooled down the reaction mixture and 100 mL of ethylene glycol with 1.0 mL of water was added and stirred at a 95 ^{o}C oil bath for 5 h. Cooled the mixture to about 50 ^{o}C, and transferred the mixture to a separation funnel to perform phase cut. The bottom ethylene glycol layer was back extracted with 50 mL of toluene. The combined toluene layers were treated with 3.1 g of activated carbon (10 w% of theoretical product) under room temperature. Filtered off, the resulted yellowish toluene solution was concentrated. The residual yellowish solid was recrystallized with 75% EtOH to afford 26.1 g (84%) of the desired product **4** as a yellowish crystalline.



Because the relative lower solubility and higher molecular weight of the diamide substrate **5**, the longer time in the reflux toluene with LR was essential for completion of the reaction according to TLC monitoring (Eqn 4). With the similar workup as the compound **4**, the resulted yellowish solid was recrystallized in toluene to afford the bright yellowish crystalline (91%). The overall preparation of pincer ligand **6** was demonstrated in Scheme 1.

Scheme 1. Modified process for synthesis of pincer ligand **6**





As can be seen from Scheme 1, it is clear that the modified process only discharged organic wastes (toluene, and toluene/heptane mixture), **C2**/ethylene glycol mixture, along with some waste carbons [40].

Conclusion

In conclusion, we have developed a highly efficient process for workup of thio-substitution with the Lawesson's reagent. In the newly developed procedure, ethylene glycol played a crucial role in the column-free and P-contained aqueous-free workup. With the preparation of thioamide as examples, ethylene glycol treatment allowed the work-up process involving phase-cut, back exaction, activated carbon treatment, and final re-crystallization in a proper solvent. Parts of the recovered solvent could be reused and the effluent was also reduced. The improved procedure was believed to be suitable for the scaling preparation with the application of the Lawesson's reagent.

Experimental

General

The NMR spectra were recorded on 400 MHz, 500 MHz and 600 MHz spectrometer in deuterium solvents using tetramethylsilane (TMS) as an internal standard. Chemical shifts were reported in parts per million (ppm, δ) downfield from TMS. The following abbreviations were used to explain the multiplicities: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad. The structure of compound **2a-2l** was confirmed by comparison with reference. Melting points were determined on BUCHI M-565 apparatus. All reagents were obtained from commercial suppliers and used without further purification. Reactions were monitored by thin-layer chromatography. Column chromatography was performed using silica gel (300−400 mesh). Amide **1a**-**1l** were prepared following the reported procedure [41].

Typical procedure for synthesizing thioamide 2 in 1 mmol scale

A mixture of amide **1** (1.0 mmol) and the Lawesson's reagent (0.60 mmol) was refluxed in toluene (4 mL). TLC monitored the reaction till the fully consumption of amide. To

the cooled reaction mixture, was added EtOH (2 mL, excess) and heated to reflux for 2 h. the volatile was removed under reduced pressure. Diluted the residual with ethyl acetate and performed the aqueous workup. The organic phase was dried over anhydrous $MgSO_4$. Solvent was removed under reduced pressure. The residual was purified with silica gel column chromatography with petroleum ether/ethyl acetate as eluent to afford the desired the thioamide **2**.

Procedure for the synthesis of *N,N'*-di-*n*-butyl pyridine-2,6-dicarboxamide (3)

With a similar procedure of synthesis of amide **1e**, the desired diamide **3** was obtained in 70% of yield as a white solid. M.p.: 155.2-158.0 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 8.33 (d, *J* = 7.8 Hz, 2H), 8.03-7.94 (m, 3H), 3.48-3.42 (m, 4H), 1.63-1.55 (m, 4H), 1.42-1.32 (m, 4H), 0.93-0.89 (m, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ = 163.7, 149.1, 139.1, 125.0, 39.5, 31.9, 20.3, 13.9.

Procedure for the synthesis of *N,N'*-di(2,4,6-trimethylphenyl) pyridine-2,6-dicarboxamide (5)

With a similar procedure of synthesis of amide **1e**, the desired diamide **5** was obtained in 92% of yield as a white solid. M.p.: 191.5-193.3 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 9.05 (s, 1H), 8.51 (d, *J* = 7.8 Hz, 2H), 8.15 (t, *J* = 7.8 Hz, 1H), 6.96 (s, 4H), 2.31 (s, 6H), 2.26 (s, 12 H). ^{13}C NMR (150 MHz, $CDCl_3$) δ = 161.8, 149.0, 139.5, 137.3, 135.1, 130.7, 129.2, 125.7, 77.4, 77.2, 77.0, 21.1, 18.5.

Procedure for the synthesis of *N*-*p*-methylphenyl thiobenzamide (2e) in 0.2 mole scale

To a 500 mL of three-necked flask, was added 42.3 g of *N*-*p*-methylphenyl benzamide (0.20 mol), 42.0 g of the Lawesson's reagent (0.104 mol) and 200 mL of toluene. The mixture was heated to reflux under nitrogen atmosphere. The reaction was completed in 3 h by TLC monitoring. Then, to the cooled mixture, was added 100 mL of ethylene glycol (excess), together with 1.0 mL of water, the resulted mixture was stirred at 95

^{o}C. TLC monitoring the toluene layer showed that by product **A** from Lawesson's reagent was unobserved after 3.5 h. The slightly cooled mixture was transferred to a separation funnel. The ethylene glycol layer was standing overnight. The precipitate of ethylene glycol layer was collected and combined to the toluene layer. Heated the toluene layer formed a clear soltion, then added 50 mL of heptane. The resulted solution was gradually cooled. The precipitation was observed at 65 ^{o}C and kept stirring to 20 ^{o}C. Filtered, the filter cake was washed with 50 mL of heptane. Dried to afford 36.0 g of the desired thioamide product **2e** (79%) as a bright yellow crystalline. M.p.: 128.5-130.1 °C; ^{1}H NMR (DMSO-d_6, 500 MHz): δ = 11.67 (s, 1H), 7.82 (d, *J* = 7.6 Hz, 2H), 7.69 (d, *J* = 7.6 Hz, 2H), 7.52 (t, *J* = 7.0 Hz, 1H), 7.46 (t, *J* = 7.6 Hz, 2H), 7.24 (d, *J* = 7.6 Hz, 2H), 2.32 (s, 3H). ^{13}C NMR (DMSO-d_6, 125 MHz): δ = 197.4, 142.7, 137.6, 135.7, 130.7, 129.0, 128.1, 127.5, 124.2, 20.8.

Procedure for synthesis of *N,N'*-di-*n*-butyl pyridine-2,6-dithiocarboxamide (4) in 0.1 mole scale

To a 500 mL of three-necked flask, was added 27.7 g of *N,N'*-di-*n*-butyl pyridine-2,6-dicarboxamide (**3**) (0.10 mol), 42.4 g of the Lawesson's reagent (0.0525 mol) and 150 mL of toluene. The mixture was heated to reflux under nitrogen atmosphere. The reaction was completed in 2.5 h by TLC monitoring. Then, to the cooled mixture, was added 100 mL of ethylene glycol (excess), together with 1.0 mL of water, the resulted mixture was stirred at 95 ^{o}C. TLC monitoring the toluene layer showed that by the product **A** from the Lawesson's reagent was unobserved after 5 h. The slightly cooled mixture was transferred to a separation funnel. The ethylene glycol layer and 50 mL of toluene were transferred backed to the flask, and stirring at 95 ^{o}C oil bath for 30 min. The combined toluene layers were treated with 3.1 g of activated carbon (10 w% of theoratical amount of dithioamide **4**). Filtered, the cake was washed with toluene. All solvent was stripped off under the reduced pressure. The residual yellowish solid was

recrystallized with 190 mL of 75% EtOH to afford 26.1 g of the dithioamide **4** (84%) as a yellowish crystalline. m.p.: 72.2-74.5 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 9.44 (s, 2H), 8.78 (d, *J* = 7.8 Hz, 2 H), 7.94 (t, *J* = 7.8 Hz, 1H), 3.91-3.86 (m, 4H), 1.84-1.77 (m, 4H), 1.55-1.48 (m, 4H), 1.02 (t, *J* = 7.4 Hz, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ = 190.4, 149.6, 138.4, 127.3, 45.9, 30.2, 20.5, 13.9.

Procedure for synthesis of *N,N'*-di(2,4,6-trimethylphenyl) pyridine-2,6-dithiocarboxamide (6) in 0.1 mole scale

To a 500 mL of three-necked flask, was added 40.1 g of *N,N'*-di(2,4,6-trimethylphenyl) pyridine-2,6-dicarboxamide (**5**) (0.10 mol), 41.2 g of the Lawesson's reagent (0.051 mol) and 200 mL of toluene. The mixture was heated to reflux under nitrogen atmosphere. TLC monitoring showed there still existed some amide-thioamide intermediate after 5 h. Another 3 h reflux showed the amide-thioamide was nearly unobserved by TLC monitoring. Then, to the cooled mixture, was added 100 mL of ethylene glycol (excess), together with 1.0 mL of water, the resulted mixture was stirred at 95 ^{o}C. TLC monitoring the toluene layer showed that by product **A** from Lawesson's reagent was unobserved after 7.5 h. The slightly cooled mixture was transferred to a separation funnel. The toluene layer was separated, and the ethylene glycol layer was stirring with 50 mL of toluene at 95 ^{o}C oil bath for 30 min. Part of solvent of the combined toluene layers was removed under the reduced pressure, the residual was heated to reflux and diluted with 100 mL of heptane. It was still a clear solution during reflux. Cooled to precipitate the crystalline solid, filtered and the wet cake was wahsed with 100 mL of heptane. The cake was treated with 200 mL of toluene and 5.0 g of activated carbon under 80 ^{o}C. Hot filtration and the filtrate was concentrated to afford 39.5 g of the desire dithioamide **6** (91%) as a bright yellow crystalline. m.p.: 190.5-193.6 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 10.71 (s, 2H), 8.99 (d, *J* = 7.8 Hz, 2H), 8.07

(t, J = 7.8 Hz, 1H), 6.99 (s, 4H), 2.33 (s, 6H), 2.23 (s, 12 H).^{13}C NMR (150 MHz, $CDCl_3$) δ = 190.8, 149.4, 138.7, 138.5, 135.1, 133.4, 129.4, 128.0, 21.3, 18.3.

Supporting Information

Supporting Information File 1:

The NMR data for compounds **2**-**6** and thio-phosphoric acid.

Acknowledgements

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