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Development of a Scalable Synthesis of a Vascular Endothelial Growth Factor Receptor-2 Kinase Inhibitor: Efficient Construction of a 6-Etherified [1,2,4]Triazolo[1,5-*a*]pyridine-2-amine Core

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ABSTRACT: A practical and scalable synthesis of the vascular endothelial growth factor receptor-2 (VEGFR-2) kinase inhibitor **1** has been developed. The key features of the process development include facile preparation of the key raw material 3-amino-4-fluorophenol, chemoselective nucleophilic aromatic substitution of 5-chloro-2-nitropyridine with phenol, a safe one-pot synthesis of a substituted urea using an isothiocyanate generated in situ from inexpensive materials, and improvement of the yield of acylation in the end game. The optimized six-step synthesis afforded **1**·H_2O in 54% overall yield, twice as much as the yield of the original synthesis, without chromatographic purification. In addition, a robust recrystallization procedure to afford the desired crystal form of **1** was also developed.

INTRODUCTION

Vascular endothelial growth factor (VEGF) is known to promote angiogenesis through binding to VEGF receptors 1 (VEGFR-1) and 2 (VEGFR-2) expressed on vascular endothelial cells, and inhibition of the VEGF/VEGFR signal transduction system is thought to suppress angiogenesis and tumor growth.[1] Compound **1**, which shows potent and selective inhibition of VEGFR-2 kinase and platelet-derived growth factor receptor kinases, has promising antitumor activity and has been developed as a candidate for an orally active antitumor drug.[2]

The medicinal chemistry synthesis of **1** was carried out in six linear steps in 25% overall yield (Scheme 1).[2b] The synthesis was initiated with acylation of 3-amino-4-fluorophenol **2** with pyrazole carbonyl chloride **3** to give phenol **4**. Nucleophilic aromatic substitution (S_NAr reaction) of 5-bromo-2-nitropyridine **5a** with **4** afforded a mixture of desired 2-nitropyridine **6** and undesired 5-bromopyridine **7a**. After column chromatography separation, **6** was hydrogenated to give 2-aminopyridine **8**, which was reacted with isothiocyanate **9** to furnish thiourea **10**. Treatment of **10** with excess amount (10 equiv) of hydroxylamine hydrochloride in the presence of 6 equiv of diisopropyl ethylamine (DIPEA) led to cyclization and afforded **11**.[3] Finally, acylation of **11** with cyclopropanecarbonyl chloride **12** completed the synthesis of the target product **1**.

Although this synthesis allowed for the initial preparation of **1** on a small scale, it suffered from several drawbacks that would prohibit further scale-up: (1) a linear route with low overall yield, (2) the use of commercially unavailable **2**,[4] (3) low selectivity in S_NAr reaction of **5a** with **4** (approximately **6**:**7a** = 60:40) and the necessity for column chromatography separation of **6**, and (4) the use of expensive and lachrymatory isothiocyanate **9**. Therefore, in order to support early preclinical studies, a practical and scalable synthesis that would allow for the multihundred gram to multikilogram synthesis of **1** was required.

RESULTS AND DISCUSSION

At this stage, the medicinal chemistry route was expected to be sufficiently reliable for the bulk supply on the condition that several key issues could be overcome. We initially focused on the development of the scalable synthesis of the commercially unavailable **2** using readily available raw materials. For the synthesis of **6**, two routes from **2** to **6** were investigated, including a new route in which **2** was first reacted with 5-halo-2-nitropyridine **5a**/**5b**, followed by acylation with **3** (Scheme 2, route A). In each route, optimization of the S_NAr reaction of **5a**/**5b** was conducted intensively to increase the ratio of the desired 5-etherified product and avoid the column chromatography separation. Based on the results of optimization, the better route was finally selected for scale-up. For the synthesis of **10**, *in situ* generation of **9** from inexpensive and readily available materials and its use for the one-pot reaction with **8** was examined. It was expected that this one-pot process would enable us to avoid the use of the expensive and lachrymatory compound **9** as a raw material. The improvement of the moderate yield for the acylation of **11** with **12** in the end game was also carried out by optimization of the reaction conditions. In addition, each step was fully refined for scale-up to achieve an efficient and scalable process to furnish **1** in good yield with good purity.

Preparation of 2. Out of the known syntheses of **2**,[5−7] two synthetic approaches that seemed to be promising from the viewpoint of a large-scale production were selected for detailed investigation. The first approach is based on the hydrolysis of diazonium salt **17** (Scheme 3).[6] Treatment of **16**, which was easily synthesized from commercially available **14**, with $NaNO_2$ in dilute aqueous H_2SO_4 gave diazonium salt **17**. Subsequent hydrolysis of **17** in refluxing dilute aqueous H_2SO_4 afforded **2** in 68% yield (HPLC assay yield). While it successfully provided **2** on a lab scale, this route was found to be unsuitable for scale-up

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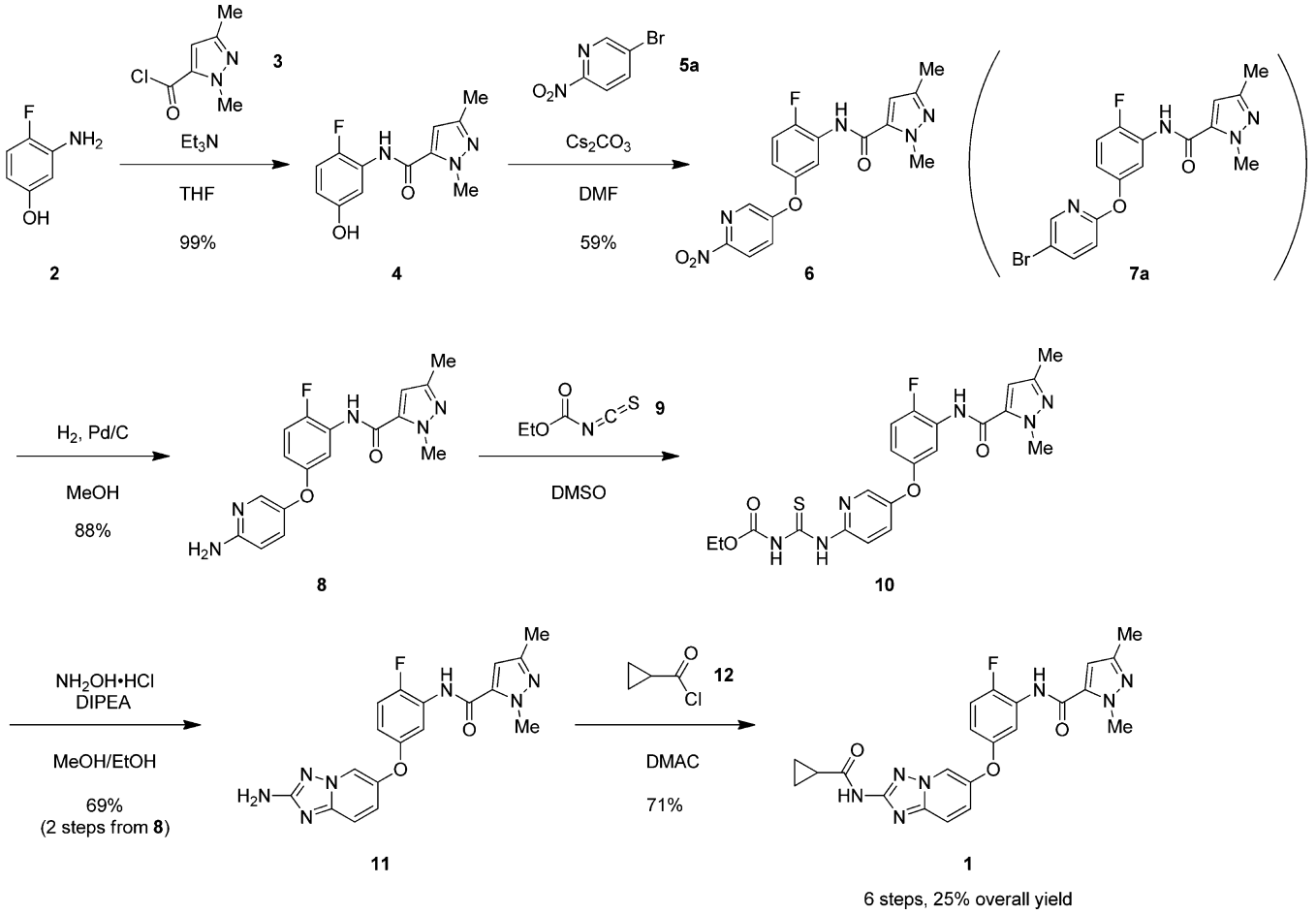
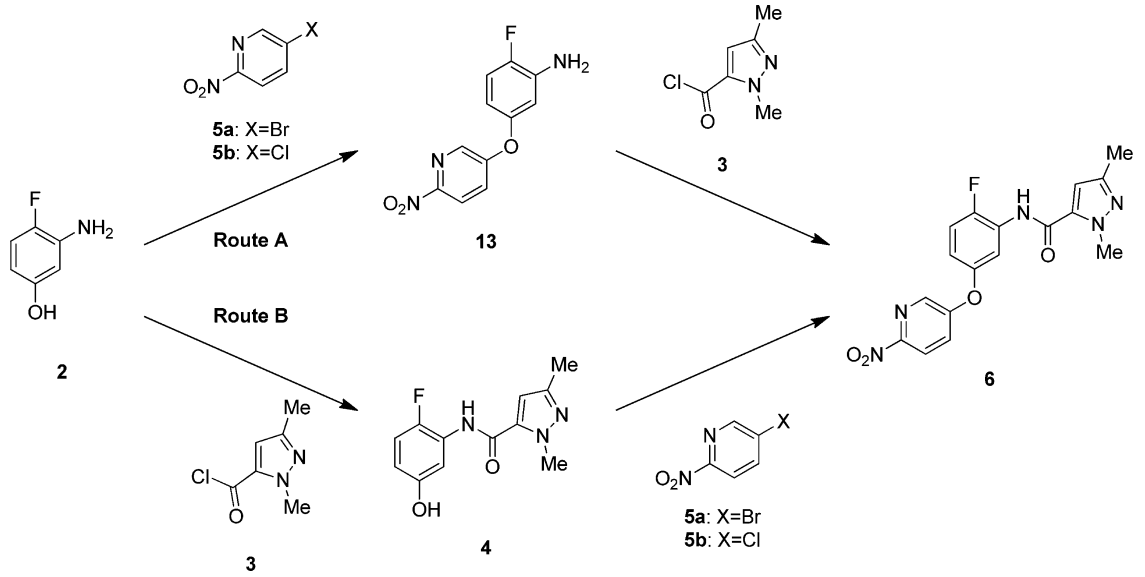
Scheme 1. Medicinal chemistry synthesis of 1



Scheme 2. Route selection for the scale-up synthesis of 6



due to the generation of a large amount of insoluble tarry product during the hydrolysis of **17**.

The second approach is based on the hydrogenation of **20** or **21** (Scheme 4).[7,8] Treatment of commercially available phenol **18** with methyl chloroformate in the presence of Na_2CO_3 in H_2O gave **19** in 95% yield. It was found that the drying of **19** should be conducted carefully, since **19** sublimed when dried under reduced pressure at high temperature (>40 °C). After testing several drying conditions, the reduced pressure and the drying temperature were set at −0.1 MPa and 30 °C, respectively. Subsequent nitration of **19** with nitric acid in concentrated sulfuric acid proceeded quite regioselectively to

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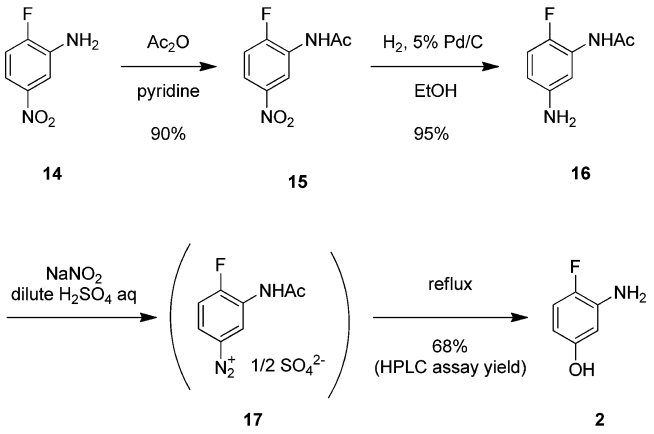
Scheme 3. Synthesis of 2 from 14

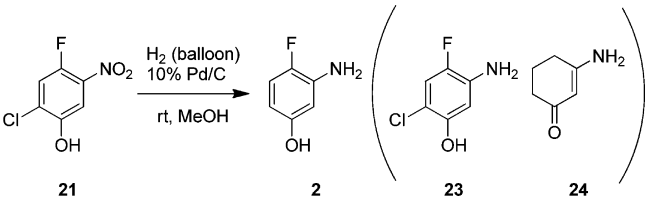


give **20** in 93% yield,[9] which was hydrolyzed with 2 M NaOH in MeOH to afford **21** in 93% yield (Scheme 4, route C).

In preliminary experiments, hydrogenation of **21** gave **2** in lower yield than expected (60−70% yield), which is in accordance with the unsatisfactory results in the literature (H_2 (50 psi), 10% Pd/C, 12 h, 70% yield;[7b] H_2 (balloon), $Pd(OH)_2/C$, 8 h, 67% yield[7c]). Since **21** was almost completely consumed in this hydrogenation, generation of unidentified impurities was suspected to cause the yield decrease. Thus, in order to find the reason for the yield decrease and a way to increase the yield, hydrogenation of **21** was closely investigated, including addition of additives and change of the amount of Pd catalyst (Table 1).

When the hydrogenation was conducted using 10% Pd/C (3 mol % of Pd loading) at room temperature for 4 h under atmospheric H_2 pressure, **2** was obtained in only moderate yield (64% HPLC assay yield, entry 1). Under this reaction condition, reduction of the nitro group was so fast that **21** was almost completely consumed within 1 h, while the dechlorination of **23** was relatively slow, resulting in 4% of remaining **23** even after 4 h. Subsequently, several kinds of acids and bases were screened as an additive (entries 2−7). Interestingly, addition of 2.0 equiv of concentrated hydrochloric acid (cHCl) strongly affected the dechlorination of **23**, leading to quite a low yield of **2** (8%, entry 3). This result implies that hydrochloric acid generated *in situ* by dechlorination of **23** prevented further dechlorination of **23**. Therefore, it was expected that addition of bases would promote dechlorination of **23** by neutralizing the hydrochloric acid generated in the reaction mixture. In fact, addition of sodium acetate (NaOAc) decreased the amount of **23** (0.1%) and

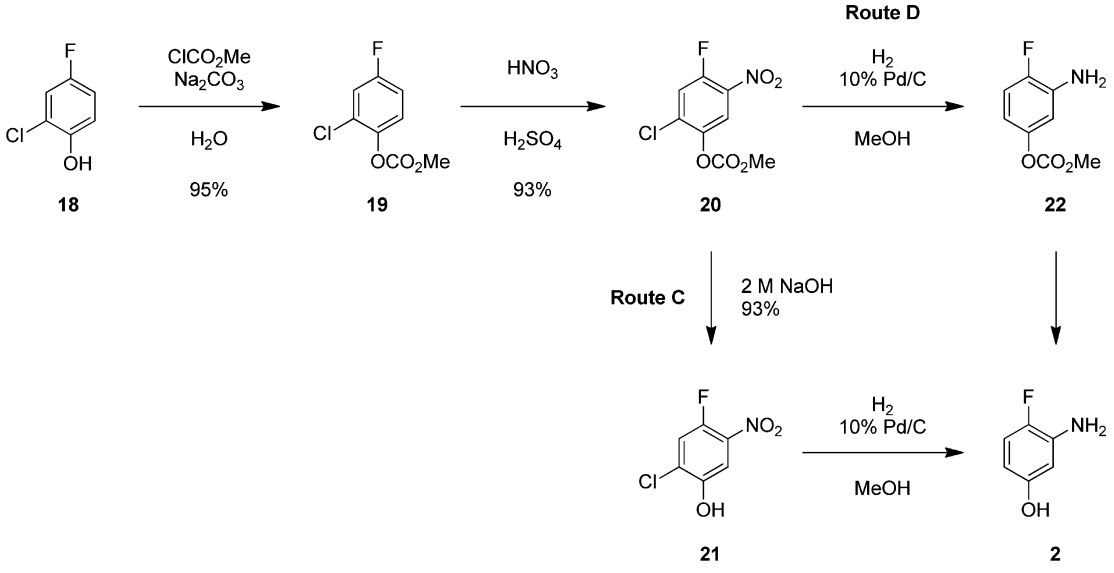
Table 1. Optimization of hydrogenation of 21



				HPLC assay yield (%)			
entry	Pd loading (mol %)	additive (equiv)	time (h)	**2**	**23**	**24**	**21**
1	3	–	4	64	4	2	0
2	3	AcOH (2.0)	4	78	6	2	0
3	3	cHCl (2.0)	4	8	80	0.2	0
4	3	NaOAc (2.0)	3	87	0.1	10	0
5	3	Na_2CO_3 (2.0)	3	37	0	58	0
6	3	8 M NaOH (2.0)	3	8	7	37	0
7	3	MeONa (2.0)	3	67	0	29	0
8	3	NaOAc (1.1)	3	85	0.5	5	0
9	5	NaOAc (1.1)	3	77	0.7	4	0
10	10	NaOAc (1.1)	3	53	1	3	0
11	2	NaOAc (1.1)	3	88 (86)[a]	0.4	4	0

[a]Isolated yield after column chromatography.

Scheme 4. Synthesis of 2 from 18



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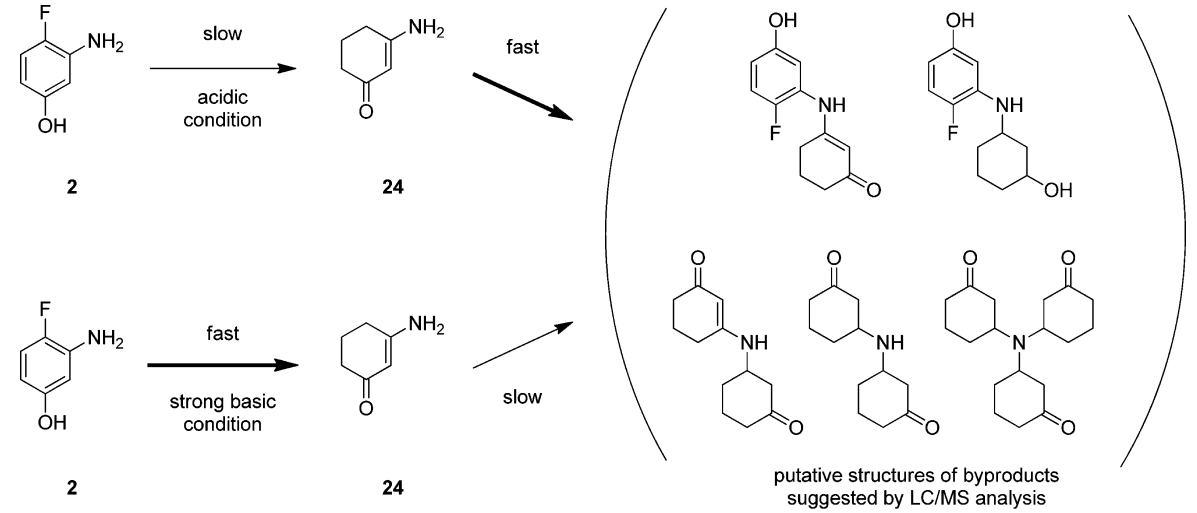
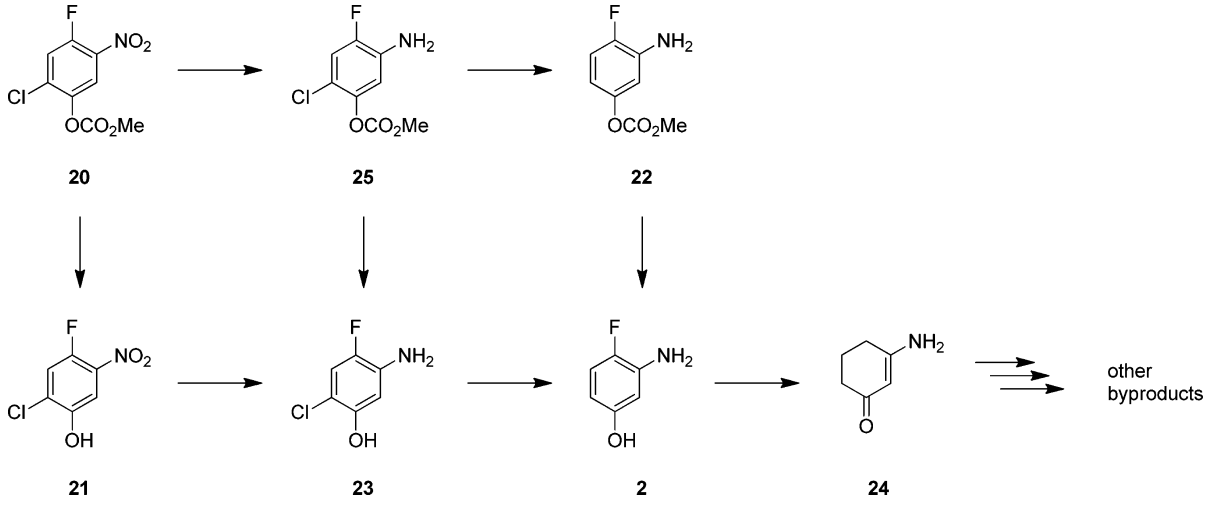
Scheme 5. Fate of over-reduced product 24



Scheme 6. Intermediates of hydrogenation of 20 in the presence of bases



afforded **2** in 87% yield (entry 4). On the other hand, although addition of Na_2CO_3 and NaOMe was also effective in decreasing the amount of **23**, these stronger bases accelerated the over-reduction of **2**, giving a large amount of over-reduced product **24** (entries 5−7).[10,11] In the course of the screening of additives, it was also found that the amount of catalyst was an important factor. When Pd loading was increased from 3 mol % to 5 mol % and 10 mol %, the yields decreased from 85% to 77% and 53%, respectively (entries 9 and 10). After several experiments, the best catalyst loading was found to be 2 mol %. When the hydrogenation was conducted in the presence of 2 mol % of Pd catalyst and 1.1 equiv of NaOAc for 3 h, the yield amounted to 88% (entry 11).

The low to moderate yield of this hydrogenation without NaOAc could be ascribed to the generation of **24** and its reaction with **2** (Scheme 5). LC/MS analysis of the reaction mixture suggested the generation of several kinds of byproducts that would be derived from **2** and **24** via enamine formation.[12] In acidic condition, it was assumed that **24** would react with **2** to give the corresponding enamine, which was further hydrogenated to give other byproducts, resulting in the moderate yield of **2**. On the other hand, in strong basic condition, enamine formation of **2** with **24** seemed to be slow, while the over-reduction of **2** to **24** was fast. This would lead to the observation of a large amount of **24** in strong basic condition. The fact that an increased amount of Pd loading led to the decreased yield of **2** also could be explained by the accelerated over-reduction of **2** to **24**. When the hydrogenation of **21** was conducted in the absence of bases, the reaction mixture became gradually acidic (pH 3−4) due to the hydrochloric acid generated by dechlorination of **23**. Probably, addition of an appropriate amount of weak bases such as NaOAc would be effective in preventing the reaction mixture from becoming too acidic and maintaining the pH in the appropriate range without promoting the over-reduction of **2** to **24**, which would lead to the comparatively high yield of **2**.

Since this type of over-reduction was thought to be characteristic for the compounds having a 3-aminophenol moiety, hydrogenation of **20** was not expected to suffer from it (Scheme 4, route D). Under the neutral condition (H_2 (balloon), 10% Pd/C (5 mol % of Pd), 25 °C, 5 h), hydrogenation of **20** resulted in low conversion to **22** due to the slow dechlorination of **25** (**22**: 29 area %, **25**: 68 area %, Scheme 6). On the other hand, under the weakly basic condition similar to the optimized hydrogenation condition of **21** (H_2 (balloon), 10% Pd/C (5 mol % of Pd), NaOAc 1.0

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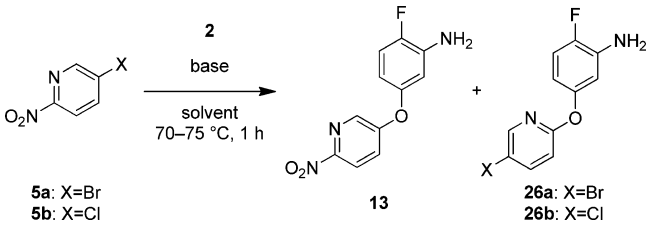
equiv, 25 °C, 5 h), relatively high conversion to **22** was observed (**22**: 88 area %, **25**: 2 area %). However, the addition of NaOAc caused slow deprotection of the methoxycarbonyl group of **20**, **25**, and **22** during the reaction (Scheme 6).[13] Due to this slow deprotection, many kinds of intermediates and byproducts were observed in the reaction mixture, which made it difficult to monitor and control the amount of each compound. This situation was not suitable for scale-up, because tight process parameters are usually required for quality control in a large-scale production. These results finally led us to reject route D and select route C for the scale-up synthesis of **2**.

The optimal hydrogenation condition described above (Table 1, entry 11) was successfully scaled up to kilogram-scale. The hydrogenation of **21** (5.4 kg) was conducted in the presence of 10% Pd/C (2 mol % of Pd loading) and 1.1 equiv of NaOAc for 4 h at 15−25 °C under 0.1 MPa H_2 pressure. After the catalyst was filtered off, solvent was concentrated under vacuum and switched to EtOAc. Following washing with brine, **2** was obtained in 80% yield by crystallization from EtOAc/*n*-heptane (1:4).

Preparation of 6. For preparation of **6**, the S_NAr reaction of commercially available 5-halo-2-nitropyridine **5a**/**5b** with **2** was first studied (route A, Table 2). In basic condition, the amino group of **2** did not react with **5a**/**5b**, and only etherified product was obtained (**13** or **26**). Screening of solvents and bases revealed that Cs_2CO_3, K_2CO_3, and K_3PO_4 gave almost comparable selectivity in DMSO (entries 3−5). Due to a relatively small amount of byproducts, K_3PO_4 was selected for further investigation. Interestingly, aqueous DMSO (2:1 DMSO/H_2O) was found to give better selectivity than DMSO (75:25, entry 8), albeit with decreased reaction rate. It was also found that the use of **5b** as a substrate gave better selectivity than the use of **5a**. The best result was obtained when **5b** was reacted with 1.2 equiv of **2** in the presence of 1.9 equiv of K_3PO_4 in DMSO/H_2O (1:1) at 75−80 °C for 9 h (entry 9). The reaction gave an 86:14 mixture of **13** and **26b**, and subsequent crystallization from diisopropyl ether provided **13** containing only 1% of **26b** in 76% yield.

Table 2. Optimization of S_NAr reaction of 2 with 5a/5b (route A)[a]

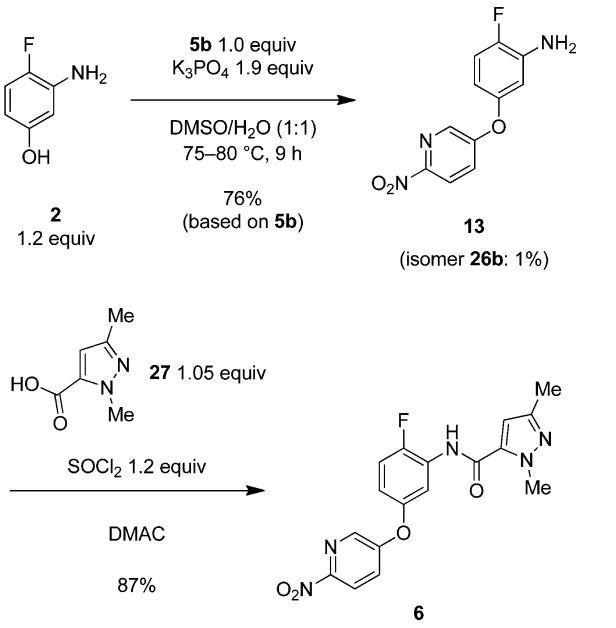


entry	substrate	base	solvent	ratio[b] **13**:**26**
1	**5a**	Cs_2CO_3	THF	21:79
2	**5a**	Cs_2CO_3	DMAC[c]	59:41
3	**5a**	Cs_2CO_3	DMSO	62:38
4	**5a**	K_2CO_3	DMSO	65:35
5	**5a**	K_3PO_4	DMSO	62:38
6	**5a**	*t*-BuONa	DMSO	48:52
7	**5a**	8 M NaOH	DMSO	59:41
8[d]	**5a**	K_3PO_4	DMSO/H_2O (2:1)	75:25
9[e]	**5b**	K_3PO_4	DMSO/H_2O (1:1)	86:14 (74)[f]

[a]The reaction was carried out using 1.0 equiv of **5a**/**5b**, 1.2 equiv of **2** and 1.25 equiv of bases at 70−75 °C for 1 h. [b]Molar ratio determined by HPLC analysis of the reaction mixture. [c]DMAC = *N*,*N*-dimethylacetamide. [d]The reaction was carried out for 10 h. [e]The reaction was carried out using 1.9 equiv of K_3PO_4 at 75−80 °C for 9 h. [f]Isolated yield of **13**.

For acylation of **13**, pyrazole carbonyl chloride **3** was prepared from inexpensive and easily available pyrazole carboxylic acid **27** using thionyl chloride in DMAC.[14] Treatment of **13** with **3** prepared *in situ* from **27** followed by crystallization from EtOAc/*n*-heptane (1:3) gave **6** in 87% yield without detectable amount of positional isomer (Scheme 7).

Scheme 7. Optimized results of route A



Although this route successfully provided **6** in good yield with good purity on a small scale, generation of a large amount of tarry product during the reaction of **2** with **5b**, which was probably due to the instability of aniline **2** under the reaction condition described above, remained as a concern for scale-up.

In route B, **2** was first acylated with **3** prepared *in situ* from **27** before S_NAr reaction with **5a**/**5b**, providing **4** in 93% yield.[14] The reaction of **4** with **5b** showed better selectivity than that with **5a** (Table 3). Among the screened bases and solvents, the combination of K_2CO_3 and DMSO gave the best result (80:20, entry 12). Also, the use of aqueous DMSO (5:1 DMSO/H_2O) as a solvent slightly increased the selectivity (82:18, entry 13). When **4** was reacted with 1.05 equiv of **5b** in the presence of 1.1 equiv of K_2CO_3 in DMSO/H_2O (5:1) at 75−85 °C for 6 h, an 82:18 mixture of **6** and **7b** was obtained with >97% conversion. Extraction with EtOAc followed by crystallization from EtOAc/*n*-heptane (1:3) gave **6** containing 2% of **7b** in 79% yield (Scheme 8). It was found that further purification of **6** was not necessary because carryover impurities including **7b** were effectively removed (<0.1%) at the subsequent step (hydrogenation of **6**).[15]

While the overall yields of route A and route B were almost comparable, route B was selected for the scale-up synthesis of **6**, because no scale-up issue was found in route B. The scale-up synthesis of **6** from **2** via **4** (route B) successfully afforded >1 kg of **6** (**7b**: 1.6 area %) in 73% yield over two steps.

Preparation of 10 Using *in Situ*-Generated 9. Hydrogenation of **6** in MeOH using 10% Pd/C (2 mol % of Pd loading) proceeded with rapid temperature rise at the

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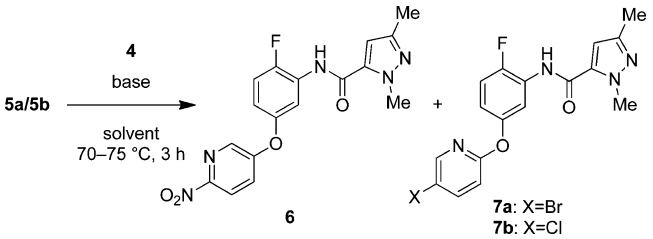
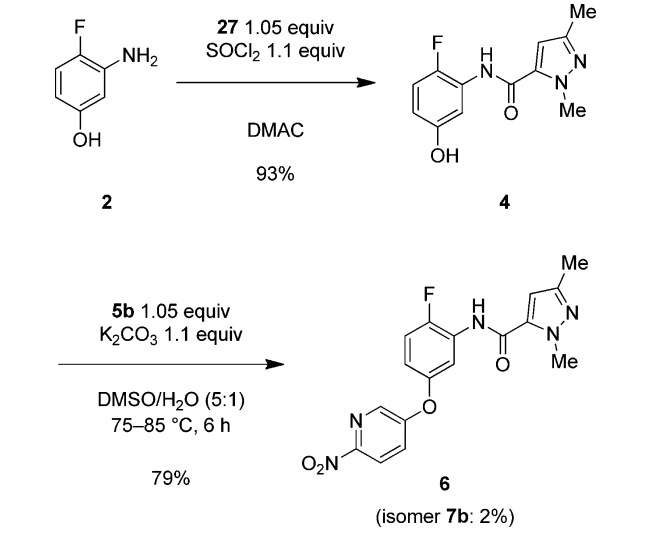
Table 3. Optimization of S_NAr reaction of 4 with 5a/5b (route B)[a]



entry	substrate	base	solvent	ratio[b] 6:7
1	**5a**	Cs_2CO_3	THF	30:70
2	**5a**	Cs_2CO_3	DMF	60:40
3	**5a**	Cs_2CO_3	DMAC	56:44
4	**5a**	Cs_2CO_3	NMP[d]	57:43
5	**5a**	Cs_2CO_3	DMSO	66:34 (54)[e]
6	**5a**	K_2CO_3	DMSO	69:31
7	**5a**	*t*-BuONa	DMSO	64:36
8	**5b**	Cs_2CO_3	DMF	72:28
9	**5b**	Cs_2CO_3	DMAC	70:30
10	**5b**	Cs_2CO_3	NMP	69:31
11	**5b**	Cs_2CO_3	DMSO	77:23
12	**5b**	K_2CO_3	DMSO	80:20
13[c]	**5b**	K_2CO_3	DMSO/H_2O (5:1)	82:18 (80)[e]

[a]The reaction was carried out using 1.0 equiv of **5a**/**5b**, 1.05 equiv of **4**, and 1.1 equiv of bases at 70−75 °C for 3 h. [b]Molar ratio determined by HPLC analysis of the reaction mixture. [c]The reaction was carried out for 6 h. [d]NMP = *N*-methylpyrrolidone. [e]HPLC assay yield of **6**.

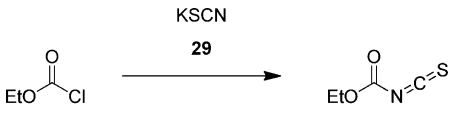
Scheme 8. Optimized results of route B



beginning of the reaction. Screening of solvents showed that hydrogenation of **6** in EtOAc proceeded more mildly without notable temperature rise. Thus, from a safety perspective, EtOAc was selected as the solvent for the hydrogenation. The scale-up of the hydrogenation of **6** (600 g per batch) was conducted in EtOAc in the presence of 10% Pd/C (2 mol % of Pd loading) for 3 h at 15−30 °C and for a further 3 h at 40−45 °C. After the catalyst was filtered off, **8** was isolated in 91% yield by crystallization from EtOAc/*n*-heptane (2:5).

Subsequently, *in situ* generation of the expensive and lachrymatory isothiocyanate **9** using inexpensive and readily available ethyl chloroformate **28** and potassium thiocyanate **29**,[16] and its use for the one-pot reaction with **8** were investigated. When **28** was reacted with 1.04 equiv of **29** in THF at 50 °C in the absence of bases, **9** was not obtained (Table 4, entry 1). In the literature, addition of a catalytic amount of bases was reported to be effective for preparation of **9**.[16c] Among the screened bases (entries 2−5), TMEDA was found to be the most effective, affording **9** in 70% yield (GC assay yield, entry 2). Interestingly, in MeCN and acetone, the reaction proceeded without addition of bases to give **9** in 73% and 53% yield, respectively (entries 6 and 7).

Table 4. *In situ* generation of 9 using 28 and 29



entry	**29** (equiv)	base (equiv)	solvent	temp (°C)	time (h)	GC assay yield of **9** (%)
1	1.04	–	THF	50	2	ND[a]
2	1.2	TMEDA (0.1)	THF	rt	5	70
3	1.2	Et_3N (0.1)	THF	rt	5	38
4	1.2	pyridine (0.1)	THF	rt	5	58
5	1.2	DMAP (0.1)	THF	rt	5	59
6	1.04	–	MeCN	70	2	73
7	1.04	–	acetone	50	1.5	57

[a]Not detected.

Then, one-pot reaction of *in situ* generated **9** with **8** was investigated. When **8** was added to the THF solution of **9** generated *in situ* under the condition of entry 2 in Table 4, the reaction proceeded smoothly to afford **10**. However, addition of H_2O to the reaction mixture gave an oily product. Fortunately, addition of H_2O to acetone solution of **10** was found to give rise to crystallization, which enabled facile isolation of **10** by filtration, while addition of H_2O to MeCN solution of **10** also gave an oily product. When acetone was used as a solvent, 2.0 equiv of **28** and 2.1 equiv of **29** were required for complete conversion of **8** to **10**. After *in situ* generation of **9** in acetone, **8** was added to the reaction mixture and reacted for 1 h at 25 °C. Dropwise addition of H_2O to the reaction mixture led to crystallization of **10**, followed by filtration and washing with EtOH/H_2O (1:1) to afford **10** in 96% yield (Scheme 9). After several experiments, it was found that **10** could be used for the next reaction without drying. On scale-up synthesis, wet solids of **10** were directly used for the next reaction.

Preparation of 1. Compound **11** was prepared by treatment of **10** with 5.0 equiv of NH_2OH hydrochloride and 3.0 equiv of DIPEA in EtOH at 50−55 °C for 6 h. Addition of H_2O to the reaction mixture led to crystallization, affording **11** as a monohydrate (**11**·H_2O) in 93% yield. However, elemental analysis unexpectedly showed that the obtained **11**·H_2O contained 2.8% of sulfur, which was assumed to be derived from air oxidation of H_2S generated during the reaction. Although the amount of residual sulfur decreased to 1.5% when the reaction was conducted under N_2 atmosphere in order to avoid the oxidation of H_2S, it was thought to be quite difficult to prevent the generation of sulfur completely. Therefore, in

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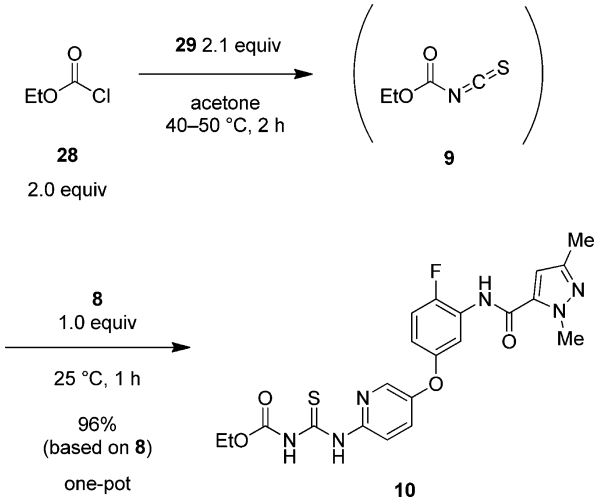
Scheme 9. One-pot synthesis of 10 from 8 using *in situ*-generated 9



order to remove the residual sulfur, reslurry of crude **11**·H_2O in several kinds of solvents or mixed solvents was investigated (Table 5).

Table 5. Reslurry of crude 11·H_2O in various solvents[a]

entry	initial amount of residual sulfur (%)[b]	solvent	temp (°C)	recovery (%)	amount of residual sulfur after reslurry (%)[b]
1	2.8	EtOH/H_2O (1:1)	rt	96	2.8
2	1.5	diisopropyl ether	60	98	0.55
3	1.5	toluene	90	96	<0.05
4	1.5	EtOAc	60	85	0.39
5	1.5	EtOAc/*n*-heptane (1:1)	60	94	<0.05

[a]Crude **11**·H_2O was suspended in each solvent and stirred for 1 h at the temperature described in the table. After cooling to room temperature, the slurry was stirred for 1 h, and then **11**·H_2O was collected by filtration. [b]Determined by elemental analysis.

While reslurry in an aqueous solvent such as EtOH/H_2O (1:1) was not effective at all (entry 1), reslurry in lipophilic solvents had a good effect in decreasing the amount of residual sulfur (entries 2–4). Reslurry in toluene was especially effective in decreasing the amount of residual sulfur (<0.05%) and gave **11**·H_2O in 96% recovery (entry 3). However, this protocol caused a large amount of scaling of **11**·H_2O on the reaction vessel wall. Meanwhile, reslurry in EtOAc decreased the amount of residual sulfur to less than 0.4% without scaling, albeit in slightly lower yield (85%, entry 4). A mixture of EtOAc and *n*-heptane (1:1) was finally found to give the best result, decreasing the amount of residual sulfur to less than 0.05% and affording **11** in 94% recovery without scaling (entry 5). By incorporating this reslurry of crude **11**·H_2O in EtOAc/*n*-heptane (1:1) into the procedure, the scale-up synthesis was conducted using wet solids of **10**, which gave **11**·H_2O in 81% yield over two steps from **8** with good purity (residual sulfur <0.05%) on a multihundred gram scale (815 g).

Since the yield of acylation of **11** with **12** in the medicinal chemistry synthesis was only moderate (71%), our next effort was directed toward increasing the yield of this acylation. Due to low solubility of **11**·H_2O in other common solvents, optimization of this reaction was carried out using aprotic polar solvents such as DMAC, NMP, and DMF (Table 6). The reaction of **11**·H_2O with 3.0 equiv of **12** in DMAC or NMP at 40 °C for 4–5 h showed good conversion (>95 area %, entries 1 and 2). Interestingly, acylation of **11**·H_2O with **12** in DMF gave only 10.4 area % of **1** and mainly gave byproduct **30** (89.1 area %, entry 3). When the amount of **12** was decreased from 3.0 to 1.5 equiv, the conversion largely decreased (63.9 area %, entry 4). To promote the conversion, addition of bases was then examined (entries 5–9). Addition of 1.2 equiv of triethyl amine caused generation of 39.1 area % of bis-acylated byproduct **31** (entry 5). Amongst the screened bases, pyridine proved the most effective in increasing the conversion (entry 9). It was found that acylation of **11**·H_2O with 2.0 equiv of **12** in the presence of 3.0 equiv of pyridine at 25–40 °C for 2 h provided 99.2 area % of **1** (entry 10).

This optimum condition (entry 10) was applied to the scale-up synthesis of **1**. Upon completion of the reaction, H_2O and seeds (monohydrate of **1**, **1**·H_2O) were added to the reaction mixture. Subsequent dropwise addition of 2 M NaOH for adjustment of pH to 6–8 gave rise to crystallization, followed by filtration and washing with H_2O to afford >1 kg of **1**·H_2O in as high as 99% yield with high purity (99.2 area %).[17]

Recrystallization of 1. Since it was found that **1** has two polymorphs (form A and form B) and one pseudopolymorph (monohydrate, **1**·H_2O), a reliable recrystallization method to give the desired crystal form (A) was required. Our first choice of solvent for recrystallization was DMSO due to the low solubility of **1** in other common solvents (<0.3 wt % at 25 °C).[18] Recrystallization of **1** from DMSO/H_2O (1:2) gave the desired form A, albeit with 1.5% of residual DMSO (Table 7, entry 1). The increase of the ratio of H_2O to DMSO (1:5 DMSO/H_2O) did not largely affect the amount of residual DMSO (1.4%, entry 2). When EtOH and H_2O were used as antisolvents, monohydrate was obtained (entry 3).

Following these results, recrystallization of **1** from EtOH was then investigated, since the solubility of **1** in EtOH (0.28 wt % at 25 °C) is higher than that in other examined solvents. First, the solubilities of form A, form B, and the monohydrate in EtOH were measured with changing the H_2O content (Figure 1). This solubility measurement showed two important facts. One is that addition of a small amount of H_2O (5–20 wt %) greatly increased the solubility of **1** in EtOH, which led to a substantial increase in batch efficiency for the recrystallization. The other fact is that the solubility of monohydrate became lower than that of form A when H_2O content was increased more than 15 wt %, which indicates that the monohydrate is preferentially obtained from EtOH/H_2O when H_2O content exceeds 15 wt %. Therefore, it was thought that H_2O content should be kept below 15 wt % to obtain form A reliably.

When **1** was recrystallized from EtOH containing 6 or 12 wt % of H_2O, form A was obtained as expected with less than 4000 ppm of residual EtOH (entries 4 and 5). Recrystallization of **1** from EtOH containing 18 wt % of H_2O also gave form A, probably due to the addition of seeds for form A (entry 6). On the other hand, recrystallization from EtOH containing approximately 50 wt % of H_2O gave monohydrate as expected from the phase diagram in Figure 1 (entry 7). Finally, the condition in entry 5 (H_2O content: 12 wt %) was adopted for the scale-up synthesis, successfully affording form A of **1** in 77%

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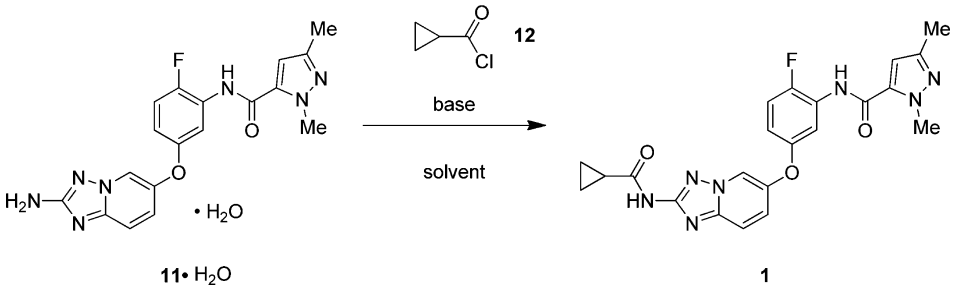
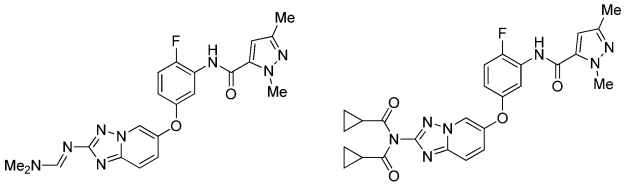
Table 6. Optimization of the acylation of 11·H_2O with 12



11• H_2O 1

entry	12 (equiv)	solvent	base (equiv)	temp (°C)	time (h)	1 (area %)[a]	11·H_2O (area %)[a]
1	3.0	DMAC	–	40	4	96.8	2.2
2	3.0	NMP	–	40	5	95.2	4.1
3[b]	3.0	DMF	–	40	3	10.4	<1
4	1.5	DMAC	–	50	5	63.9	34.6
5[c]	1.5	DMAC	Et_3N (1.2)	50	3	40.8	18.1
6[d]	1.5	DMAC	DBU (1.2)	50	3	44.8	50.9
7	1.5	DMAC	*t*-BuOK (1.2)	50	3	35.3	27.5
8	1.5	DMAC	K_2CO_3 (1.2)	50	3	71.3	26.3
9	1.5	DMAC	pyridine (1.2)	50	3	83.1	16.5
10	2.0	DMAC	pyridine (3.0)	25–40	2	99.2	<1

[a]Area % in HPLC analysis of the reaction mixture. [b]89.1 area % of **30** was observed. [c]39.1 area % of **31** was observed. [d]2.2 area % of **31** was observed.



30 31

Table 7. Recrystallization of 1[a,b]

entry	solvent (v/w)	antisolvent (v/w)	aging temp (°C)	yield (%)	crystal form	residual solvent (ppm)[j]
1[c,d]	DMSO (5)	H_2O (10)	rt	89	A	DMSO: 15000
2[c,e]	DMSO (5)	H_2O (25)	rt	95	A	DMSO: 14000
3[c,f]	DMSO (5)	EtOH (10)	rt	95	monohydrate	DMSO: 800
		H_2O (10)				EtOH: 2000
4[g]	6 wt % H_2O/EtOH (40)	–	0–5	78	A	EtOH: 3600
5[g]	12 wt % H_2O/EtOH (20)	–	rt	79	A	EtOH: 3000
6[g]	18 wt % H_2O/EtOH (25)	–	rt	68	A	EtOH: 2300
7[h,i]	20 wt % H_2O/EtOH (35)	H_2O (17)	0–5	94	monohydrate	EtOH: 1400

[a]In entries 1–3 and 7, **1** was used as a substrate. In entries 4–6, **1**·H_2O was used as a substrate. [b]In all experiments, seeds for form A (0.1 wt %) were added before addition of antisolvent or lowering the temperature. [c]After dissolving **1** into DMSO at 40–50 °C, seeds were added at 40–45 °C. [d]H_2O was added at 35–40 °C. [e]H_2O was added at 45–55 °C. [f]EtOH was added first, and then H_2O was added at 45–55 °C. [g]**1**·H_2O was suspended in the solvent and heated to 65–75 °C. After confirming that **1**·H_2O completely dissolved into the solvent, the solution was gradually cooled to 55 °C. At this point, seeds were added, and the mixture was aged at 45–55 °C for 3–4 h. Then the slurry was gradually cooled to 0–5 °C or room temperature, and aged for 9–12 h. [h]After dissolving **1** into 20 wt % H_2O/EtOH at 60–65 °C, seeds were added at 50–55 °C. Then H_2O was added at 55–65 °C. [i]After addition of H_2O (17 v/w), the composition of the solvent became approximately 50 wt % H_2O/EtOH. [j]Determined by ^1H NMR analysis.

yield (99.9 area %, residual EtOH: 1600 ppm) on a multihundred gram scale (553 g).

■ CONCLUSIONS

In summary, a practical and scalable synthesis of **1** was developed. A detailed investigation into the hydrogenation of **21** revealed that addition of NaOAc as an additive and optimization of the amount of Pd catalyst were effective for improving the yield. This finding led to successful preparation of multikilograms of **2** using commercially available starting materials. The chemoselectivity in the S_NAr reaction of **5b** with **4** was successfully increased by the use of K_2CO_3 as a base and aqueous DMSO as a solvent, which gave the desired 5-etherified product **6** in good yield without chromatographic separation. *In situ* generation of **9** from inexpensive and readily available **28** and **29**, and its one-pot reaction with **8** enabled a safe synthesis of thiourea **10** suitable for a large-scale production. The use of pyridine improved the yield for the acylation of **11**·H_2O with **12**, affording >1 kg of **1**·H_2O in excellent yield with good purity. As a result of many kinds of

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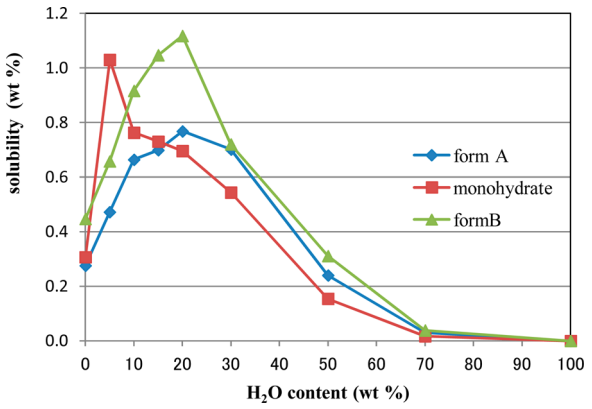

Figure 1. Solubilities of form A, form B, and monohydrate in EtOH/H_2O at 25 °C.

improvements, a practical and scalable synthesis of **1**·H_2O was achieved in six steps from **2** in 54% overall yield, more than twice as much as the yield of the medicinal chemistry synthesis. In addition, a reliable recrystallization procedure which affords the desired crystal form A was also developed and successfully scaled up to a multihundred gram scale.

EXPERIMENTAL SECTION

All materials were purchased from commercial suppliers and used without any additional purification. Pd/C (10%, PE type) was purchased from N.E. CHEMCAT Corporation. Elemental analyses and GC analysis of residual solvents in the final bulk product **1** were conducted by Takeda Analytical Research Laboratories, Ltd.

HPLC conditions. (A) Inertsil ODS-3 column, 5 μm, 150 mm × 4.6 mm i.d.; UV detector at 254 nm; isocratic elution with CH_3CN/50 mM aqueous KH_2PO_4 (40:60) at 1.0 mL/min flow rate; column temperature: 25 °C. Retention times: **1** (4.6 min), **2** (2.8 min), **4** (3.8 min), **8** (2.8 min), **10** (12.7 min), **11** (3.6 min), **20** (22.0 min), **21** (9.7 min), **22** (6.2 min), **23** (4.3 min), **24** (1.5 min), **25** (13.3 min), **27** (1.6 min), **30** (4.1 min), **31** (21.8 min).

(B) Inertsil ODS-3 column, 5 μm, 150 mm × 4.6 mm i.d.; UV detector at 254 nm; isocratic elution with CH_3CN/50 mM aqueous KH_2PO_4 (50:50) at 1.0 mL/min flow rate; column temperature: 25 °C. Retention times: **2** (2.3 min), **4** (2.7 min), **5b** (4.3 min), **6** (6.2 min), **7a** (11.8 min), **7b** (10.5 min), **13** (6.0 min), **26a** (9.8 min), **26b** (8.8 min).

(C) Inertsil ODS-3 column, 5 μm, 150 mm × 4.6 mm i.d.; UV detector at 254 nm; isocratic elution with CH_3CN/50 mM aqueous KH_2PO_4 (60:40) at 1.0 mL/min flow rate; column temperature: 25 °C. Retention times: **18** (3.5 min), **19** (5.6 min).

(D) Inertsil ODS-3 column, 5 μm, 150 mm × 4.6 mm i.d.; UV detector at 254 nm; isocratic elution with CH_3CN/10 mM aqueous $AcONH_4$ (40:60) at 1.0 mL/min flow rate; column temperature: 25 °C. Retention times: **6** (12.7 min), **8** (4.6 min).

(E) Inertsil ODS-3 column, 5 μm, 150 mm × 4.6 mm i.d.; UV detector at 254 nm; isocratic elution with MeOH/50 mM aqueous KH_2PO_4 (50:50) at 1.0 mL/min flow rate; column temperature at 25 °C. Retention times: **19** (22.1 min), **20** (19.4 min).

GC conditions. SPB-5 column, 30 m × 0.53 mm i.d., 5 μm film; FID detector, He carrier gas (approximately 6 mL/min); oven heating 80 °C for 5 min, 3 °C/min to 125 °C for 1 min. Retention times: **28** (3.7 min), **9** (14.0 min).

2-Chloro-4-fluorophenyl Methyl Carbonate (19). A 300 L glass lined (GL) vessel was charged with 2-chloro-4-fluorophenol **18** (10.0 kg, 68.2 mol), Na_2CO_3 (7.96 kg, 75.1 mol) and H_2O (100 L). The mixture was heated to 40−45 °C and stirred for 1 h. Then the reaction mixture was cooled to 10 °C and methyl chloroformate (1.23 kg, 13.0 mol) was slowly added at 10−25 °C. At this point, **19** (30.0 g) was added as seeds, followed by slow addition of methyl chloroformate (6.51 kg, 68.9 mol) at 10−25 °C. The resulting slurry was stirred at 10−25 °C for 1 h and then filtered. The wet cake was washed with H_2O (60 L), chilled EtOH/H_2O (1:3, 40 L), and dried *in vacuo* (−0.08 to −0.10 MPa) at 30 °C to afford **19** as a white solid (13.2 kg, 95%). HPLC purity: 99.7 area % (HPLC condition C); Mp 74−75 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.90 (s, 3H), 7.32 (ddd, $^3J_{HF}$ = 8.0 Hz, J = 9.0, 3.0 Hz, 1H), 7.53 (dd, $^4J_{HF}$ = 5.0 Hz, J = 9.0 Hz, 1H), 7.64 (dd, $^3J_{HF}$ = 8.5 Hz, J = 3.0 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 56.0 (q), 115.5 (dd, $^2J_{CF}$ = 22.5 Hz), 117.4 (dd, $^2J_{CF}$ = 27.5 Hz), 125.0 (dd, $^3J_{CF}$ = 10.0 Hz), 126.7 (sd, $^3J_{CF}$ = 11.3 Hz), 143.2 (sd, $^4J_{CF}$ = 2.5 Hz), 152.6 (s), 159.5 (sd, $^1J_{CF}$ = 245.0 Hz); IR (ATR) 1768, 1758, 1597, 1493, 1438, 1400, 1268, 1245, 1184, 1072, 1041, 949, 932, 914, 858, 825, 798, 774, 735, 688, 677, 577, 555, 518, 452, 438 cm^{-1}; Anal. Calcd for $C_8H_6ClFO_3$: C, 46.97; H, 2.96; Cl, 17.33; F, 9.29. Found: C, 46.94; H, 3.03; Cl, 17.08; F, 8.99.

2-Chloro-4-fluoro-5-nitrophenyl Methyl Carbonate (20). A 300 L GL vessel was charged with concentrated sulfuric acid (47 L) and **19** (13.2 kg, 64.5 mol). The mixture was cooled to 0−5 °C and nitric acid (65%, 7.51 kg, 77.5 mol) was slowly added, maintaining the temperature below 15 °C. The reaction mixture was stirred at 0−10 °C for 1 h and then slowly poured into H_2O (132 L), maintaining the temperature below 25 °C. The resulting slurry was stirred at 0−10 °C for 1 h and then filtered. After washing with H_2O (3 × 60 L), the crude product was suspended in H_2O (46 L). The slurry was stirred at room temperature for 1 h and then filtered. The wet cake was washed with H_2O (3 × 60 L) and dried *in vacuo* to afford **20** as a yellow solid (15.0 kg, 93%). HPLC purity: 99.1 area % (HPLC condition E); Mp 57−59 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.90 (s, 3H), 8.10 (d, $^3J_{HF}$ = 10.8 Hz, 1H), 8.44 (d, $^4J_{HF}$ = 7.2 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 56.6 (q), 120.6 (dd, $^2J_{CF}$ = 26.1 Hz), 121.6 (dd, $^3J_{CF}$ = 1.9 Hz), 133.6 (sd, $^3J_{CF}$ = 10.7 Hz), 136.0 (sd, $^2J_{CF}$ = 8.6 Hz), 142.9 (sd, $^4J_{CF}$ = 3.8 Hz), 152.3 (s), 152.6 (sd, $^1J_{CF}$ = 264.4 Hz); IR (ATR) 3459, 3371, 2362, 2337, 1756, 1639, 1508, 1464, 1443, 1304, 1261, 1227, 1190, 1170, 1070, 1003, 937, 862, 839, 815, 778, 732, 669, 653, 628, 528, 490, 480, 469, 455, 442, 433, 419 cm^{-1}; Anal. Calcd for $C_8H_5ClFNO_5$: C, 38.50; H, 2.02; Cl, 14.21; F, 7.61; N, 5.61. Found: C, 38.42; H, 2.08; Cl, 14.19; F, 7.54; N, 5.67.

2-Chloro-4-fluoro-5-nitrophenol (21). A 300 L GL vessel was charged with **20** (15.0 kg, 60.0 mol), MeOH (30 L), and 2 M NaOH (45 L). The mixture was stirred at 20−40 °C for 10 min. Then additional 2 M NaOH (15 L) was added, and the mixture was stirred at 30−40 °C for 1.5 h. The mixture was cooled to room temperature, and toluene (45 L) and H_2O (15 L) were added. After phase separation, the aqueous layer was concentrated under reduced pressure until approximately 30 L of solvent was removed. To this solution was slowly added 2 M HCl (60 L), and the pH was adjusted to approximately 1, maintaining the temperature below 30 °C. The resulting slurry

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was cooled to 0−10 °C, stirred for 1 h, and then filtered. The wet cake was washed with H_2O (3 × 30 L) and dried *in vacuo* at 40 °C to afford **21** as a yellow solid (10.8 kg, 94%). HPLC purity: 99.9 area % (HPLC condition A); Mp 109−112 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.59 (d, $^4J_{HF}$ = 7.0 Hz, 1H), 7.70 (d, $^3J_{HF}$ = 11.0 Hz, 1H), 11.1 (br s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 111.9 (dd, $^3J_{CF}$ = 2.5 Hz), 119.8 (dd, $^2J_{CF}$ = 25.5 Hz), 127.4 (sd, $^3J_{CF}$ = 9.3 Hz), 135.4 (sd, $^2J_{CF}$ = 8.4 Hz), 147.7 (sd, $^1J_{CF}$ = 256.2 Hz), 150.1 (sd, $^4J_{CF}$ = 2.8 Hz); IR (ATR) 3376, 3116, 3062, 1616, 1591, 1524, 1487, 1420, 1359, 1349, 1334, 1293, 1232, 1198, 1184, 1099, 1022, 1004, 901, 865, 844, 799, 756, 705, 637, 599, 556, 494, 468, 455, 433, 417 cm^{-1}; MS (ESI): *m/z* 192 $[M + H]^+$; Anal. Calcd for $C_6H_3ClFNO_3$: C, 37.62; H, 1.58; Cl, 18.51; F, 9.92; N, 7.31. Found: C, 37.51; H, 1.76; Cl, 18.54; F, 9.87; N, 7.39.

3-Amino-4-fluorophenol (2). A 300 L GL vessel was charged with MeOH (108 L), **21** (5.40 kg, 28.2 mol), and NaOAc (2.54 kg, 30.6 mol). After the reaction vessel was evacuated and backfilled with nitrogen, 10% Pd/C (PE type, 52.7% H_2O wet, 1.32 kg, 0.587 mol as Pd) was quickly added to the solution. The reaction vessel was evacuated and backfilled with nitrogen and then evacuated and backfilled with hydrogen three times. The reaction mixture was stirred at 15−25 °C for 4 h while maintaining hydrogen pressure at 0.1 MPa. The hydrogen was vented, and the reaction vessel was evacuated and backfilled with nitrogen. The reaction mixture was filtered, and the cake was washed with MeOH (32 L). The combined filtrate was concentrated under reduced pressure. EtOAc (22 L) was added to the residue and concentrated under reduced pressure again. Then EtOAc (54 L) and H_2O (27 L) were added, and the layers were separated. After washing with 5% aqueous NaCl (27 L), the organic layer was concentrated to 10.8 L under reduced pressure. EtOAc (43 L) was added, and the solution was concentrated to 10.8 L under reduced pressure again. To this solution was slowly added *n*-heptane (43 L), and the resulting slurry was stirred at 15−25 °C for 30 min. After cooling to 0−10 °C, the slurry was stirred for 2 h and then filtered. The wet cake was washed with EtOAc/*n*-heptane (1:4, 10.8 L) and dried *in vacuo* at 50 °C to afford **2** as a pale-brown solid (2.85 kg, 80%). HPLC purity: 94.5 area % (HPLC condition A); Mp 143−145 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.91 (br s, 2H, NH_2), 5.86 (ddd, $^4J_{HF}$ = 6.4 Hz, *J* = 8.6, 3.1 Hz, 1H), 6.18 (dd, $^4J_{HF}$ = 7.9 Hz, *J* = 3.1 Hz, 1H), 6.69 (dd, $^3J_{HF}$ = 11.4 Hz, *J* = 8.6 Hz, 1H), 9.10 (br s, 1H, OH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 102.4 (dd, $^3J_{CF}$ = 6.6 Hz), 103.0 (dd, $^3J_{CF}$ = 3.7 Hz), 115.0 (dd, $^2J_{CF}$ = 19.5 Hz), 137.0 (sd, $^2J_{CF}$ = 14.3 Hz), 145.1 (sd, $^1J_{CF}$ = 226.6 Hz), 154.1 (s); IR (ATR) 3387, 3295, 3045, 2953, 2832, 2723, 2362, 1631, 1605, 1509, 1360, 1317, 1208, 1159, 1132, 1080, 966, 837, 770, 726, 696, 616, 597, 595, 442 cm^{-1}; MS (ESI): *m/z* 128 $[M+H]^+$; Anal. Calcd for C_6H_6FNO: C, 56.69; H, 4.76; F, 14.95; N, 11.02. Found: C, 56.67; H, 4.84; F, 14.91; N, 10.99.

2-Fluoro-5-[(6-nitropyridin-3-yl)oxy]aniline (13). A flask was charged with H_2O (50 mL), DMSO (50 mL), 5-chloro-2-nitropyridine **5b** (10.0 g, 63.1 mmol), **2** (9.62 g, 75.7 mmol), and K_3PO_4 (25.4 g, 120 mmol). The mixture was heated to 75−80 °C and stirred for 9 h. After the mixture was cooled to room temperature, toluene (200 mL) and 1 M NaOH (100 mL) were added, and then layers were separated. The organic layer was washed with H_2O (100 mL) and concentrated under reduced pressure. The residue was suspended in diisopropyl ether (50 mL) and stirred at 50 °C for 1 h. The slurry was cooled to room temperature and stirred for 1 h, and then filtered. The wet cake was washed with diisopropyl ether (20 mL) and dried *in vacuo* at 50 °C to afford **13** as a white solid (11.9 g, 76%). HPLC purity: 98.3 area %, residual **26b**: 1.0 area % (HPLC condition B). An analytical sample was prepared by recrystallization from EtOAc/*n*-heptane (1:2). Mp 96−97 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.48 (br s, 2H), 6.33 (ddd, $^4J_{HF}$ = 6.5 Hz, *J* = 8.7, 2.9 Hz, 1H), 6.57 (dd, $^4J_{HF}$ = 7.6 Hz, *J* = 2.9 Hz, 1H), 7.09 (dd, $^3J_{HF}$ = 11.2 Hz, *J* = 8.7 Hz, 1H), 7.58 (dd, *J* = 9.0, 2.9 Hz, 1H), 8.32 (d, *J* = 9.0 Hz, 1H), 8.38 (d, *J* = 2.9 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 106.6 (dd, $^3J_{CF}$ = 7.1 Hz), 107.3 (dd, $^3J_{CF}$ = 5.2 Hz), 116.2 (dd, $^2J_{CF}$ = 20.4 Hz), 120.6 (d), 126.2 (d), 138.3 (d), 138.6 (sd, $^2J_{CF}$ = 14.9 Hz), 148.2 (sd, $^1J_{CF}$ = 235.1 Hz), 150.6 (sd, $^4J_{CF}$ = 2.0 Hz), 150.9 (s), 159.0 (s); IR (ATR) 3499, 3402, 1635, 1567, 1513, 1453, 1396, 1352, 1286, 1235, 1198, 1150, 1140, 1111, 972, 911, 873, 853, 841, 810, 767, 747, 710, 690, 627, 607, 472, 451, 416, 406 cm^{-1}; Anal. Calcd for $C_{11}H_8FN_3O_3$: C, 53.02; H, 3.24; N, 16.86. Found: C, 52.99; H, 3.26; N, 16.60.

***N*-(2-Fluoro-5-hydroxyphenyl)-1,3-dimethyl-1*H*-pyrazole-5-carboxamide (4).**[17] **4** was synthesized according to the reported procedure. HPLC purity: 98.9 area % (HPLC condition A); ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.21 (s, 3H), 4.21 (s, 3H), 6.64 (ddd, $^4J_{HF}$ = 7.0 Hz, *J* = 8.9, 3.8 Hz, 1H), 6.85 (br s, 1H), 7.06 (dd, $^4J_{HF}$ = 6.2 Hz, *J* = 3.8 Hz, 1H), 7.07 (dd, $^3J_{HF}$ = 10.1 Hz, *J* = 8.9 Hz, 1H), 9.48 (br s, 1H), 9.85 (br s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 13.3 (q), 38.8 (q), 107.7 (d), 113.1 (dd, $^3J_{CF}$ = 4.0 Hz), 113.2 (dd, $^3J_{CF}$ = <4.0 Hz), 116.1 (dd, $^2J_{CF}$ = 21.3 Hz), 125.3 (sd, $^2J_{CF}$ = 13.7 Hz), 135.5 (s), 145.8 (s), 149.7 (sd, $^1J_{CF}$ = 237.1 Hz), 153.6 (sd, $^4J_{CF}$ = 1.8 Hz), 158.3 (s).

***N*-{2-Fluoro-5-[(6-nitropyridin-3-yl)oxy]phenyl}-1,3-dimethyl-1*H*-pyrazole-5-carboxamide (6).** *Preparation via Route A.* A flask was charged with 1,3-dimethyl-1*H*-pyrazole-5-carboxylic acid **27** (1.18 g, 8.43 mmol) and DMAC (9 mL). To the mixture was slowly added $SOCl_2$ (1.18 g, 9.93 mmol) at 0−15 °C. The mixture was stirred at 10 °C for 1 h, and then **13** (2.00 g, 8.03 mmol) was added portionwise, followed by addition of DMAC (3 mL). The reaction mixture was stirred at room temperature for 1 h, and H_2O (20 mL), 8 M NaOH (2.2 mL), and EtOAc (40 mL) were added in this sequence. After phase separation, the organic layer was washed with H_2O (10 mL) and concentrated under reduced pressure. The crude product was suspended in EtOAc (10 mL), followed by slow addition of *n*-heptane (30 mL). The resulting slurry was stirred at room temperature for 1 h and then filtered. The wet cake was washed with *n*-heptane (10 mL) and dried *in vacuo* at 50 °C to afford **6** as a pale-yellow solid (2.60 g, 87%). HPLC purity: 99.4 area % (HPLC condition B); Mp 132−133 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.20 (s, 3H), 3.99 (s, 3H), 6.88 (s, 1H), 7.20 (ddd, *J* = 6.9, 3.2, 3.2 Hz, 1H), 7.47 (t like, *J* = 9.1 Hz, 1H), 7.59 (dd, *J* = 6.3, 3.0 Hz, 1H), 7.66 (dd, *J* = 9.0, 2.9 Hz, 1H), 8.36 (d, *J* = 8.9 Hz, 1H), 8.44 (d, *J* = 2.7 Hz, 1H), 10.2 (br s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 13.2 (q), 38.8 (q), 108.0 (d), 117.7 (dd, $^2J_{CF}$ = 22.2 Hz), 118.3 (d), 118.5 (dd, $^3J_{CF}$ = 8.2 Hz), 120.7 (d), 126.7 (d), 126.8 (sd, $^2J_{CF}$ = 14.0 Hz), 135.0 (s), 138.5 (d), 145.7 (s), 149.8 (sd, $^4J_{CF}$ = 2.6 Hz), 151.2 (s), 152.8 (sd, $^1J_{CF}$ = 252.8 Hz), 158.3 (s), 158.6 (s); IR (ATR) 1686, 1624, 1573, 1541, 1523, 1433, 1348, 1242, 1190, 1167, 1111, 1014, 972, 877, 865, 855, 825, 813, 759, 745, 692, 667, 646, 610, 592, 507 cm^{-1}; MS (ESI): *m/z* 372 $[M + H]^+$; Anal. Calcd for $C_{17}H_{14}FN_5O_4$: C, 54.99; H, 3.80; N, 18.86. Found: C, 55.00; H, 3.82; N, 18.73.

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Preparation via Route B. A 10 L glass vessel was charged with DMSO (3.6 L), **4** (1.20 kg, 4.81 mol), **5b** (802 g, 5.06 mol), K_2CO_3 (732 g, 5.30 mol), and H_2O (720 mL). The reaction mixture was heated to 75−85 °C and stirred for 6 h. After the mixture was cooled to room temperature, EtOAc (15.6 L) and 5% aqueous NaCl (9.6 L) were added, and then layers were separated. The organic layer was washed with 5% aqueous NaCl (2 × 9.6 L) and concentrated to 8.4 L under reduced pressure. To this solution was added EtOAc (15.6 L), and the solution was concentrated to 6.0 L under reduced pressure. The mixture was stirred at 20−25 °C for 1 h, and then *n*-heptane (16.8 L) was slowly added over 1 h. The resulting slurry was stirred at 20−25 °C for 1 h and then filtered. The wet cake was washed with chilled EtOAc/*n*-heptane (1:5, 10.2 L) and dried *in vacuo* at 50 °C to afford **6** as a pale-brown solid (1.39 kg, 78%). HPLC purity: 97.2 area %, **7b**: 1.6 area % (HPLC condition B).

***N*-{5-[(6-Aminopyridin-3-yl)oxy]-2-fluorophenyl}-1,3-dimethyl-1*H*-pyrazole-5-carboxamide (8).** A 20 L glass vessel was charged with crude **6** (600 g, 1.62 mol) and EtOAc (11.4 L). Nitrogen was introduced to the solution via a glass tube, and nitrogen bubbling was continued for 10 min. After 10% Pd/C (PE type, 55.5% H_2O wet, 77.9 g, 32.3 mmol as Pd) was quickly added to the mixture, hydrogen was introduced via glass tube. Under hydrogen bubbling, the mixture was stirred at 15−30 °C for 3 h and at 40−45 °C for 3 h. Then, the reaction mixture was filtered, and the cake was washed with EtOAc (1.8 L). This hydrogenation was conducted twice, and the filtrate was combined for workup. The combined filtrate was concentrated to 5.4 L under reduced pressure, followed by dropwise addition of *n*-heptane (12 L). The resulting slurry was stirred at 20−25 °C for 0.5 h and then filtered. The wet cake was washed with EtOAc/*n*-heptane (2:5, 3.6 L) and dried *in vacuo* at 50 °C to afford **8** as a white solid (1.00 kg, 91%). HPLC purity: 99.4 area % (HPLC condition D); Mp 141−142 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.20 (s, 3H), 3.99 (s, 3H), 5.92 (br s, 2H), 6.53 (dd, J = 8.9, 0.4 Hz, 1H), 6.80−6.86 (m, 2H), 7.15 (dd, J = 6.3, 3.1 Hz, 1H), 7.23 (ddd, J = 8.9, 2.9, 1.8 Hz, 1H), 7.27 (d, J = 8.9 Hz, 1H), 7.79 (d, J = 2.6 Hz, 1H), 9.97 (br s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 13.2 (q), 38.8 (q), 107.9 (d), 108.9 (d), 114.2 (d), 114.6 (dd, $^3J_{CF}$ = 7.6 Hz), 116.7 (dd, $^2J_{CF}$ = 21.9 Hz), 125.9 (sd, $^2J_{CF}$ = 14.0 Hz), 130.5 (d), 135.2 (d), 139.8 (s), 143.4 (s), 145.7 (s), 150.9 (sd, $^1J_{CF}$ = 241.8 Hz), 154.7 (sd, $^4J_{CF}$ = 2.1 Hz), 157.3 (s), 158.2 (s); IR (ATR) 3470, 3424, 3291, 3158, 1684, 1633, 1609, 1538, 1524, 1493, 1435, 1398, 1369, 1328, 1310, 1284, 1248, 1233, 1174, 1146, 1132, 1101, 1046, 1012, 972, 922, 888, 871, 830, 801, 788, 748, 720, 658, 644, 634, 605, 592, 552, 526, 518, 503, 471, 449, 423, 403 cm^{-1}; MS (ESI): m/z 342 $[M + H]^+$; Anal. Calcd for $C_{17}H_{16}FN_5O_2$: C, 59.82; H, 4.72; N, 20.52. Found: C, 59.70; H, 4.69; N, 20.55.

***N*-{5-[(2-Amino-[1,2,4]triazolo[1,5-*a*]pyridin-6-yl)oxy]-2-fluorophenyl}-1,3-dimethyl-1*H*-pyrazole-5-carboxamide Hydrate (11·H_2O).** A 20 L glass vessel was charged with acetone (6.8 L) and potassium thiocyanate **29** (538 g, 5.54 mol). The mixture was warmed to 40−45 °C, and ethyl chloroformate **28** (572 g, 5.27 mol) was slowly added at this temperature. The reaction mixture was stirred at 40−45 °C for 2 h and then cooled to room temperature. To this mixture was added **8** (900 g, 2.64 mol), followed by addition of acetone (0.45 L). The mixture was stirred at 20−25 °C for 1 h, and then H_2O (7.2 L) was slowly added. The resulting slurry was stirred at 20−25 °C for 1 h and then filtered. The wet cake was washed with EtOH/H_2O (1:1, 2.7 L) to give ethyl {[5-(3-{[(1,3-dimethyl-1*H*-pyrazol-5-yl)carbonyl]amino}-4-fluorophenoxy)pyridine-2-yl]carbamothioyl}carbamate **10** as a white solid. **10** was used for the next reaction without drying. A 20 L glass vessel was charged with wet solids of **10**, EtOH (9.0 L), hydroxylamine hydrochloride (916 g, 13.2 mol), and DIPEA (1.02 kg, 7.91 mol). The mixture was heated to 50−55 °C and stirred for 6 h (**CAUTION**: generation of H_2S occurs). To this mixture was slowly added H_2O (9.0 L) at 50−55 °C over 0.5 h. The reaction mixture was cooled to room temperature and stirred for 1 h. The resulting slurry was filtered and washed with EtOH/H_2O (1:1, 2.7 L). The obtained solids were suspended in EtOAc/*n*-heptane (1:1, 9.0 L), and the slurry was heated to 50−55 °C and stirred for 1 h. After cooling to 20−25 °C, the slurry was stirred for 1 h and then filered. The wet cake was washed with EtOAc/*n*-heptane (1:1, 2.7 L) and dried *in vacuo* at 50 °C to afford **11**·H_2O as a white solid (815 g, 81% yield over two steps from **8**).

10: HPLC purity: 98.6 area % (HPLC condition A); Mp 156−157 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.26 (t, J = 7.1 Hz, 3H), 2.19 (s, 3H), 3.97 (s, 3H), 4.23 (q, J = 7.1 Hz, 2H), 6.83 (s, 1H), 6.98−7.05 (m, 1H), 7.30−7.37 (m, 2H), 7.62 (dd, J = 9.1, 3.0 Hz, 1H), 8.23 (d, J = 3.0 Hz, 1H), 8.63 (br s, 1H), 10.1 (s, 1H), 11.5 (br s, 1H), 12.1 (br s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 13.2 (q), 14.3 (q), 38.8 (q), 62.4 (t), 107.9 (d), 116.4 (d), 116.7 (d), 116.9 (d), 117.0 (d), 117.3 (s), 117.3 (d), 126.3 (sd, $^2J_{CF}$ = 14.0 Hz), 128.1−128.2 (s, br m), 135.1 (s), 139.2 (s, br m), 145.7 (s), 148.6 (sd, $^1J_{CF}$ = 243.2 Hz), 150.8 (s), 152.2 (sd, $^4J_{CF}$ = 2.2 Hz), 153.4−153.7 (s, br m), 158.2 (s); IR (ATR) 3420, 3155, 2997, 1716, 1694, 1623, 1519, 1485, 1431, 1409, 1373, 1320, 1229, 1184, 1147, 1106, 1039, 970, 950, 917, 883, 852, 834, 785, 766, 746, 678, 660, 632, 606, 549, 529, 487, 457, 445, 424, 409, 401 cm^{-1}; MS (ESI): m/z 473 $[M + H]^+$; Anal. Calcd for $C_{21}H_{21}FN_6O_4S$: C, 53.38; H, 4.48; N, 17.79. Found: C, 53.29; H, 4.56; N, 17.64.

11·H_2O: HPLC purity: 99.6 area % (HPLC condition A); Mp 153 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.19 (s, 3H), 3.35 (s, 2H, H_2O), 3.97 (s, 3H), 6.03 (br s, 2H), 6.82 (s, 1H), 6.96 (ddd, J = 8.8, 3.8, 3.8 Hz, 1H), 7.26−7.34 (m, 3H), 7.42 (dd, J = 9.5, 1.0 Hz, 1H), 8.62 (dd, J = 2.5, 0.6 Hz, 1H), 10.0 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 13.5 (q), 39.1 (q), 108.2 (d), 113.1 (d), 115.4 (d), 115.7 (dd, $^3J_{CF}$ = 8.8 Hz), 117.2 (dd, $^2J_{CF}$ = 21.3 Hz), 120.5 (d), 124.4 (d), 126.4 (sd, $^2J_{CF}$ = 12.5 Hz), 135.5 (s), 143.7 (s), 146.0 (s), 148.9 (s), 151.8 (sd, $^1J_{CF}$ = 241.3 Hz), 154.1 (sd, $^4J_{CF}$ = 2.5 Hz), 158.5 (s), 167.2 (s); IR (ATR) 3464, 3389, 3214, 1688, 1638, 1564, 1535, 1521, 1510, 1434, 1376, 1347, 1326, 1272, 1239, 1179, 1170, 1138, 1117, 1043, 1013, 979, 917, 888, 877, 849, 817, 798, 781, 754, 741, 658, 633, 604, 589, 512, 466, 454, 439, 409 cm^{-1}; MS (ESI): m/z 382 $[M + H]^+$ for anhydrate; Anal. Calcd for $C_{18}H_{18}FN_7O_3$: C, 54.13; H, 4.54; N, 24.55. Found: C, 54.02; H, 4.51; N, 24.65.

***N*-[5-({2-[(Cyclopropylcarbonyl)amino][1,2,4]triazolo-[1,5-*a*]pyridin-6-yl}oxy)-2-fluorophenyl]-1,3-dimethyl-1*H*-pyrazole-5-carboxamide Hydrate (1·H_2O).** A 20 L glass vessel was charged with **11**·H_2O (890 g, 2.23 mol), pyridine (529 g, 6.69 mol), and DMAC (3.56 L). To this solution was slowly added cyclopropanecarbonyl chloride **12** (466 g, 4.46 mol) at 25−40 °C, and the reaction mixture was stirred at this temperature for 1 h. Then H_2O (780 mL) was slowly added to the reaction mixture at 30−40 °C. At this point, **1**·H_2O (2.23 g) was added as seeds, followed by dropwise addition of H_2O (1 L). To the mixture was slowly added 2M NaOH (2.67 L) to

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adjust pH to 6.0−8.0, maintaining the temperature below 40 °C. Then H_2O (5.34 L) was added at 40−45 °C, and the resulting slurry was stirred for 1 h at this temperature. After cooling to 20−30 °C, the slurry was stirred for 2 h and then filtered. The wet cake was washed with H_2O (4.45 L) and dried *in vacuo* at 50 °C to afford **1**·H_2O as a white solid (1.04 kg, 99%). HPLC purity: 99.2 area % (HPLC condition A); Mp 128−129 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.95 (br d, J = 5.1 Hz, 4H), 1.98 (br s, 1H), 2.19 (s, 3H), 3.34 (s, 2H, H_2O), 3.98 (s, 3H), 6.84 (s, 1H), 6.97 (ddd, J = 9.0, 3.6, 3.6 Hz, 1H), 7.30−7.37 (m, 2H), 7.54 (dd, J = 9.6, 2.3 Hz, 1H), 7.75 (dd, J = 10.1, 0.5 Hz, 1H), 8.89 (d, J = 1.7 Hz, 1H), 10.0 (s, 1H), 11.2 (br s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 8.0 (t, 2C), 13.2 (q), 14.1 (d), 38.8 (q), 107.9 (d), 115.3 (d), 115.6 (dd like), 115.9 (dd, $^3J_{CF}$ = 7.3 Hz), 117.0 (dd, $^2J_{CF}$ = 22.1 Hz), 120.8 (d), 125.8 (s), 126.2 (sd, $^2J_{CF}$ = 14.2 Hz), 135.1 (d), 145.3 (s), 145.7 (s), 147.3 (s), 151.8 (sd, $^1J_{CF}$ = 243.2 Hz), 153.2 (s), 158.2 (s), 159.1 (s), 171.4 (s); IR (ATR); 3434, 3297, 3262, 3089, 3016, 1718, 1654, 1619, 1570, 1550, 1509, 1490, 1426, 1398, 1369, 1314, 1299, 1286, 1273, 1252, 1185, 1155, 1133, 1116, 1049, 1035, 1014, 970, 949, 886, 806, 786, 733, 689, 657, 592, 531, 511, 457, 443, 412 cm^{-1}; MS (ESI): m/z 450 $[M + H]^+$ for anhydrate; Anal. Calcd for $C_{22}H_{22}FN_7O_4$: C, 56.53; H, 4.74; F, 4.06; N, 20.97. Found: C, 56.48; H, 4.71; F, 4.00; N, 21.01.

Recrystallization of 1. A 20 L glass vessel was charged with **1**·H_2O (750 g, 1.60 mol), EtOH (12.2 L), and H_2O (1.35 L). The mixture was heated to 65−75 °C and stirred until **1**·H_2O completely dissolved into the solvent. Then the solution was filtered through 0.45 μm filter, followed by washing with EtOH/H_2O (9:1, 1.5 L). The combined filtrate was heated to 65−75 °C and then cooled to 50−55 °C. At this point, seeds (form A, 1.50 g) were added, and the slurry was aged for 1 h at this temperature. The mixture was heated to 60 °C again and stirred for 15 min. The mixture was cooled to 45−55 °C and stirred for 4 h, and then cooled to room temperature and stirred for 12 h. The slurry was heated to 45−55 °C again and stirred for 3 h, and then cooled to room temperature and filtered. The wet cake was washed with EtOH/H_2O (9:1, 1.5 L) and dried *in vacuo* at 50 °C to afford **1** as a white solid (553 g, 77%, form A, residual EtOH: 1600 ppm). HPLC purity: 99.6 area % (HPLC condition A); Mp 217 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.95 (br d, J = 5.1 Hz, 4H), 1.98 (br s, 1H), 2.19 (s, 3H), 3.98 (s, 3H), 6.84 (s, 1H), 6.97 (ddd, J = 9.0, 3.6, 3.6 Hz, 1H), 7.30−7.37 (m, 2H), 7.54 (dd, J = 9.6, 2.3 Hz, 1H), 7.75 (dd, J = 10.1, 0.5 Hz, 1H), 8.89 (d, J = 1.7 Hz, 1H), 10.0 (s, 1H), 11.2 (br s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 8.0 (t, 2C), 13.2 (q), 14.1 (d), 38.8 (q), 107.9 (d), 115.3 (d), 115.6 (dd), 115.9 (dd, $^3J_{CF}$ = 7.3 Hz), 117.0 (dd, $^2J_{CF}$ = 22.1 Hz), 120.8 (d), 125.8 (s), 126.2 (sd, $^2J_{CF}$ = 14.2 Hz), 135.1 (d), 145.3 (s), 145.7 (s), 147.3 (s), 151.8 (sd, $^1J_{CF}$ = 243.2 Hz), 153.2 (s), 158.2 (s), 159.1 (s), 171.4 (s); IR (ATR); 3298, 3247, 3087, 3028, 1660, 1621, 1550, 1538, 1510, 1492, 1470, 1432, 1408, 1376, 1330, 1309, 1285, 1273, 1243, 1189, 1172, 1116, 1086, 1048, 1035, 1015, 980, 965, 949, 900, 881, 852, 831, 820, 807, 786, 764, 756, 746, 714, 683, 658, 642, 601, 589, 536, 507, 459 cm^{-1}; MS (ESI): m/z 450 $[M + H]^+$; Anal. Calcd for $C_{22}H_{20}FN_7O_3$: C, 58.79; H, 4.49; F, 4.23; N, 21.82. Found: C, 58.69; H, 4.46; F, 4.12; N, 21.84.

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Notes

The authors declare no competing financial interest.

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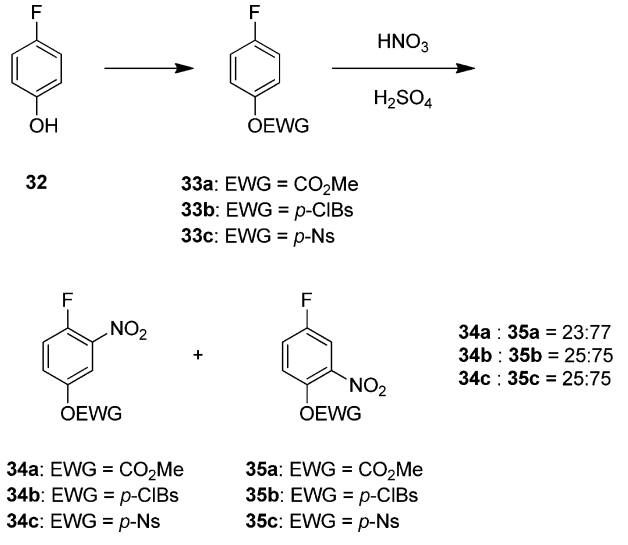
(8) **20** was synthesized from **18** according to the literature with a modification . Hennequin, L. F.; Thomas, A. P.; Johnstone, C.; Stokes, E. S. E.; Plé, P. A.; Lohmann, J.-J. M.; Ogilvie, D. J.; Dukes, M.; Wedge, S. R.; Curwen, J. O.; Kendrew, J.; Brempt, C. L. *J. Med. Chem.* **1999**, *42*, 5369−5389.

(9) The chlorine atom is essential for this regioselective nitration. Although we tried regioselective nitration of **33** by introducing a strong electron-withdrawing group on the hydroxyl group, an approximately 25:75 mixture of **34** and **35** was obtained.



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(11) The structure of **24** was confirmed by ^{1}H NMR, LC/MS, and comparison with a commercially available authentic sample (purchased from Alfa Aesar).
(12) In HPLC analysis, these byproducts were observed as only small peaks. Since some of these byproducts are assumed to have only weak UV absorption, the exact amount of byproducts was difficult to determine by HPLC analysis using a UV detector.
(13) The stability of **20** in MeOH in the presence or absence of NaOAc was investigated. When **20** and 1.1 equiv of NaOAc were dissolved in MeOH and stirred at 25 and 40 °C, approximately 8% and 30% of **20** was deprotected and converted to **21** per hour, respectively. On the contrary, in the absence of NaOAc, no deprotection was observed at 25 and 40 °C.
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(15) Recrystallization of this crude **6** from EtOAc/*n*-heptane (1:3) reduced the amount of **7b** less than 0.6% and gave **6** in 91% yield.
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(17) Although it was possible to obtain **1** as an anhydrate (form A) by using the seeds of form A for crystallization, a slurry of anhydrate (form A) in DMAC/H_2O required a long time for filtration. On the contrary, a slurry of monohydrate (**1**·H_2O) in DMAC/H_2O was easily filtered to give the product.
(18) Solubility of **1** in common solvents at 25 °C is as follows: EtOH, 0.28 wt %; acetone, 0.19 wt %; 2-butanone, 0.16 wt %; 2-propanol, 0.08 wt %; EtOAc, 0.07 wt %; MeOAc, 0.11 wt %.