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Graphical Abstract

Practical and scalable preparation of Minodronic acid and Zolpidem from 2-chloroimidazole[1,2-*a*]pyridines

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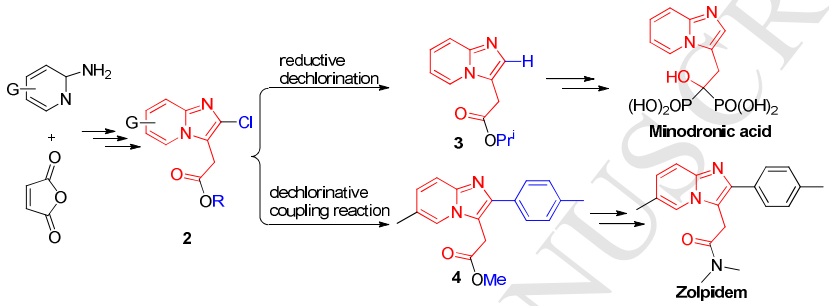

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ABSTRACT

Practical and scalable procedures for Minodronic acid and Zolpidem are developed with short reaction sequences from 2-aminopyridines and maleic anhydride, respectively. The new procedures avoid column chromatography for the purification in all synthetic steps. Key aspects of this development involve reductive hydrodechlorination and Suzuki coupling reaction of 2-chloroimidazole[1,2-*a*]pyridines, and their application towards synthesis of the two drugs is also addressed.

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1. Introduction

With an aging population and budget restrictions on national health insurers, those aging-related diseases increasingly impose a large economic burden on the individual and society, and the price of drugs has become a major challenge in today's world. There is still interest to develop innovative, simple and overall more cost-effective industrial processes for the preparation of the drugs[1], especially those related to the chronic and costly diseases.

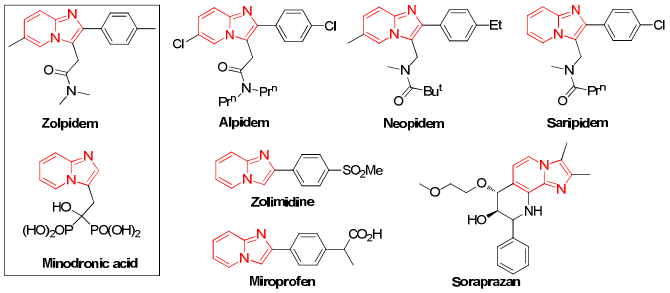


Figure 1. The selected drugs containing imidazo[1,2-*a*]pyridine.

Imidazo[1,2-*a*]pyridine, as one important nitrogen-containing heterocycle, is very prevalent in pharmaceuticals (Figure 1). Such heterocycle derivatives show a wide range of biological activities[2], and several marketed drugs contain this privileged scaffold. Among them, Minodronic acid[3] and Zolpidem[4] are clinically used in treatment of osteoporosis and insomnia, respectively, and have demonstrated great benefit to the patients.

Therefore, there is continuous interest in the development of new synthetic methods for this scaffold, and so far different synthetic strategies and various approaches have been achieved.[5] Despite great achievements, the current processes for both Minodronic acid[6] and Zolpidem[7] still require multi-step preparation, with the condensation of α-haloketone or its equivalents with 2-amino-pyridines as the key step for the preparation of the imidazo[1,2-*a*]pyridine scaffold. Meantime, in order to install the side chain on the parent core, some uneasily available staring materials or toxic reagents are required in subsequent multi-step transformations.[8a] Although one atom-economic approach was developed to reach both Zolpidem and Minodronic acid by V. Gevorgyan and us[8], the procedures still included the use of expensive reagents (such as proponynates), chromatography purification and difficult scale-up to some extent. Thus, developing a cost-efficient, scalable and diverse process for the two drugs is highly in demand.

Inspired by the common parent core of the two drugs, our novel, diverse and cost-efficient approach is proposed, as shown in Figure 2. Obviously, the key step will be reductive hydrodechlorination or coupling reaction of 2-chloroimidazo[1,2-*a*]pyridines (**2**), which can be easily obtained from 2-aminopyridines and cheap maleic anhydride, including amidation/cyclization[9], routine esterification and subsequent chlorinative aromatization of the resulting lactam upon treatment with $POCl_3$[10,12b,14a].

Although less reactive heteroaryl chlorides have been found to be workable in some metal-mediated hydrodechlorination reactions or cross-coupling reactions, they are still problematic substrates in some cases[11], and the reaction of heteroaryl chlorides is strongly dependent on the specific catalysts or the substrates.[12-14] Our initial literature survey showed very few reports for the two transformations with imidazo[1,2-*a*]pyridine chlorides except the iodides and triflates.[15] Recently, Chai and co-workers provided the almost same synthetic strategy for Minodronic acid, wherein the key step was Pd/C-catalyzed hydrodechlorination of **2** in the presence of Et_3N under H_2 atmosphere.[16a-b] However, this procedure appears to be tricky and difficult to reproduce (*vide infra*).[16c-d] Herein, we describe our results on reductive dechlorination and coupling reaction of 2-chloroimidazole[1,2-*a*]pyridines, as well as their application to practical and scalable synthesis of both Minodronic acid and Zolpidem in a simple and cost-efficient manner.

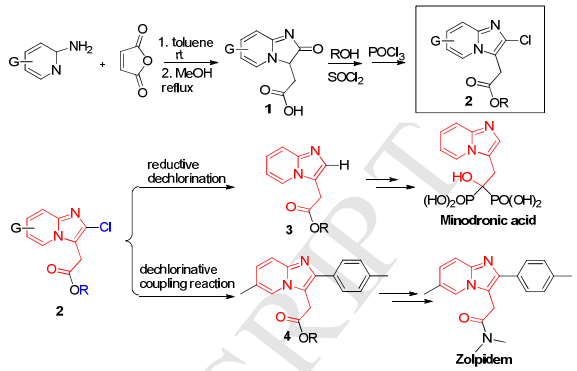


Figure 2. The diverse approach to reach both Zolpidem and Minohydronic acid.

2. Results and discussion

2.1. Hydrodechlorination of 2-chloroimidazole[1,2-a]pyridines

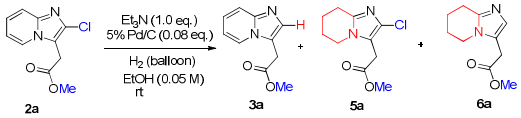
Starting from 2-aminopyridines (2.0 equiv.) and maleic anhydride, acylation was carried out in toluene （0.5-0.3 M）at rt for 2-4 h, and the resulting white precipitate underwent intramolecular Michael addition in refluxing MeOH for 0.5-1 h, giving the white precipitated acid (**1**) without any further purification (Figure 2).[9] Next, **1** was suspended in one kind of suitable alcohols except *t*-BuOH (reaction concentration: 0.5-0.3 M), and upon treating with $SOCl_2$ (2.0 equiv.) at rt for 4-5 h, the crude ester was obtained as a hydrochloride salt from the reaction solution after removing the solvent. After that, the crude salt was refluxed in $POCl_3$ (8.0 equiv.) for 2-4 h, and upon removal of $POCl_3$ under reduced pressure, the resulting black residue was carefully poured into crushed ice, neutralized and extracted with AcOEt, conveniently giving the crude 2-chloroimidazo[1,2-*a*]pyridines (**2**). The purified product for analysis could be obtained through simple recrystallization or column chromatography.

With a series of 2-chloroimidazo[1,2-*a*]pyridines in hand, we initially investigated reductive hydrodechlorination according to Chai's procedure[16a-b], and the results were shown in Table 1. To our surprise, Pd/C-catalyzed hydrodechlorination with H_2 gas gave the desired product **3a** in poor yield, with reduction of pyridine ring as the predominant side reaction. Tremendous efforts to optimize this transformation failed to suppress this overreduction, including solvent screening, pressure, additives, temperature, and Pd or $Pd(OH)_2/C$ (5%, 10%, or 99.5%) available from different commercial resources. The above results and some literatures[16c-d] implied this trick transformation was not easy to reproduce.

Considering both diversity and cost-efficiency, we then tested air- and moisture-stable (NHC)Pd(allyl)Cl complexes according to Nolan's method, which was reported to work well for both hydrodechlorination and cross-coupling reaction with aryl chlorides[17]. However, in the case of **2a**, all these catalysts did not give a promising performance in either hydrodechlorination or coupling reaction. Although organozinc species from **2a** might be used for both hydrodechlorination and Negishi coupling reaction,

the attempt to prepare this organozinc species was not fruitful.[18] Furthermore, screening free redical[19]-type and Ru[20]-, Ni[21]-, or Pd[12]-catalyzed hydrodechlorination methods did not afford acceptable results. As a consequence, we had to focus our attention on the tricky Pd-catalyzed hydrodechlorination with different hydride sources, and the results were shown in Table 2.

Table 1. Pd/C-catalyzed hydrodechlorination under H_2 gas



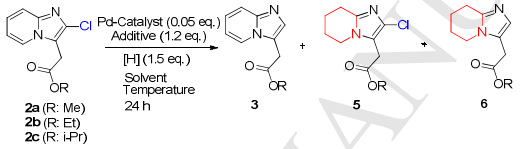
Entry	Time	2a	3a	5a	6a
1	6 h	65%	17%	5%	13%[a,b]
2	12 h	37%	29%	6%	28%
3	24 h	17%	29%	5%	49%
4	32 h	8%	15%	3%	74%
5	48 h	0%	0%	0%	100%

[a]The reaction was carried out with 1.0 mmol of purified **2a**, and monitored by ^{1}H NMR. The yields were obtained by ^{1}H NMR analysis of the crude reaction mixture. [b]The standard samples of **2a**-**6a** were obtained by column chromatography and determined by ^{1}H NMR and ESI-MS.

When 10% Pd/C was used as the catalyst in the hydrodechlorination of **2a**, HCO_2Na, as the hydride source, gave the similar result of H_2 (Entry 1,2). However, for the substrates with different ester groups, the conversion could be improved, along with a slightly increasing selectivity (Entry 3,4). Comparing with Pd/C (10%) and $Pd(OH)_2$ (10%), less active $Pd/CaCO_3$ (10%) afforded a promising selectivity albeit with a very low conversion (Entry 7, **3c**:13%; **6c**: 0%). Optimization of the reaction temperature demonstrated the hydrodechlorination should be carried out at 55 ^{o}C with an improved result (Entry 8, **3c**: 23%; **6c**: 4%).

Subsequently, a series of additives were screened to improve the conversion (Entry 9-15, 19), and K_2CO_3 was found to offer a significantly improved result (Entry 14, **3c**: 84%, **6c**: 0%). In addition to HCO_2Na, other hydride sources, such as HCO_2NH_4, HCO_2H and HCO_2K, were also tested in the transformation (Entry 16-18), and HCO_2K performed better than HCO_2Na, giving **3c** in 89% yield without generating **6c** (Entry 18). The above results indicated that the catalyst, the suitable basic medium, less hydrolyzable substrates and controllable hydride source were very important to reach a good and selective conversion.

Table 2. Optimization on the hydrodechlorination with 2-chloroimidazole[1,2-*a*]pyridines



entry	R	Catalyst	[H]	Additive	Solvent	Temp. (^{o}C)	Yield (%)[a] 2	3	5	6
1	Me	10% Pd/C	H_2 (balloon)		MeOH	rt	26	25	7	34
2	Me	10% Pd/C	HCO_2Na		MeOH	rt	24	35	8	30
3	Et	10% Pd/C	HCO_2Na		EtOH	rt	15	50	7	24
4	i-Pr	10% Pd/C	HCO_2Na		*i*-PrOH	rt	13	55	5	22
5	i-Pr	10% $Pd(OH)_2$	HCO_2Na		*i*-PrOH	rt	65	0	0	33
6	i-Pr	10% $Pd/BaSO_4$	HCO_2Na		*i*-PrOH	rt	85	9	0	0
7	i-Pr	10% $Pd/CaCO_3$	HCO_2Na		*i*-PrOH	rt	81	13	0	0
8	i-Pr	10% $Pd/CaCO_3$	HCO_2Na		i-PrOH	55	70	23	0	4
9	i-Pr	10% $Pd/CaCO_3$	HCO_2Na	KF	*i*-PrOH	rt	53	37	0	8
10	i-Pr	10% $Pd/CaCO_3$	HCO_2Na	KF	*i*-PrOH	55	0	82	3	11
11	i-Pr	10% $Pd/CaCO_3$	HCO_2Na	KF	*i*-PrOH	65	0	59	11	15
12	i-Pr	10% $Pd/CaCO_3$	HCO_2Na	Cs_2CO_3.	*i*-PrOH	55	0	38	10	46
13	i-Pr	10% $Pd/CaCO_3$	HCO_2Na	Na_2CO_3.	*i*-PrOH	55	27	66	0	0
14	i-Pr	10% $Pd/CaCO_3$	HCO_2Na	K_2CO_3.	*i*-PrOH	55	8	84	0	0
15	i-Pr	10% $Pd/CaCO_3$	HCO_2Na	Et_3N.	*i*-PrOH	55	36	35	0	18
16	i-Pr	10% $Pd/CaCO_3$	HCO_2NH_4	K_2CO_3.	*i*-PrOH	55	15	33	16	35
17	i-Pr	10% $Pd/CaCO_3$	HCOOH	K_2CO_3.	*i*-PrOH	55	18	64	0	15
18	i-Pr	10% $Pd/CaCO_3$	HCO_2K	K_2CO_3.	*i*-PrOH	55	3	89	0	0
19	i-Pr	10% $Pd/CaCO_3$	HCO_2K	AcOK	*i*-PrOH	55	40	29	0	24

[a]The reaction was carried out with 1.0 mmol of the purified sample of **2**. The yields were obtained by ^{1}H NMR analysis of the crude reaction mixture with 1,3,5-trimethoxybenzene as internal reference standard.

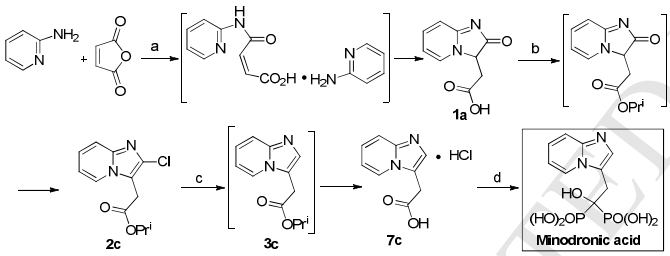
In order to better evaluate the substrate scope of this novel method, a series of 2-chloroimidazole[1,2-*a*]pyridines were subjected to the optimal conditions, and the results were shown in Table 3. We found many functional groups, such as F, Me,

OMe, $CONH_2$, $CONMe_2$ and CO_2R, were tolerated and afforded the desired products in rational yields except CO_2H. Notably, in contrast to the *i*-propyl ester (**2c**), the methyl or ethyl ester (**2a**-**2b**, **2g**-**2j**) had to be carried out in a suitable reagent-grade alcohol to avoid interference of ester exchange, affording the desirable products in mediate yields. In these cases, we also found the formation of non-reactive 2-chloro acids through ester hydrolysis when the reagent grade methanol or ethanol was used. Interestingly, in the case of **2k**, the defluorinated product (**3c**) could be isolated in 30% yield together with the dechlorinated product **3k** in 58% yield. To our best knowledge, this is one rare example demonstrating the cleavage of C-F bond of fluoro imidazole[1,2-*a*]pyridines through Pd-catalyzed hydrogenation.

2.2 Process optimization of Minodronic acid

Having identified the optimal conditions for the key hydrodechlorination, we pursued its practical application in our designed process for Minodronic acid, as shown in Scheme 1.

In the first step, **1a** was conveniently prepared according to the above mentioned procedure[9] (more than 0.20 mmol-scale, 5 runs) with no need of further purification, and the average yield was 62% with a purity of 97%. In the second step, the esterification of **1a** was also easy to conduct by treating the suspension of **1a** in *i*-PrOH (0.3 M) with $SOCl_2$ (5.0 equiv.), and upon the removal of the solvent under reduced pressure, the crude ester from the reaction solution could be used in the subsequent step without further purification. After the crude ester was refluxed in $POCl_3$, the resulting black solution was carefully poured into crushed ice, neutralized, extracted, dried, filtrated and evaporated under reduced pressure, affording the crude semisolid **2c** in 72% yield with a purity of 92%.

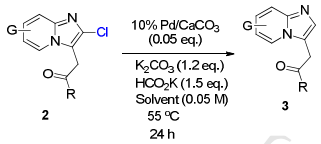


Scheme 1. Synthesis of Minodronic acid. *Reagents and conditions*: a) i. maleic anhydride (2.0 eq.), toluene, rt, 2 h; ii. MeOH, reflux, 0.5 h; yield: 62%, purity: 97% (5 runs); b) i. *i*-PrOH, $SOCl_2$ (5.0 eq.), reflux, 5 h; ii. $POCl_3$ (8.0 eq.), reflux, 5 h; yield: 72%, purity: 92%; c) i. $Pd/CaCO_3$ (10 mol%), HCOOK (1.5 eq.), K_2CO_3 (1.2 eq.), *i*-PrOH, 55 °C, 20 h; ii. 36% HCl (conc.); yield: 69%, purity: 97%; d) i. H_3PO_3 (2.2 eq), PCl_3 (3.3 eq.), chlorobenzene, 90 °C, overnight; 36% HCl (conc.), reflux, 4 h; yield: 66%, purity: 97%.

In the key third step, **2c** was subjected to the optimal conditions for hydrodechlorination in the reagent grade *i*-PrOH with no trouble of ester hydrolysis. As expected, the scale-up was smooth albeit with a little sacrifice of conversion (83-85%) due to poor stirring efficiency. In order to avoid the interference from the residual **2c**, the amount of Pd supported on $CaCO_3$ was increased to 15 mol% for full conversion of this reaction. After filtration and removal of solvent, the crude **3c** was obtained as syrup solid. Due to the solidity of the corresponding acid (**3d**), further ester hydrolysis was carried out in a refluxing concentrated HCl aqueous solution (36%), and after complete hydrolysis, filtration and simple recrystallization in acetone could provide a white solid (**7c,**), as hydrogen chloride salt of **3d**, in 69% yield with a purity of 97%.

In the final step, according to the standard procedure[6], **7c** could be transformed into Minhydronic acid in 66% yield with a purity of 97%. In summary, starting from 2-aminopyridine and maleic anhydride, Minhydronic acid was prepared via one short reaction sequence with the overall yield of about 20% in a simple and cost-efficient manner.

Table 3. The Pd-catalyzed hydrodechlorination with 2-chloroimidazole[1,2-*a*]pyridines



2	R	G	Solvent	Yield of 3[a,b]
2a	OMe	H	MeOH	44%[c]
2b	OEt	H	EtOH	63%[c]
2c	OPr^i	H	i-PrOH	85%
2d	OH	H	i-PrOH	ND[d]
2e	NH_2	H	i-PrOH	63%
2f	NMe_2	H	MeOH	71%
2g	OMe	5-Me	MeOH	49%
2h	OMe	4-Me	MeOH	53%
2i	OMe	5-F	MeOH	31%[c]
2j	OMe	5-OMe	MeOH	42%
2k	OPr^i	5-F	i-PrOH	58%[e]
2l	OPr^i	5-OMe	i-PrOH	83%

[a]The reaction was carried out with 1.0 mmol of the purified sample of **2**. [b]The products were isolated through column chromatography. [c]In case of **2a** or **2b**, acid **2d** was formed besides the desirable product. [d]Not determined. [e]The further defluorinated side product (**3c**) was isolated in 30% yield as well.

2.3. Coupling reaction of 2-chloroimidazole[1,2-a]pyridines

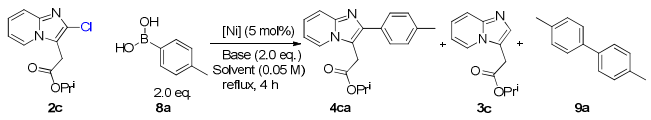
From the aspect of simple, environment-friendly and cost-efficient process, Negishi or Suzuki coupling reaction might be an attractive approach to Zolpidem from 2-choroimidazo[1,2-*a*]pyridines **2**. However, the organozinc species of 2-choroimidazo[1,2-*a*]pyridines as one of Negishi coupling partners could not be obtained as above mentioned. In addition, the initial effort failed to couple **2c** with PhZnCl under the routine Negishi coupling conditions. As a result, we focused on Suzuki coupling reaction of **2c** and 4-methylphenylboronic acid (**8a**). After screening different Pd- or Ni-based complexes reported to work well for aryl chloride substrates[14,15], only $NiCl_2(dppe)$[14c] showed promising performance. Therefore, we sought to optimize the Ni-catalyzed coupling condition with **2c** and **8a**, and the results were depicted in Table 4.

We found $NiCl_2(dppf)$ could efficiently catalyze the coupling reaction, and its usage could be reduced to 5 mmol% of **2c** without a loss of yield (**4ca**: 93%, Table 4, Entry 4). An excellent yield required using 2.5 equivalents of **8a** due to production of homo-coupling compound **9a**, otherwise, **2c** could not be completely consumed and thus led to lower yield for hydrodechlorinated product (**3c**). The optimal usage of K_3PO_4 was 2.0 equivalents, and meanwhile, toluene was the best solvent. However, decreasing the temperature resulted in a lower yield.

In order to evaluate the substrate scope of this novel method, a variety of 2-chloroimidazole[1,2-*a*]pyridines (**2**) and arylboronic acids (**8**) were subjected to the optimal conditions, and the results were shown in Table 5. Many functional groups, such as F, Me, OMe, SMe and $CONMe_2$ were tolerated and the reaction

afforded the desired products in satisfying yields, especially with **2g** and **8a** (Table 5, Entry 5, 84% isolated yield). However, for those arylboronic acids bearing the strong electron-withdrawing group such as CF_3 and NO_2, the catalytic system did not work well (see Entry 17-18).

Table 4. Optimization on Ni-catalyzed Suzuki coupling reaction with 2-chloroimidazole[1,2-*a*]pyridines



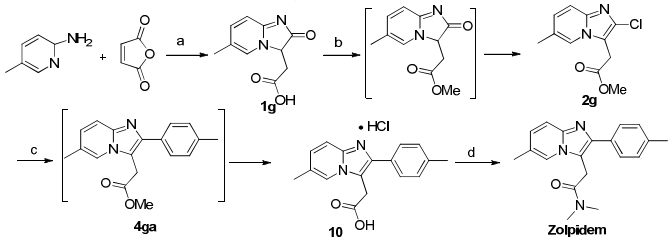
Entry	[Ni]	Base	Solvent	Yield[a,b]
1	$NiCl_2$(dppe)	K_3PO_4	toluene	43%
2	$NiCl_2$(dppp)	K_3PO_4	toluene	33%
3	$NiCl_2$(dppf)	K_3PO_4	toluene	93%[c]
4	$NiCl_2(PCy_3)_2$	K_3PO_4	toluene	38%
5	$NiCl_2(PPh_3)_2$	K_3PO_4	toluene	22%
6	$NiCl_2$(DavePhos)	K_3PO_4	toluene	15%
7	$NiCl_2$(XantPhos)	K_3PO_4	toluene	11%
8	$NiCl_2$(dppf)		toluene	0%
9	$NiCl_2$(dppf)	*t*-BuOK	toluene	0%
10	$NiCl_2$(dppf)	K_2CO_3	toluene	40%
11	$NiCl_2$(dppf)	Cs_2CO_3	toluene	10%
12	$NiCl_2$(dppf)	CsF	toluene	60%
13	$NiCl_2$(dppf)	K_3PO_4	dioxane	16%
5	$NiCl_2$(dppf)	K_3PO_4	i-PrOH	21%

[a]The reaction was carried out with 1.0 mmol of purified **2c**. [b]The yields were obtained by ^{1}H NMR analysis of the crude reaction mixture with 1,3,5-trimethoxybenzene as internal reference standard. [c]The yield was obtained with 2.5 equivalents of **8a**, compared with the yield of 83% with 2.0 equivalents of **8a**.

2.4. Process optimization of Zolpidem

Having obtained the optimal conditions for the key Suzuki coupling reaction of 2-chloroimidazole[1,2-*a*]pyridines, we pursued its practical application in our designed process for Zolpidem, as shown in Scheme 2.

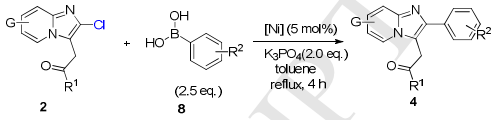
In the novel process, **2g** was conveniently prepared via 2 steps using the above mentioned procedure, and the average yield (5 runs) was 48% with a purity of 96%. In the key third step, **2g** was subjected to the optimal conditions for the coupling reaction. As expected, the scale-up was smooth, and after routine work-up (including quenched with a saturated aqueous $NaHCO_3$ solution, extracted with AcOEt, washed with water, dried by Na_2SO_4, filtration and evaporation under reduced pressure), the crude **4ga** was obtained as a sticky solid.



Scheme 2. Synthesis of Zolpidem. *Reagents and conditions*: a) i. maleic anhydride (2.0 eq.), toluene, rt, 2 h; ii. MeOH, reflux, 0.5 h; yield: 48%, purity: 97% (5 runs); b) i. MeOH, $SOCl_2$ (5.0 eq.), reflux, 4 h; ii. $POCl_3$ (8.0 eq.), reflux, 5 h; yield: 87%, purity: 96%; c) i. $NiCl_2$(dppf) (5 mol%), 4-Me-$C_6H_4B(OH)_2$ (2.5 eq.), K_3PO_4 (2.0 eq.), toluene, reflux, 4 h; ii. 36% HCl (conc.); yield: 71%, purity: 99%; d) PCl_5, CH_2Cl_2, Me_2NH (gas), rt; yield: 92%, purity: 98%.

Next, further ester hydrolysis of **4ga** was carried out in a concentrated HCl aqueous solution. After filtration and concentration, simple recrystallization in acetone could provide **10** as a white solid in an average yield of 71% with a purity of 99%.

Table 5. The Ni-catalyzed coupling reaction with 2-chloroimidazole[1,2-*a*]pyridines and arylboronic acids



Entry	G	R^1	R^2	Yield of 4[a,b]
1	H	OMe	4-Me	87%[c]
2	H	OEt	4-Me	86%
3	H	OPr^i	4-Me	90%
4	H	NMe_2	4-Me	81%
5	5-Me	OMe	4-Me	84%
6	6-Me	OMe	4-Me	81%
7	5-OMe	OMe	4-Me	78%
8	5-F	OMe	4-Me	88%
9	H	OMe	H	81%
10	H	OMe	4-OMe	81%
11	H	OMe	3-OMe	84%
12	H	OMe	4-Et	85%
13	H	OMe	4-Ph	71%
14	H	OMe	4-F	80%
15	H	OMe	2-Me	66%
16	H	OMe	4-SMe	77%
17	H	OMe	3-NO_2	Trace[c]
18	H	OMe	4-CF_3	Trace[c]

[a]The reaction was carried out with 1.0 mmol of the purified sample of **2**. [b]The products were isolated through column chromatography. [c]The desired product was not isolated.

Finally, according to the standard procedure[7], Zolpidem was prepared from **10** by treating the corresponding acid chloride with Me_2NH in an average yield of 92% with a purity of 98%. In summary, Zolpidem could be prepared via one short reaction sequence with the overall yield of about 28% in a simple and cost-efficient manner.

3. Conclusion

Inspired by the common parent core of Minodronic acid and Zolpidem, one novel, diverse and cost-efficient approach has been developed, and the key aspects of this development involve careful control of reductive hydrodechlorination or Suzuki coupling reaction of 2-chloroimidazole[1,2-*a*]pyridines.

As for the reductive hydrodechlorination, the catalyst (10% $Pd/CaCO_3$), suitable basic medium (K_2CO_3 in toluene) and controllable hydride source (HCO_2K) proved to be very important factors to achieve good and selective conversion of 2-chloroimidazole[1,2-*a*]pyridines. Additionally, in the Suzuki

coupling reaction, the catalyst ($NiCl_2$(dppf)), suitable basic medium (K_3PO_4 in toluene) and aryl boric acids without electron-withdrawing substituents ($ArB(OH)_2$) were key factors for this good transformation.

Based on the above results, efficient and scalable procedures for Minodronic acid and Zolpidem have been developed from the corresponding 2-aminopyridines and maleic anhydride, respectively. Our new methods involve using cheap reagents, simple operations and short synthetic routes, thus they are cost-efficient and easy to reproduce in large scales, which may be attractive to the industry.

4. Experimental

4.1. Chemistry

General. All chemicals were purchased from Adamas, SCRC, Alfa, Aesar, and used without further purification. Deuterated solvents were purchased from Cambridge Isotope Laboratories. All non-aqueous reactions were carried out using oven-dried (110 ^oC) or heat gun dried glassware under a positive pressure of anhydrous argon unless otherwise noted. THF and dichloromethane were purified by distillation and dried by passage over activated 4 Å molecular sieves under an argon atmosphere. ^1H, ^{13}C and ^{19}F NMR data were recorded on a Varian Model Mercury 400 MHz or Bruker 600 MHz spectrometers using solvent signals ($CDCl_3$: δ_H 7.26/δ_C 77.0; $CFCl_3$: δ_F 0) as references. ^1H NMR chemical shifts (δ) are given in ppm (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet) downfield from Me_4Si. LC-MS data were recorded on an Agilent 1260/6120 quadrupole LC/MS spectrometer, and high resolution mass spectra obtained on an AB SCIEX Triple TOF™ 5600+ mass spectrometer, IR spectra data were recorded on an Nicolet AVATAR 360 FT-IR spectrophotometer, Optical rotations were recorded on a Rudolf Autopol IV automatic polarimeter. HPLC Method for Minodronic acid: Agilent 1260 infinity series Chemostation; Agilent 5 μm C18, 250 × 4.6 mm column; mobile phase A (70%), sodium pyrophosphate aqueous (0.03 mol/L) including tetrabutylammonium bromide (adjusted pH to 7.5 with H_3PO_4); mobile phase B (30%), MeOH; flow rate = 1 mL/min; column temperature: 30 °C; detector temperature: 25 °C; detection wavelength =280 nm; injection volume = 10.0 μL. HPLC Method for Zolpidem: Agilent 1260 infinity series Chemostation; Agilent 5 μm C18, 250 × 4.6 mm column; mobile phase (18/23/59): acetonitrile, MeOH and 0.05 mol/L aqueous H_3PO_4, (adjusted pH to 7.5 with Et_3N); flow rate = 1 mL/min; column temperature: 30 °C; detector temperature: 25 °C; detection wavelength =254 nm; injection volume = 10.0 μL.

*4.1.1. General procedure for the synthesis of compounds (**3**)*

To a solution of compound **2** (2.00 mmol, 1.0 equiv) and 10% Pd/$CaCO_3$ catalyst (0.10 mmol, 0.05 equiv.) in anhydrous ROH, such as methanol, ethanol and *iso*-propanol (5 mL), was added K_2CO_3 (2.40 mmol, 1.2 equiv) and HCO_2K (3.00 mmol, 1.5 equiv) under Ar, both of which should be pre-dried *in vacuo* for 0.5 h. The reaction vessel was then heated at 55 °C in oil for 24 h. After the reaction was completed, the solvent was removed the under reduced pressure, then added with water (20 mL), and extracted with ethyl acetate (20 mL × 3). The combined organic phase was washed with brine (10 mL), dried (Na_2SO_4), filtrated and concentrated. Purification by flash chromatography with a micture of Petroleum Ether (PE) and EtOAc as eluent could give the compound **3**.

For a representative example, the spectra data of **3a** was followed: white solid, R_f = 0.21 (PE/EtOAc = 1/3), Mp 110~113 ^oC. ^1H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, J = 6.9 Hz, 1H), 7.63 (d, J = 9.1 Hz, 1H), 7.55 (s, 1H), 7.20 (m, 1H), 6.85 (m, 1H), 3.95 (s, 2H), 3.71 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.5, 145.9, 133.2, 123.9, 123.5, 117.9, 116.5, 112.3, 52.4, 30.2. HRMS-ESI (*m/z*): $[M + H]^+$ Calcd. For $C_{10}H_{11}N_2O_2$: 191.0815, found: 191.0816.

In the case of Pd/C-catalyzed dechlorinative hydrogenation, two side products (**5a** and **6a**) could be isolated. For compound **5a**, faint yellow liquid, R_f = 0.45 (EtOAc/MeOH = 6/1). ^1H NMR (400 MHz, $CDCl_3$) δ 3.80 (t, J = 5.3 Hz, 2H), 3.71 (s, 3H), 3.59 (s, 2H), 2.81 (t, J = 6.0 Hz, 2H), 1.97 (m, 2H), 1.89 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ169.8, 143.7, 127.5, 117.2, 52.4, 43.3, 28.7, 24.5, 22.5, 20.3. HRMS-ESI (*m/z*): $[M + H]^+$ Calcd. For $C_{10}H_{14}ClN_2O_2$: 229.0738, found: 229.0740. For compound **6a**, faint yellow liquid, R_f = 0.21 (EtOAc/MeOH = 6/1). ^1H NMR (400 MHz, $CDCl_3$) δ 6.85 (s, 1H), 3.82 (t, J = 5.6 Hz, 2H), 3.71 (s, 3H), 3.58 (s, 2H), 2.86 (t, J = 5.8 Hz, 2H), 1.99-1.97 (m, 2H), 1.90-1.88 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ170.3, 145.4, 126.5, 122.4, 52.1, 42.6, 29.7, 24.7, 22.7, 20.3. HRMS-ESI (*m/z*): $[M + H]^+$ Calcd. For $C_{10}H_{15}N_2O_2$: 195.1128, found: 195.1130.

*4.1.2. General procedure for the synthesis of compounds (**4**)*

An anhydrous toluene (10 mL) solution of compound **2** (1.00 mmol, 1.0 equiv), K_3PO_4 (2.00 mmol, 2.0 equiv), $NiCl_2$(dppf) (0.05 mmol, 0.05 equiv) and arylboronic acid (2.50 mmol, 2.5 equiv) was transferred into a reaction bottle. The reaction mixture was then refluxed for 4–6 h under Ar. After the mixture was cooled to 20 °C, the reaction was quenched with a saturated sodium bicarbonate solution (20 mL). The organic and aqueous layers were separated, and the latter was extracted with ethyl acetate (20 × 3 mL). The combined organic layers were washed with brine (10 mL) and dried (Na_2SO_4), and then the filtrate was concentrated *in vacuo*. The residue was purified by flash column chromatography with PE and EtOAc as eluent to give compound **4**.

For a representative example, the spectra data of **4ca** was followed: white solid, R_f = 0.26 (PE/EtOAc = 3/2), Mp 158~159 ^oC. ^1H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, J = 6.9 Hz, 1H), 7.67-7.74 (m, 3H), 7.28 (d, J = 7.8 Hz, 2H), 7.25 – 7.19 (m, 1H), 6.89 – 6.84 (m, 1H), 5.07 (h, J = 6.2 Hz, 1H), 3.98 (s, 2H), 2.41 (s, 3H), 1.24 (d, J = 6.4 Hz, 6H) ^{13}C NMR (150 MHz, $CDCl_3$) δ168.9, 144.7, 137.8, 130.8, 129.3, 128.5, 128.4, 124.6, 123.7, 117.3, 113.0, 112.4, 69.3, 31.0, 21.7, 21.2. HRMS-ESI (*m/z*): $[M + H]^+$ Calcd. For $C_{19}H_{21}N_2O_2$: 309.1598, found: 309.1609.

Besides, we also isolated side product. For compound **9a**, yellow solid, R_f = 0.34 (PE/EtOAc = 5/1), Mp 118~121 ^oC. ^1H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, J = 7.2 Hz, 4H), 7.23 (d, J = 7.3 Hz, 4H), 2.38 (s, 6H). ESI-MS (*m/z*): $[M+H]^+$ 183.1. The spectrum was consisted with literature[22].

4.1.3. A scalable process for the synthesis of Minodronic acid

To a solution of 2-aminopyridine (94.1 g, 1.00 mol, 2.0 equiv) in toluene (1000 mL) was slowly added a solution of maleic anhydride (49.3 g, 0.50 mol, 1.0 equiv) in toluene (500 mL) at 0 °C over 0.5 h. The mixture continued to stir for 2 h at rt. The white precipitated salt was filtered and washed with ether (300 mL). The salt was dissolved in methanol (1500 mL) and refluxed for 30 min. After cooled to rt, the resulting white solid was filtered, dried to give **1a** (59.5 g, yield: 62%, purity by HPLC: 97%). For the spectra data of the analytic sample of **1a**: a white solid, Mp 221~223 ^oC. ^1H NMR (400 MHz, D_2O) δ 8.53 (d, J = 6.5 Hz, 1H), 8.30 (d, J = 8.8 Hz, 1H), 7.60 – 7.41 (m, 2H), 3.31 (s, 2H). ^{13}C NMR (150 MHz, D_2O) δ 176.9, 176.2, 155.5, 149.0,

138.9, 121.5, 113.4, 64.9 (t, J = 22.5 Hz), 38.6. HRMS-ESI (*m/z*): $[M + H]^+$ Calcd. For $C_9H_9N_2O_3$: 193.0608, found: 193.0606.

To a stirring suspension of **1a** (59.5 g, 0.30 mol, 1.0 equiv) in *iso*-propanol (1200 mL) was slowly added $SOCl_2$ (150 mL, 1.50 mol, 5.0 equiv) at 0 °C over 0.5 h. The mixture continued to stir until the solid disappeared and the solution became transparent. Removal of the solvent under vacuum gave a white solid, and then the crude product was refluxed in $POCl_3$ (228 mL, 2.40 mol, 8.0 equiv) for 4 h. The black sticky liquid was afforded after removal of $POCl_3$ under reduced pressure, and the residue was carefully poured into the crashed ice, neutralized with a saturated Na_2CO_3 solution, and extracted with CH_2Cl_2 (600 mL × 3). The organic phase was washed with H_2O (600 mL), brine (300 mL), dried (Na_2SO_4), filtrated and concentrated to obtain **2c** (57.9 g, yield: 72%, purity by HPLC: 92%). For the spectra data of the analytic sample of **2c**: a white solid, Mp 112~114 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, J = 6.9 Hz, 1H), 7.55 (d, J = 9.0 Hz, 1H), 7.26 – 7.21 (m, 1H), 6.89 (m, 1H), 5.02 (h, J = 6.4 Hz, 1H), 3.92 (s, 2H), 1.22 (d, J = 6.4 Hz, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.0, 143.5, 135.1, 124.9, 123.6, 117.2, 112.8, 112.3, 69.4, 29.7, 21.7. HRMS-ESI (*m/z*): $[M + H]^+$ Calcd. For $C_{12}H_{14}ClN_2O_2$: 253.0738, found: 253.0750.

To a solution of compound **2c** (57.9 g, 0.20 mol, 1.0 equiv) and 10% Pd/$CaCO_3$ catalyst (31.8 g, 30.0 mmol, 0.15 equiv) in *iso*-propanol (500 mL) was added pre-dried K_2CO_3 (33.2 g, 0.24 mol, 1.2 equiv) and HCO_2K (25.2 g, 0.30 mol, 1.5 equiv). The reaction was purged with argon and heated at 55°C for 20 h. After the reaction was completed, the solvent was removed under vacuum, added with water (500 mL), and extracted with ethyl acetate (500 mL × 3). The organic phase was washed with brine (500 mL), dried (Na_2SO_4), filtrated and concentrated. The residue was diluted with 36% HCl (500 ml) and heated at 45°C for 5 h. After removal of the solvent under vacuum, the residue was mixed with acetone (300 mL) for 5 h at rt to give a white solid **7c** (29.3 g, yield: 69%, purity by HPLC: 97%). For the spectra data of the analytic sample of **7c**: a white solid, Mp 253~255 °C. ^{1}H NMR (400 MHz, D_2O) δ 8.38 (d, J = 6.8 Hz, 1H), 7.91 – 7.77 (m, 2H), 7.69 (s, 1H), 7.40 (d, J = 3.9 Hz, 1H), 3.93 (s, 2H). The spectrum was consisted with literature[6a]. HRMS-ESI (*m/z*): $[M + H]^+$ Calcd. For $C_9H_9N_2O_2$: 177.0659, found: 177.0662.

After addition of **7c** (29.3 g, 138 mmol, 1.0 equiv), H_3PO_3 (24.6 g, 304 mmol, 2.2 equiv) and chlorobenzene (300 mL) into reaction bottle, the mixture was heated to 100 °C for 0.5 h, then cooled to 80 °C, added dropwise with PCl_3 (39.7 mL, 0.50 mol, 3.3 equiv) in a slow speed and continued to stir at 90 °C for overnight. After removal of chlorobenzene under vacuum, 6 M HCl (600 mL) was added into the residue and refluxed for 4 h. The mixture was cooled to 80 °C and mixed with 3.0 g active carbon for 0.5 h. After filtration to remove active carbon, concentration, the residue was recrystallized in methanol (300 mL) to obtain a white solid of Minodronic acid (29.4 g, yield: 66%, purity by HPLC: 97%). For the spectra data of the analytic sample of Minodronic acid: a white solid, Mp 223~225 °C. ^{1}H NMR (400 MHz, D_2O) δ 8.59 (d, J = 6.6 Hz, 1H), 7.45 (s, 1H), 7.38 (d, J = 9.0 Hz, 1H), 7.18 (t, J = 7.9 Hz, 1H), 6.82 (t, J = 6.7 Hz, 1H), 3.53 (t, J = 11.7 Hz, 2H). The spectrum was consisted with literature[6a]. HRMS-ESI (*m/z*): $[M + H]^+$ Calcd. For $C_9H_{13}N_2O_7P_2$: 323.0193, found: 323.0188.

4.1.4. A scalable process for the synthesis of Zolpidem

To a solution of 5-methyl-2-aminopyridine (108 g, 1.00 mol, 2.0 equiv) in toluene (1000 mL) was slowly added a solution of maleic anhydride (49.3 g, 0.50 mol, 1.0 equiv) in toluene (500 mL) at 0 °C over 0.5 h. The mixture was stirred for 2.5 h at rt. The precipitated salt was filtered and washed with ether (300 mL). The salt was dissolved in methanol (1000 mL) and refluxed for 30 min to produce a white solid. After filtration and drying, the solid was recrystallized from 70 % ethanol (500 mL) to give **1g** (49.5 g, yield: 48%, purity by HPLC: 97%). For the spectra data of the analytic sample of **1g**: a white solid, Mp 228~231°C. ^{1}H NMR (400 MHz, D_2O) δ 8.37 (s, 1H), 8.16 (d, J = 13.4 Hz, 1H), 7.42 (d, J = 7.8 Hz, 1H), 3.28 (s, 2H), 2.36 (s, 3H). ^{13}C NMR (150 MHz, D_2O) δ 176.4, 153.0, 150.4, 137.4, 133.0, 112.6, 64.9 (t, J = 22.4 Hz), 38.6, 18.7. HRMS-ESI (*m/z*): $[M + H]^+$ Calcd. For $C_{10}H_{11}N_2O_3$: 207.0764, found: 207.0765.

1g (49.5 g, 240 mmol, 1.0 equiv) was suspended in methanol (480 mL), and then $SOCl_2$ (50 mL, 0.50 mol, 2.0 equiv) was slowly added into the stirring solution at 0 °C over 0.5 hours. The mixture continued to stir until the solid disappeared and the solution became transparent. Removal of the solvent under vacuum gave a white solid, and then the crude product was refluxed in $POCl_3$ (190 mL, 2.00 mol, 8.0 equiv) for 4 h. The black sticky liquid was afforded after removal of $POCl_3$ under reduced pressure, and the residue was carefully poured into the crashed ice, neutralized with a saturated Na_2CO_3 solution, and extracted with CH_2Cl_2 (500 mL × 3). The organic phase was washed with H_2O (500 mL), brine (250 mL), dried (Na_2SO_4), filtrated and concentrated to obtain **2g** (53.2 g, yield: 87%, purity by HPLC: 96%). For the spectra data of the analytic sample of **2g**: a white solid, Mp 112~115 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, J = 7.2 Hz, 1H), 7.29 (s, 1H), 6.73 (d, J = 6.9 Hz, 1H), 3.94 (s, 2H), 3.72 (s, 3H), 2.40 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.0, 143.8, 136.0, 134.6, 122.8, 115.5, 111.1, 52.4, 29.0, 21.2. HRMS-ESI (*m/z*): $[M + H]^+$ Calcd. For $C_{11}H_{12}ClN_2O_2$: 239.0582, found: 239.0591.

An anhydrous toluene (800 mL) solution of K_3PO_4 (84.8 g, 0.40 mol, 2.0 equiv), $NiCl_2$(dppf) (5.70 g, 8.40 mmol, 0.05 equiv), **2g** (53.2 g, 209 mmol, 1.0 equiv) and an arylboronic acid (68.0 g, 0.50 mol, 2.5 equiv) was transferred into a reaction bottle. The reaction mixture was then refluxed for 4–6 h under Ar. After the mixture was cooled to 20 °C, the reaction was quenched with a saturated sodium bicarbonate solution (500 mL) was added. The organic and aqueous layers were separated, and the latter was extracted with ethyl acetate (500 × 3 mL). The combined organic layers were washed with brine (300 mL) and dried (Na_2SO_4), and then the filtrate was concentrated *in vacuo*. The residue was mixed with 36% HCl (500 ml) and heated at 45°C for 5 h. Removal of the solvent under reduced pressure, the residue was stirred in acetone (300 mL) for 5 h to produce a white precipitate. After filtration, the precipitate was mixed with 300 mL water until most solid disappeared. Then the aqueous pH was adjusted to 5.0 to 6.0 with acetic acid. The precipitate was filtered, washed, dried and recrystallized from methanol to obtain **10** (41.5 g, yield: 71%, purity by HPLC: 99%). For the spectra data of the analytic sample of **10**: a white solid, Mp 253~255 °C. ^{1}H NMR (400 MHz, D_2O) δ 8.38 (d, J = 6.8 Hz, 1H), 7.91 – 7.77 (m, 2H), 7.69 (s, 1H), 7.40 (d, J = 3.9 Hz, 1H), 3.93 (s, 2H). The spectrum was consisted with literature[7a]. HRMS-ESI (*m/z*): $[M + H]^+$ Calcd. For $C_9H_9N_2O_2$: 177.0659, found: 177.0662.

A mixture of **10** (41.5 g, 148 mmol), CH_2Cl_2 (500 mL) and PCl_5 (33.9 g, 163 mmol, 1.1 equiv) was refluxed for reaction completion. The reaction mass was cooled to 0 °C, and the dimethyl amine gas was purged into it till the reaction completion. Most of the solvent was removed under vacuum, and water (300 mL) was added to the residue. The mixture was heated to 90 °C to remove traces of dichloromethane. The reaction mass was cooled to room temperature, pH was adjusted to 9.0-10.0 using

caustic lye and stirred for solid isolation. The solid was filtered, washed with water (300 mL) and dried. Finally, recrystallization in acetone yielded a white solid of Zolpidem (41.9 g, yield: 92%, purity by HPLC: 98%). For the spectra data of the analytic sample of Zolpidem: a white solid, Mp 194~196 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, J = 7.0 Hz, 1H), 7.55 (d, J = 7.5 Hz, 2H), 7.40 (s, 1H), 7.27 (d, J = 4.0 Hz, 2H), 6.73 – 6.59 (m, 1H), 4.11 (s, 2H), 2.92 (s, 3H), 2.84 (s, 3H), 2.40 (s, 6H). The spectrum was consisted with literature[7a]. HRMS-ESI (*m/z*): $[M + H]^+$ Calcd. For $C_{19}H_{22}N_3O$: 308.1757, found: 308.1759.

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Supplementary Material

Supplementary data associated with this article, such as compound **2**, **3** and **4**, can be found in Supporting Information.

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