A one-step, atom economical synthesis of thieno[2,3-*d*]pyrimidin-4-amine derivatives via a four-component reaction

Taoda Shi,^[a] Christopher J. Zerio,^[a] Jared Sivinski,^[a] Andrew J. Ambrose,^[a] Kohlson T. Moore,^[a] Thomas Buckley,^[a] Lynn Kaneko,^[a] Mae Zhang,^[a] Donna D. Zhang,^[a] and Eli Chapman^{*[a]}

Dedication

Abstract: A Na₂HPO₄-catalyzed four-component reaction between a ketone, malononitrile, S₈ and formamide has been realized for the first time. This reaction provides a concise approach to thieno[2,3-*d*]pyrimidin-4-amines, previously requiring 5 steps. The utility of this reaction was validated by preparing a multi-targeted kinase inhibitor and an inhibitor of the NRF2 pathway with excellent atom- and step-economy.

Introduction

Thieno[2,3-*d*]pyrimidin-4-amines (TPAs) have been discovered to possess many important bioactivities, including inhibition of hepatitis C virus (HCV) replication^[1], inhibition of kinases,^[2] modulation of the NRF2 anti-oxidant response pathway,^[3] and inhibition of human farnesyl pyrophosphate synthase (hFPPS)^[4] (Figure 1). Notably, GDC-0941 is currently being evaluated as an anticancer agent in a phase II clinical trial,^[2a] while GDC-0980 and SNS-314 are both being tested as anticancer agents in phase I clinical trials^{[2b],[2c]}. In light of the biological and pharmaceutical value of TPAs, the organic synthesis community

has been interested in facile syntheses of these molecules. Currently, the reported synthesis of TPAs requires 5 steps starting with malononitrile and acetyltrimethylsilane (Scheme 1, top).^[4] To develop a general, straightforward method of synthesizing TPAs, we designed a one-step synthesis using a four-component reaction between ketones, malononitrile, S₈ and formamide based on the Gewald reaction (Scheme 1, bottom).^[5]

Scheme 1. The previously reported route of TPA synthesis and the presently reported route.

This design is expected to improve atom economy,^[6] step economy,^[7] structural diversity^[8] and ease of purification.

Results and Discussion

To test our proposed atom-economical thieno[2,3-*d*]pyrimidin-4-amine synthesis, we started with 1 equivalent of acetophenone (**1a**), 1.5 equivalents of malononitrile (**2**), 1.1 equivalents of S₈ (**3**) and 12 equivalents of formamide (**4**). We were surprised to find that by simply heating the reaction to 170°C, even in the absence of a catalyst, we could isolate the desired product **5a** in 34% yield (Table 1, Entry 1). Next, we evaluated a panel of potential catalysts including L-proline/Et₂NH, Na₂CO₃, Na₂HPO₄, K₂CO₃, and K₃PO₄ (Table 1, Entries 2-6), and found Na₂HPO₄ as the optimal catalyst giving **5a** in 85% yield (Table 1, Entry 4). Compared to other catalysts tested, Na₂HPO₄ is the only one that could function as both a base and an acid, which is a possible reason for its superior catalytic effects. Using Na₂HPO₄ as the catalyst, we next explored solvent effects (Table 1, Entries 7-10). Water, *tert*-butanol, *sec*-butanol, and isopropanol all caused a decrease in the yield of **5a**. This result indicated that the reactant formamide, **4**, is also an excellent solvent for the reaction. Next,

Figure 1. Bioactive molecules bearing a thieno[2,3-*d*]pyrimidin-4-amine core.

[a] Dr. T. Shi, C. J. Zerio, Dr. J. Sivinski, A. J. Ambrose, K. T. Moore, T. Buckley, L. Kaneko, M. Zhang, Prof. D. D. Zhang, and Prof. E. Chapman
Department of Pharmacology and Toxicology, College of Pharmacy, University of Arizona, 1703 East Mabel Street, P.O. Box 210207, Tucson, AZ 85721, United States
Email: chapman@pharmacy.arizona.edu
www.pharmacy.arizona.edu/directory/profile/eli-chapman-phd

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in order to optimize the efficiency of the reaction, we explored the minimum amount of **4** that could be used (Table 1, Entries 4, 11-13). With 4 eq. of **4**, the yield of **5a** was slightly lower, but when we investigated the substrate scope with 4 eq. of **4**, we found many of the substrates gave a poor yield in these conditions. When the amount of **4** dropped to 2 eq., the yield of **5a** decreased from 86% to 75%, and was further reduced to 62% if 1.5 eq. of **4** was used. Therefore, 12 eq. of **4** gives the highest yield and, importantly, the greatest substrate scope. We next explored time and temperature and found the yield increased to 91% and the reaction time could be decreased from 6 hours to 0.5 hour by increasing the temperature to 200°C (Table 1, Entry 14). Further, in the presence of 10 mol% triphenylphosphine as an additive, the yield of **5a** further increased to 96% (Table 1, Entry 15). But with Ph₃P and no Na₂HPO₄, the yield dropped to 55% (Table 1, Entry 16). The presence of Ph₃P possibly prevents the dimerization of **5a**.^[9] Overall, we chose 20 mol% Na₂HPO₄ as catalyst, 10 mol% Ph₃P, and 200°C for 0.5 h, as the standard conditions for a survey of the substrate scope.

Table 1. Optimization of conditions of a four-component reaction between acetophenone **1a**, malononitrile **2**, S₈ **3**, and formamide **4**.^[a]

Entry	Catalyst	Eq. of 4	Solvent	T/°C	% Yield ^[d]
1	None	12	-	170	34
2	L-proline/Et ₂ NH	12	-	170	61
3	Na ₂ CO ₃	12	-	170	35
4	Na ₂ HPO ₄	12	-	170	85
5	K ₂ CO ₃	12	-	170	52
6	K ₃ PO ₄	12	-	170	45
7	Na ₂ HPO ₄	12	H ₂ O	170	10
8	Na ₂ HPO ₄	12	<i>t</i> -BuOH	170	45
9	Na ₂ HPO ₄	12	<i>s</i> -BuOH	170	41
10	Na ₂ HPO ₄	12	<i>i</i> -PrOH	170	32
11	Na ₂ HPO ₄	4	-	170	84
12	Na ₂ HPO ₄	2	-	170	75
13	Na ₂ HPO ₄	1.5	-	170	62
14 ^[b]	Na ₂ HPO ₄	12	-	200	91

15 ^{[b], [c]}	Na ₂ HPO ₄	12	-	200	96
16 ^[b]	PPh ₃	12	-	200	55

[a] 1.0 eq. ketone (**1a**), 1.5 eq. malononitrile (**2**), 1.1 eq. S₈ (**3**), 12.0 eq. formamide (**4**), and 20 mol% catalyst were used for 6 hours. [b] 0.5 hour. [c] 10 mol% Ph₃P added. [d] Isolated yields.

After optimizing conditions, a set of aromatic moieties at the R¹ position were evaluated. Electron-withdrawing groups (EWG) gave an 81% average yield (Scheme 2, **5b** and **5c**). *Para*-halide substituents gave an 85% average yield (Scheme 2, **5d-5g**). *Meta*- and *ortho*-F substituents gave 85% and 82% yields, respectively. Electron-donating groups (EDG) offered desired products in 77% average yield (Scheme 2, **5j-5m**). The structure of **5l** was unambiguously assigned by X-ray crystallography (Figure 2; CCDC 1904050). Heterocyclic groups including furanyl and thiophenyl generated **5n** and **5o** in 62% and 65% yields, respectively.

Scheme 2. Substrate scope of a four-component reaction of ketones **1**, malononitrile **2**, S₈ **3**, and formamide **4**.

Figure 2. ORTEP diagram of **5l** with atomic labeling scheme. Thermal ellipsoids at a 50 % probability level are shown. CCDC 1904050.

Next, we set R¹ = Phenyl, and looked at the effect of changing the R² group. Both phenyl and methyl groups had excellent compatibility in the reaction, providing **5p** and **5q** with 97% and 91% yields, respectively. Finally, an alkyl group at both R¹ and R² was tested, producing **5r** in 87% yield. Generally, the reaction has broad ketone substrate scope.

Scalability of an organic reaction is one of the important features when it is used by medicinal chemists and chemical process scientists.^[10] We were able to scale-up the reaction to 50 mmol, furnishing 9 grams of product **5a** in 79% yield after a simple work-up and recrystallization (Scheme 3).

Scheme 3. Scalable four-component reaction of acetophenone **1a**, malononitrile **2**, S_8 **3** and formamide **4**.

The practicality of the reaction was demonstrated by the rapid synthesis of the NRF2 regulator AEM1 and the multi-target kinase inhibitor (MTKI; Scheme 4). AEM1 could be obtained via a conventional N-alkylation of **5c** with 74% overall yield in two steps from the readily available **1c**. This is the first disclosure of the synthesis of AEM1. MTKI was synthesized with a 49% overall yield in 2 steps from the inexpensive *para*-nitro starting material, **1i**. The quick access to intermediate **5i** via the four-component reaction of **1i**, **2**, **3**, and **4** makes this route an attractive alternative to the preparation the MTKI.

Scheme 4. Total synthesis of AEM2 and MTKI using a Na_2HPO_4 -catalyzed four-component reaction of ketones (**1c** or **1i**), malononitrile (**2**), S_8 (**3**) and formamide (**4**).

Finally, we propose a possible mechanism of the four-component reaction of ketones, malononitrile, S_8 and formamide (Scheme 5). The reaction is initiated by Na_2HPO_4 extracting the proton of **2**. Then the ketone is subjected to nucleophilic attack of activated **2**, leading to the formation of intermediate **A**. The product of a Knoevenagel reaction^[11], **B**, is generated through the elimination of **A** with the help of Na_2HPO_4 . Subsequently, Na_2HPO_4 activated **B** opens the S_8 ring through nucleophilic attack to yield intermediate **C**. Intermediate **C** undergoes intramolecular addition to the cyano group to form **D**. Then Na_2HPO_4 -promoted aromatization of **D** leads to the formation of Gewald reaction product **E**.^[12] Condensation of **E** and **4** produces intermediate **F** which undergoes intramolecular addition to the cyano group to give **G**. Finally, the Na_2HPO_4 -catalyzed tautomerization of **G** gives the product **5**.

Conclusion

Scheme 5. Proposed mechanism of the Na_2HPO_4 -catalyzed four-component reaction of ketone, malononitrile, S_8 and formamide

In conclusion, we have developed a four-component reaction between ketones, malononitrile, S_8 and formamide, to prepare TPAs in 62-97% yield. This reaction provides a facile synthesis of high value intermediates with excellent atom economy, short reaction times, high structural diversity, and facile purification. In addition, the reaction could be scaled up to a multi-gram scale that did not require chromatography for purification. To demonstrate the general applicability of our four-component reaction, the reaction was applied to prepare the NRF2 regulator AEM2 and MTKI in two steps with high overall yields. In the future, the invention of this reaction is expected to accelerate the synthesis of TPA-based molecules for both drug discovery efforts and process chemistry.

Experimental Section

General procedure for the preparation of compounds 5a-r. To a 10 mL reaction vial, was added 1.0 mmol (1.0 eq.) ketone (**1a-r**), 1.5 mmol (1.5 eq.) malononitrile (**2**), 1.1 mmol (1.1 eq.) S_8 (**3**), 12 mmol (12.0 eq.) formamide (**4**), 20 mol% Na_2HPO_4 , and 10 mol% PPh_3 . The mixture was heated to 200°C in a sand bath for 0.5 hour. **1** was confirmed to be consumed by TLC analysis. Then 2 mL of water was poured into the reaction mixture after it cooled to 22°C. The resulting mixture was extracted with ethyl acetate (EtOAc) 3 times (5 mL EtOAc per extraction). The organic layers were combined and washed with 15 mL water. Subsequently, the organic layer was dried with anhydrous magnesium sulfate. The crude product was obtained after removing the EtOAc with vacuum rotation. Further purification was performed with flash column chromatography to afford products **5a-r** as solids.

Acknowledgements

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Keywords: atom economy • multi-component reaction •
thieno[2,3-*d*]pyrimidin-4-amines • structural diversity

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*Taoda Shi, Christopher J. Zerio, Jared Sivinski, Andrew J. Ambrose, Kohlson Taylor Moore, Thomas Buckley, Lynn Kaneko, Mae Zhang, Donna D. Zhang, and Eli Chapman**

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Improving atom economy in the synthesis of Thieno[2,3-d]pyrimidin-4-amine derivatives via a four-component reaction with ketones, malononitrile, S₈ and formamide

Concise synthesis of thieno[2,3-d]pyrimidin-4-amines with improved atom economy, increased step economy, enhanced structural diversity and simplified purification has been realized.

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General information All reactions were carried out under air with magnetic stirring. All ^1H NMR, and ^{13}C NMR spectra were recorded using a Bruker-500 MHz or Bruker-400 MHz spectrometer in Chloroform-*d* or DMSO-*d*₆ unless otherwise noted. Chemical shifts are reported in parts per million as follows: chemical shift, multiplicity (s =singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br =broad).

General procedure for the preparation of compounds 5a-r. To a 10 mL vial, was added 1.0 eq. ketone (**1a-r**), 1.5 eq. malononitrile (**2**), 1.1 eq. S₈ (**3**), 12.0 eq. formamide (**4**), 20 mol% Na₂HPO₄, and 10 mol% PPh₃. The mixture was heated to 200°C for 0.5 hour. **1** was confirmed to be consumed by TLC analysis. Then 2 mL water was poured into the reaction mixture after it cooled to 22°C. The resulting mixture was extracted with ethyl acetate (EtOAc) 3 times (5 mL EtOAc per extraction). The organic layers were combined and washed with 15 mL water. Subsequently, the organic layer was dried with anhydrous magnesium sulfate. The crude product was obtained after removing the EtOAc with vacuum rotation. Further purification was performed with flash column chromatography to afford products **5a-r** as solids.

5a,^[1] 96%, brownish white solid δ_{H} (500 MHz, Chloroform-*d*) 8.48 (s, 1H), 7.68 – 7.40 (m, 5H), 7.19 (s, 1H), 5.41 (s, 2H). δ_{C} (125 MHz, Chloroform-*d*) 168.14, 157.52, 152.75, 135.82, 135.05, 129.10, 128.80, 121.25, 113.90; Melting Point: 195-198°C;

5b, 80%, yellowish white solid, δ_{H} (500 MHz, Chloroform-*d*) 8.47 (s, 1H), 7.44 – 7.37 (m, 2H), 7.29 (s, 1H), 7.14 (s, 1H), 7.08 – 7.02 (m, 2H), 3.91 (s, 3H). δ_{C} (125 MHz, Chloroform-

d)) 168.12, 165.11, 160.09, 157.68, 152.73, 134.79, 130.37, 127.88, 120.92, 114.47, 55.34. Melting Point: 230-233°C. MS: $C_{13}H_{14}N_3OS[M+H]^+$: 260.0779, found 258.0697.

5c, 82%, yellowish white solid, δ_H (500 MHz, Chloroform-*d*) 8.47 (s, 1H), 7.47 – 7.25 (m, 4H), 7.13 (s, 1H), 5.40 (s, 2H), 2.47 (s, 3H). δ_C (125 MHz, Chloroform-*d*) 168.07, 157.81, 153.18, 138.72, 135.03, 132.94, 129.72, 128.98, 120.74, 114.03, 21.32. Melting Point: 160-162°C. MS: $C_{13}H_{12}N_3S[M+H]^+$: 242.0674, found 242.0742.

5d, 86%, yellowish white solid, δ_H (500 MHz, Chloroform-*d*) 8.49 (s, 1H), 7.55 – 7.40 (m, 2H), 7.34 – 7.10 (m, 3H), 5.34 (s, 2H). δ_C (125 MHz, Chloroform-*d*) 168.18, 163.93, 161.95, 157.58, 153.05, 133.81, 131.79, 130.95, 130.88, 121.53, 116.24, 116.07. δ_F (375 MHz, Chloroform-*d*) -111.79. Melting Point: 208-209°C. MS: $C_{12}H_9FN_3S[M+H]^+$: 246.0423, found 246.0496.

5e, 85%, white solid, δ_H (500 MHz, Chloroform-*d*) 8.45 (s, 1H), 7.57 – 7.25 (m, 4H), 7.14 (s, 1H), 5.45 (s, 2H). δ_C (125 MHz, $CDCl_3$) 168.23, 158.01, 153.72, 134.93, 134.35,

133.65, 130.41, 129.24, 121.35, 113.68. Melting Point: 211-213°C. MS: $C_{12}H_9ClN_3S[M+H]^+$: 262.0127, found 262.0197.

5f

5f, 86%, yellowish white solid, δ_H (500 MHz, DMSO-*d*₆) 8.37 (s, 1H), 8.11 – 7.83 (m, 1H), 7.77 – 7.55 (m, 4H). δ_C (125 MHz, DMSO-*d*₆) 168.07, 158.72, 154.33, 140.54, 134.02, 133.15, 130.20, 122.95, 119.30. Melting Point: 209-210°C. MS: $C_{12}H_9BrN_3S[M+H]^+$: 305.9622, found 305.9694.

5g

5g, 84%, yellowish white solid, δ_H (500 MHz, Chloroform-*d*) 8.49 (s, 1H), 7.93 – 7.81 (m, 3H), 7.28 (s, 1H), 7.27 – 7.21 (m, 2H), 7.18 (s, 1H). δ_C (125 MHz, Chloroform-*d*) 157.60, 153.22, 138.21, 135.28, 134.30, 133.80, 130.84, 121.58, 113.58, 94.74. Melting Point: 194-195°C. MS: $C_{12}H_9IN_3S[M+H]^+$: 353.9484, found 353.9548.

5h

5h, 85%, yellowish white solid, δ_H (500 MHz, Chloroform-*d*) 8.49 (s, 1H), 7.57 – 7.45 (m, 2H), 7.32 – 7.24 (m, 2H), 7.24 – 7.17 (m, 2H), 5.40 (s, 2H). δ_C (125 MHz, Chloroform-*d*) 168.29, 157.50, 153.14, 137.89, 133.62, 130.77, 124.79, 121.86, 116.48, 116.30, 115.93,

115.76. δ_F (375 MHz, Chloroform-*d*) -110.81. Melting Point: 200-203°C. MS: $C_{12}H_9FN_3S[M+H]^+$: 246.0423, found 246.0491.

5i

5i, 82%, yellowish white solid, δ_H (500 MHz, Chloroform-*d*) 8.48 (s, 1H), 7.56 – 7.47 (m, 2H), 7.44 (td, $J=7.5, 1.8$, 1H), 7.36 – 7.22 (m, 2H), 5.26 (s, 2H). δ_C (125 MHz, Chloroform-*d*) 167.96, 160.79, 157.84, 153.45, 131.64, 130.98, 127.37, 124.73, 122.63, 116.61, 116.44, 114.42. δ_F (375 MHz, Chloroform-*d*) -113.38. Melting Point: 178-180°C. MS: $C_{12}H_9FN_3S[M+H]^+$: 246.0423, found 246.0486.

5j

5j, ^[2] 80%, yellowish white solid, δ_H (499 MHz, Chloroform-*d*) 8.50 (s, 1H), 7.86 – 7.73 (m, 2H), 7.70 – 7.58 (m, 2H), 7.26 (d, $J=27.5$, 1H), 5.36 (s, 2H). δ_C (125 MHz, $CDCl_3$) 168.49, 157.69, 153.56, 139.56, 133.47, 131.05, 130.79, 129.50, 126.01, 124.91, 122.74, 122.22, 113.47. δ_F (375 MHz, Chloroform-*d*) -62.67.

5k

5k, 81%, white solid, δ_H (500 MHz, DMSO-*d*₆) 8.37 (d, $J=2.4$, 1H), 8.09 – 7.86 (m, 2H), 7.73 – 7.57 (m, 3H). δ_C (125 MHz, DMSO) 168.07, 158.73, 154.33, 140.55, 134.01,

133.15, 130.21, 122.94, 119.28, 112.75, 111.27. Melting Point: 270-274°C. MS: $C_{13}H_9N_4S[M+H]^+$: 253.0470, found 253.0540.

5l

5l, 82%, transparent crystal, δ_H (500 MHz, Chloroform-*d*) 8.50 (s, 1H), 8.23 – 8.17 (m, 3H), 7.61 – 7.55 (m, 2H), 7.29 (s, 1H), 7.23 (s, 1H), 4.45 (q, $J=7.1$, 2H), 1.45 (t, $J=7.1$, 3H). δ_C (125 MHz, Chloroform-*d*) 168.58, 166.01, 157.81, 153.63, 140.38, 134.09, 130.81, 129.12, 121.89, 113.55, 61.29, 14.19. Melting Point: 175-179°C. MS: $C_{15}H_{14}N_3O_2S[M+H]^+$: 300.0728, found 300.0798.

5m

5m,^[2] 68%, yellow solide, δ_H (500 MHz, DMSO-*d*₆) 8.38 (s, 1H), 8.37 – 8.33 (m, 2H), 7.98 (dd, $J=13.5$, 1.7, 1H), 7.78 – 7.72 (m, 2H), 7.70 (s, 2H). δ_C (125 MHz, DMSO) 168.30, 158.84, 154.49, 147.63, 142.52, 133.69, 130.58, 124.41, 123.34, 112.67.

5n

5n, 62%, yellowish white solid, δ_H (499 MHz, Chloroform-*d*) 8.48 (s, 1H), 7.60 (dd, $J=1.9$, 0.8, 1H), 7.43 (s, 1H), 6.74 – 6.52 (m, 2H), 6.29 – 5.99 (m, 2H). δ_C (125 MHz, Chloroform-*d*) 168.54, 157.80, 153.31, 148.91, 142.58, 124.25, 122.00, 113.09, 112.24, 109.67. Melting Point: 170-174°C. MS: $C_{10}H_8N_3OS[M+H]^+$: 218.0310, found 218.0375.

5o

5o, 65%, yellowish white solid, δ_{H} (499 MHz, Chloroform-*d*) 8.48 (s, 1H), 7.57 – 7.36 (m, 1H), 7.30 (d, $J=12.9$, 2H), 7.19 (dd, $J=3.2$, 0.6, 1H), 5.58 (s, 2H). δ_{C} (125 MHz, Chloroform-*d*) 167.76, 157.79, 153.44, 136.34, 127.87, 127.76, 127.23, 126.73, 123.48, 113.96. Melting Point: 199-200°C. MS: $\text{C}_{10}\text{H}_8\text{N}_3\text{S}_2[\text{M}+\text{H}]^+$: 234.0081, found 234.0149.

5p

5p, 97%, white solid, δ_{H} (500 MHz, Chloroform-*d*) 8.45 (s, 1H), 7.51 – 7.46 (m, 3H), 7.43 – 7.38 (m, 2H), 7.29 (s, 2H), 7.28 – 7.23 (m, 5H). δ_{C} (125 MHz, Chloroform-*d*) 166.16, 157.01, 151.36, 137.72, 135.08, 132.71, 130.31, 129.75, 129.47, 129.39, 129.01, 128.58, 128.33, 116.03. Melting Point: 267-270°C. MS: $\text{C}_{18}\text{H}_{14}\text{N}_3\text{S}[\text{M}+\text{H}]^+$: 304.0830, found 304.0891.

5q

5q, 91%, white solid, δ_{H} (500 MHz, Chloroform-*d*) 8.40 (s, 1H), 7.66 – 7.43 (m, 3H), 7.45 – 7.32 (m, 2H), 5.12 (s, 2H), 2.38 (s, 3H). δ_{C} (125 MHz, Chloroform-*d*) 165.64, 156.47, 151.80, 134.89, 133.89, 130.22, 129.96, 129.14, 128.74, 115.36, 14.00. Melting Point: 189-191°C. MS: $\text{C}_{13}\text{H}_{14}\text{N}_3\text{S}[\text{M}+\text{H}]^+$: 244.0830, found 242.0736

5r

5r,^[3] 87%, white solid, δ_H (500 MHz, Chloroform-*d*) 8.36 (s, 1H), 5.52 (s, 2H), 3.02 – 2.73 (m, 4H), 2.02 – 1.78 (m, 4H). δ_C (125 MHz, Chloroform-*d*) 166.68, 157.31, 152.29, 134.19, 125.65, 116.04, 26.19, 25.46, 22.51.

Procedure of synthesis of MTKI: To a 10 mL vial, 0.5 mmol **5i** and 2 mL methanol was added, then 2.0 eq. zinc powder was added when **5i** was completely dissolved in methanol. To the mixture which is cooled to 0°C, 2 drops of con. HCl was added to start the reduction. The reaction was worked-up by adding saturated bicarbonate solution. The resulting mixture was extracted with 15 mL ethyl acetate for 3 times, and the combined organic layer was wash with brine, and then was dried with sodium sulfate. The vapor was removed by rotation in vacuum. The crude product was dissolved into dichloromethane, and 1.5 eq. triethylamine was added to the solution at 0°C, then 1.2 eq meta-methylphenyl isocyanate was added dropwise, then the reaction was allowed to warm up to room temperature. The reaction was quenched with saturated ammonium chloride when the starting material amine disappeared by monitoring with TLC. The mixture was extracted with 15 mL ethyl acetate for 3 times. Then the combined organic layer was washed with brine and dried with sodium sulfate. The solvent was evaporated under vacuum to offer crude product. Further purification was done by flash chromatography to provide MTKI as white solid.

MTKI,^[4] 49%, white solid, δ_H (500 MHz, DMSO-*d*₆) 9.01 (s, 1H), 8.79 (s, 1H), 8.39 (s, 1H), 7.68 – 7.58 (m, 1H), 7.48 (s, 2H), 7.43 – 7.37 (m, 2H), 7.32 (d, *J*=1.9, 1H), 7.29 – 7.23 (m, 2H), 7.18 (t, *J*=7.8, 1H), 6.81 (ddt, *J*=7.5, 1.8, 0.9, 2H), 2.29 (s, 3H). δ_C (125 MHz, DMSO-*d*₆) 167.03, 153.41, 153.02, 140.64, 140.03, 138.48, 135.35, 129.94, 129.15, 129.00, 123.17, 121.13, 119.22, 118.69, 115.89, 113.61, 21.56.

Procedure of synthesis of AEM2: To a 20 mL three-neck round bottle, 0.5 mmol **5c** and 6 mL THF was added, then the solution was cooled down to 0°C. 1.2 eq. sodium hydride was added dropwise under Ar protection. The resulting mixture was stirred for 30 min, then 2 mL solution of halide was added to the reaction mixture dropwise. The reaction was allowed to warm up to room temperature and stirred and the **5c** was completely consumed based TLC observation. Saturated ammonium chloride was added to quench the reaction at 0°C. The mixture was extracted with 15 mL ethyl acetate for 3 times. Then the combined organic layer was washed with brine and dried with sodium sulfate. The solvent was evaporated under vacuum to offer crude product. Further purification was done by flash chromatography to provide AEM2 as yellowish white solid.

AEM2,^[5] 74%, yellowish white solid, ¹H NMR (500 MHz, Chloroform-*d*) δ = 8.55 (s, 1H), 7.43 – 7.35 (m, 1H), 7.16 – 7.06 (m, 3H), 6.73 (d, *J*=7.8, 2H), 6.66 – 6.58 (m, 2H), 5.97 (s, 2H), 5.08 (t, *J*=5.5, 2H), 4.53 (d, *J*=5.2, 2H). ¹³C NMR (125 MHz, Chloroform-*d*) δ = 166.85, 163.91, 161.93, 157.13, 154.08, 147.92, 147.06, 133.46, 131.93, 131.66, 130.99, 120.75, 116.06, 115.89, 114.09, 108.27, 107.99, 101.11, 44.56.

Spectra of compound 5a-r, MTKI, and AEM2

Figure S1. ^1H NMR of 5a

Figure S2. ^{13}C NMR of **5a**

Figure S3. ^1H NMR of **5b**

Figure S4. ^{13}C NMR of **5b**

Figure S5. ¹H NMR of 5c

Figure S6. ^{13}C NMR of **5c**

Figure S8. ^{13}C NMR of **5d**

Figure S9. ^{19}F NMR of **5d**

Figure S10. ¹H NMR of **5e**

Figure S11. ^{13}C NMR of **5e**

Figure S12. ^1H NMR of 5f

Figure S13. ¹³C NMR of **5f**

Figure S14. ^1H NMR of **5g**

Figure S15. ^{13}C NMR of **5g**

Figure S16. ¹H NMR of **5h**

Figure S17. ^{13}C NMR of **5h**

5h

Figure S18. ^{19}F NMR of 5h

Figure S19. ¹H NMR of **5i**

Figure S20. ^{13}C NMR of **5i**

Figure S21. ^{19}F NMR of **5i**

Figure S22. ¹H NMR of **5j**

Figure S23. ¹³C NMR of **5j**

Figure S24. ¹⁹F NMR of **5j**

Figure S25. ¹H NMR of **5k**

Figure S26. ^{13}C NMR of **5k**

Figure S27. ^1H NMR of **5I**

Figure S28. ^{13}C NMR of 5I

Figure S29. ^1H NMR of **5m**

Figure S30. ^{13}C NMR of 5m

Figure S31. ^1H NMR of 5n

Figure S32. ^{13}C NMR of **5n**

Figure S33. ^1H NMR of **5o**

Figure S34. ^{13}C NMR of **5o**

Figure S35. ^1H NMR of **5p**

Figure S36. ^{13}C NMR of **5p**

Figure S37. ¹H NMR of 5q

Figure S38. ^{13}C NMR of **5q**

Figure S39. ^1H NMR of **5r**

Figure S40. ^{13}C NMR of **5r**

Figure S41. ^1H NMR of MTKI

Figure S42. ^{13}C NMR of MTKI

Figure S43. ¹H NMR of AEM2

Figure S44. ¹³C NMR of AEM2

Crystallography Information

Molecular structure. The displacement ellipsoids are at 50% probability level; the hydrogen atoms at carbons are at predicted positions. There are 2 molecules in an asymmetric unit cell (see below). One of them (molecule A) is shown here with the atom numbering.

Crystal structure determination of [mo_pCO2EtTPA_0m]

Crystal Data for $C_{15}H_{13}N_3O_2S$ ($M = 299.34$ g/mol): triclinic, space group P-1 (no. 2), $a = 10.526(3)$ Å, $b = 10.952(3)$ Å, $c = 12.744(4)$ Å, $\alpha = 72.898(10)^\circ$, $\beta = 88.091(10)^\circ$, $\gamma = 81.951(11)^\circ$, $V = 1390.3(7)$ Å³, $Z = 4$, $T = 100$ K, $\mu(\text{MoK}\alpha) = 0.241$ mm⁻¹, $D_{\text{calc}} = 1.430$ g/cm³, 35277 reflections measured ($3.344^\circ \leq 2\theta \leq 51.502^\circ$), 5297 unique ($R_{\text{int}} = 0.0298$, $R_{\text{sigma}} = 0.0198$) which were used in all calculations. The final R_1 was 0.0317 ($I > 2\sigma(I)$) and wR_2 was 0.1197 (all data).

Datablock: I

The following ALERTS were generated:

PLAT720 ALERT 4 G Number of Unusual/Non-Standard Labels 29 Note

- S55

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