Organic Process Research & Development **2010,** *14,* 362–368

Synthesis and Process Optimization of Amtolmetin: An Antiinflammatory Agent†

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Abstract:

Efforts toward the synthesis and process optimization of amtolmetin guacil 1 are described. High-yielding electrophilic substitution followed by Wolf−Kishner reduction are the key features in the novel synthesis of tolmetin 2 which is an advanced intermediate of 1.

Introduction

Amtolmetin guacil **1** (Figure 1) is a nonacidic prodrug of tolmetin **2** that has similar nonsteroidal antiinflammatory drug (NSAID) properties to those of **2** with additional gastroprotective advantages.[1,2] The term "nonsteroidal" is used to distinguish these drugs from steroids that have similar eicosanoid-depressing and antiinflammatory actions. Moreover, it possesses a more potent and long-lasting antiinflammatory activity than tolmetin **2** and is marketed for the treatment of rheumatoid arthritis, osteoarthritis, and juvenile rheumatoid arthritis.[1,2]

Various synthetic routes are reported for the synthesis of tolmetin **2,** a key starting material of **1**. For instance, Rogers et al. synthesized[3] an advanced intermediate of **2**, *N*-methylpyrrole acetonitrile, by Mannich reaction on *N*-methylpyrrole followed by methiodide salt. Thereafter, the methiodide salt was further converted to *N*-methylpyrrole acetonitrile as a precursor of **2**, employing NaCN in water. In 1971, the first synthesis of **2** was reported by Carson and co-workers.[4] Later, the same group patented the above procedure with a modification in aroylation.[5,6] The key step was aroylation of *N*-methylpyrrole acetonitrile using *p*-toluoyl chloride and $AlCl_3$ in dichloromethane but the yields were found to be less because of the formation of additional undesired aroyl regioisomer. Subsequently, another five steps synthesis of tolmetin from the noncommercially available *N*-methyl-2-oxomethyl-5-chloropyrrole was patented by Calzada Badia.[7] In 1982, Marino Artico and co-workers reported another synthesis slightly better yielding than Carson's synthesis starting from *N*-methylpyrrole.[8] Baciocchi et al reported[9] short synthesis of tolmetin ester, but fifteen equivalents of expensive *N*-methylpyrrole was required. Kondo et al reported[10] another synthesis using chloral as a key starting material. Most of the syntheses involve either low yielding aroylation or expensive raw materials.

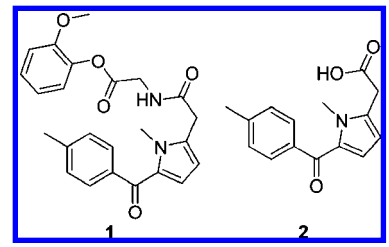

Figure 1. **Structure of amtolmetin 1 and tolmetin 2.**

Herein, we report our efforts to develop relatively high yielding and cost-effective alternate synthesis for tolmetin **2** and followed by amtolmetin **1**.

Results and Discussion

Synthesis of Tolmetin 2. Synthesis of **2** starts with the Lewis acid free electrophilic substitution of *N*-methylpyrrole employing oxalyl chloride to afford **3** in 91% yields after quenching the reaction mixture with aq. KOH solution. Thereafter, Wolf-Kishner reduction of **3** afforded advanced intermediate **4** in 92% yields. Initially, reduction of **3** was performed in ethylene glycol employing hydrazine hydrate and KOH. The work up process was found to be cumbersome and we were not able to isolate intermediate **4** in >75% yields. The process was simplified by replacing ethylene glycol with water and the yield of **4** was significantly improved from 75 to 92%.

Subsequently, esterification of **4** to afford ester **5** followed by aroylation and hydrolysis provided tolmetin **2** in 55% yields for the two steps as shown in Scheme 1.

Synthesis of Amtolmetin 1. The precedented approach[11] as shown in Scheme 2 involves carbonyl diimidazole (CDI)-mediated amidation of **2** with HCl salt of methyl ester of glycine, ester hydrolysis, and CDI-mediated esterfication with *o*-methoxyphenol. All the steps in this synthesis are low yielding and employed unrecoverable THF due to aqueous work.

In order to develop a novel and high-yielding synthesis for **1**, we adopted an *N*-protection-based strategy. The advantage

† DRL-IPD Communication number: IPDO IPM - 00202

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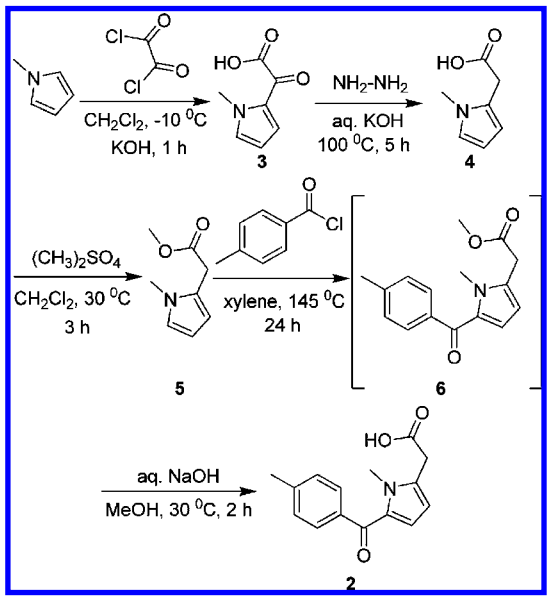
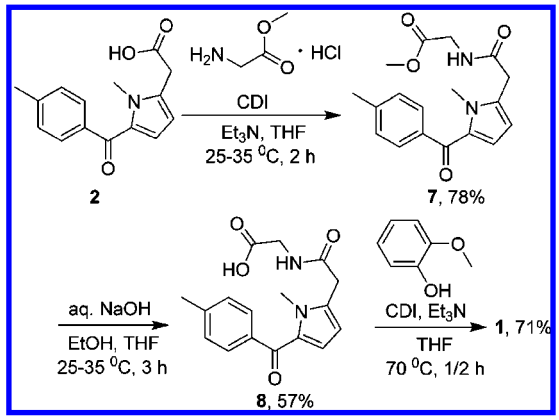
Published on Web 01/15/2010

10.1021/op900284w

Scheme 1. **Improved synthesis of tolmetin 2**



Scheme 2. **Precedented approach to the synthesis of 1**



of keeping the relatively hydrophobic *N*-protecting group, i.e. Boc, in the intermediate **9** is to improve solubility in the organic solvent and the homogeneity of reaction mixture and to make the synthesis convergent. Such a strategy allows us to design high-yielding steps by avoiding the yield loss that we usually encounter in linear synthesis.

By following the well-stabilized protection approach,[12] Boc-protected glycine **9** was synthesized in 90% yield. The C terminus of intermediate **9** was esterified with *o*-methoxyphenol using DCC/HOBt to afford unprecedented intermediate **10** in 95% yield. Boc deprotection of **10** to obtain intermediate **11** was achieved by using dry HCl gas in 92% yield.

We attempted the deprotection with several acids as summarized in Table 1; eventually, dry HCl was found to be effective.

So far, most of the steps are found to be high yielding. Unfortunately, the final step of this synthesis that involves potassium carbonate and DCC-/HOBt-mediated coupling of **2** and HCl salt of **11** afforded the amtolmetin **1** only in 60% yield as shown in Scheme 3. Here in this step, we attempted the coupling in presence of various bases as summarized in Table

(12) Yanjie, X.; Ligong, C.; Xuemin, D.; Yi, M.; Liqin, J.; Meiling, L.; Guangle, Z.; Yang, L. *Tetrahedron Lett.* **2005**, *46*, 4377.

Table 1. **Screening of acids for Boc group deprotection**

acid	yield (**11**) (%)	remarks
aq HCl	–	ester was hydrolyzed
H_2SO_4	–	ester was hydrolyzed
CF_3COOH	–	ester was hydrolyzed
formic acid	–	no product
boric acid	–	no product
silica	–	no product
H_3PO_4	20	–
acetic acid	30	–
CH_3SO_3H	60	95% HPLC
dry HCl gas	90	98% HPLC

Scheme 3. **Novel approach to the synthesis of 1**

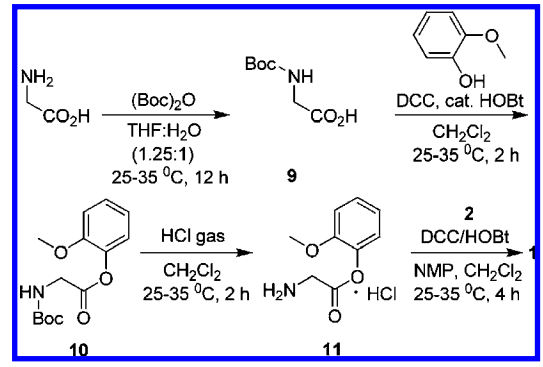


Table 2. **Screening of bases for coupling of 2 and HCl salt of 11**

solvent	volume	base	yield (**1**) (%)	remarks
CH_2Cl_2	10	Et_3N	35	impurities formed
CH_2Cl_2	10	NMM[a]	43	impurities formed
CH_2Cl_2	25	NMM[a]	54	impurities formed
toluene	25	NMM[a]	44	impurities formed
EtOAc	25	NMM[a]	46	impurities formed
THF	25	NMM[a]	50	impurities formed
DMF	25	K_2CO_3	54	–
acetone	10	NMM[a]	40	–
acetone	25	NMM[a]	52	–
acetone	50	NMM[a]	52	–
acetone	25	$NaHCO_3$	50	–
acetone	25	K_2CO_3	60	best condition
acetone	50	K_2CO_3	60	best condition

[a] *N*-methylmorpholine.

2, only K_2CO_3 was found to be effective. In our endeavor, we could avoid the use of THF except first step and improve the yield up to great extent. Over all outcome of this synthesis in terms of cost containment, operational simplicity and greenness of the process is slightly advantageous over the precedented synthesis.

In order to generate immense cost advantage herein, we opted to improvise the synthetic route presented in Scheme 2, and herein we also describe the modified cost-effective and scalable process for amtolmetin **1** as showed in Scheme 4.

In the first step, we have screened different coupling reagents to replace CDI, and eventually DCC was found to be the best reagent with the catalytic amount of HOBt (Table 3). Yield for the coupling of **2** and HCl salt of methyl ester of glycine to afford **7** was increased significantly by replacing the expensive CDI as a reagent and THF as a solvent with DCC and catalytic HOBt as reagent alternative and dichloromethane as a solvent, respectively (results are summarized in Table 3).

Scheme 4. **Improved process for the synthesis of 1**

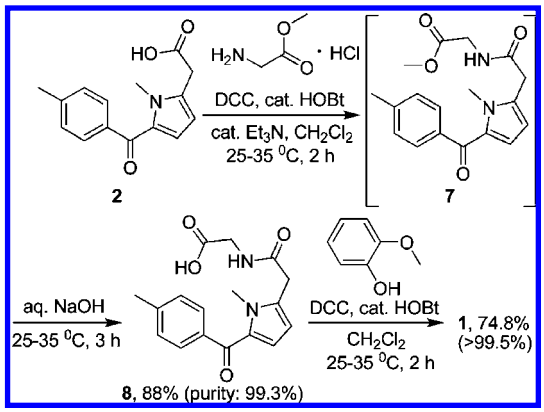


Table 3. **Screening of coupling reagents to obtain 7 *in situ***

reagent	solvent	yield (7) (%)	remarks
CDI	THF	78	
$SOCl_2$	THF	–	no reaction
$SOCl_2$	CH_2Cl_2	–	no reaction
$SOCl_2$	neat	–	no reaction
boric acid	toluene	53	
phenyl boronic acid	toluene	56	
p-fluorophenyl boronic acid	toluene	60	
DCC	THF	75	
DCC and HOBt (cat.)	THF	85	
DCC and HOBt (cat.)	CH_2Cl_2	90	best result[a]

[a] As evident in Table 3, we attempted to avoid the use of eco-unfriendly CH_2Cl_2 by using other solvents (data not shown) (e.g., EtOAc, acetone, and DMF), but none of them offered a better result than CH_2Cl_2.

Table 4. **Comparison of yield and cost of Schemes 2 and 4**

entry	stepwise yield (%) in precedented approach (Scheme *2*)	stepwise yield (%) in improved process (Scheme *4*)
step 1	78	not isolated
step 2	57	88
step 3	71	74.8
overall yield (%)	31.6	65.8
	cost (in U.S. $)[a]	
	1156	234

[a] Based on current commercial cost of the raw materials, reagents, and solvents.

In our endeavor, with the modifications, the workup process was simplified, avoiding the several acid/base extractions; this also allows the use of a single solvent for the whole process. Without isolating intermediate **7**, we proceeded for ester hydrolysis in water. After acidic and basic treatment, product **8** was isolated in 88% yield with respect to tolmetin **2**. Subsequently, acid **8** was esterified by using *o*-methoxy phenol and DCC and catalytic amount of HOBt in dichloromethane solvent instead of CDI and THF (precedented approach). Thereafter, the final product **1** was isolated in isopropyl alcohol with >99.5% purity. The overall yield of the modified process of amtolmetin was found to be 65.8% in comparison to the 31.6% yield that is reported with patent process,[11] and the details are summarized in Table 4.

Impurity Control Strategy. In the final esterification process, a trace of methanol leads to the formation of transesterified major species **7** (considered as an impurity present in the different batches of **1**) and the removal of this one resulted in a significant yield loss of **1**. This impurity **7** was controlled by ensuring the reaction mass and workup free from methanol that avoided the formation of **7**.

Table 5. **Impurity profile by HPLC (%)**

entry	OMP	HOBt	DCU	**7**	**8**	**12**	**13**	**14**
reaction mass	1.5	8.1	4.5	0.05	0.06	0.06	0.14	0.06
post DCU filtration	2.0	9.9	0.28	0.05	0.05	0.08	0.19	0.09
2% $NaHCO_3$[a]	2.4	2.2	0.25	0.07	0.06	0.07	0.23	0.10
2% Na_2CO_3[a]	2.5	1.4	0.26	0.06	0.08	0.06	0.25	0.09
2% Na_2CO_3[a]	2.7	0.2	0.24	0.07	0.09	0.07	0.26	0.12
2% Na_2CO_3[a]	2.8	0.03	0.25	0.07	0.09	0.08	0.25	0.12
4% Na_2CO_3[a]	3.0	0.03	0.29	0.08	0.15	0.06	0.19	0.11
water[a]	2.1	nil	0.24	0.07	0.15	0.07	0.18	0.10
water[a]	2.2	nil	0.27	0.07	0.14	0.07	0.16	0.11

[a] Washing with 2 volumes. OMP: *o*-methoxyphenol, HOBt: 1-hydroxybenzotriazole, DCU: dicylohexyl urea.

Another impurity **12** was detected due to unreacted glycine methyl ester which might have reacted with the intermediate **8** to afford diamide ester derivative (not shown) followed by transesterification to give rise to **12** during final coupling of **8** with *o*-methoxyphenol to obtain **1**. Impurity **12** was effortlessly washed out during final crystallization to obtain ICH grade of **1**. Moreover, dicyclohexyl urea (DCU) impurity was effectively controlled by filtering the reaction mass at 0−5 °C after stirring for 2 h and washing with chilled dichloromethane solvent.

During crystallization, we have observed another impurity **13**. Noticeably, this impurity would have been formed due to the transesterification of **8** with isopropyl alcohol. This impurity was observed up to 0.4% in the process. The removal of impurity **13** by employing multiple washings resulted in a significant yield loss of **1**. Unfortunately, washings did not improve the purity, and the results are summarized in Table 5.

In our investigation, we found out that increase in base concentration leads to degradation of **1** to afford the higher level of **8** and *o*-methoxyphenol. This observation clearly indicates that amtolmetin **1** is sensitive to base concentration. In the process of crystallization, once the amount of **8** increases in the reaction mass, it immediately starts reacting with IPA solvent to give rise to impurity **13**.

Impurity **13** was successfully controlled by increasing the mole ratio of *o*-methoxy phenol from 1.0 equiv to 1.2 in the reaction, so that there should not be any amount of **8** left in the reaction. Tolmetin guacil ester impurity **14** is formed if any amount of tolmetin **2** was left in the first step. Tolmetin **2** acid in nature reacts with *o*-methoxyphenol in the final esterification step to afford **14**. This impurity was eliminated during final crystallization of the API.

As we described above, among the observed impurities, two impurities **12** and **13** were found to be unknown. These impurities were synthesized, indentified, and characterized as shown in Figure 2.

Synthesis of **12** was accomplished by treating intermediate **8** with *o*-methoxyphenyl ester of glycine **11**in presence of DCC/HOBt as shown in Scheme 5.

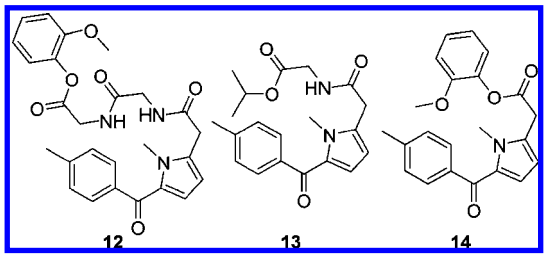
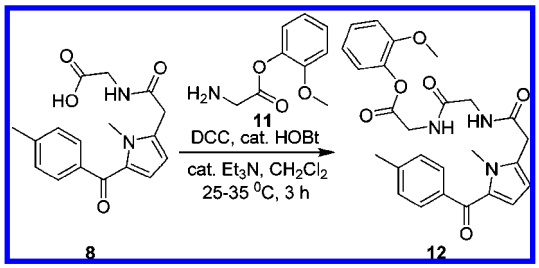
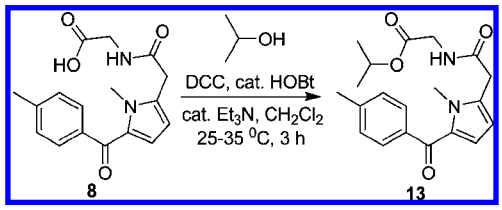


Figure 2. **Structure of impurities 12−14.**

Scheme 5. **Synthesis of impurity 12**



Scheme 6. **Synthesis of impurity 13**



Similarly, synthesis of **13** was achieved by treating intermediate **8** with isopropanol in the presence of DCC/HOBt as shown in Scheme 6.

Polymorphism. We have studied the polymorphism of amtolmetin guacil in detail. In commercial scale, we have noticed that undesired crystalline polymorph-I was obtained in one of the batches. To investigate such an anomaly, we have studied the critical parameters which might affect the polymorphism, e.g. rounds per minute (stirring speed), different stirring blades, and temperature and its cooling rate. We have concluded that fast cooling gives an undesired crystalline polymorph, i.e. bringing the temperature from 75−80 °C to 45−50 °C in approximately 30 min. Very slow crystallization in IPA solvent gives the required crystalline polymorph-II. Slow cooling (bringing temperature from 75−80 to 45−50 °C in 2−2.5 h) was found to be the key to obtain the desired polymorph.

Conclusion

We reported an alternate novel cost-effective synthesis for the preparation of tolmetin which was further used for the synthesis of amtolmetin by two efficient processes; one is the modified cost-effective process of a known scheme for commercial production, and the other is an alternate new synthetic route for amtolmetin.

Experimental Section

Solvents and reagents were obtained from commercial sources and used without further purification. The ^{1}H and ^{13}C spectra were measured in $CDCl_3$ or DMSO-d_6 using 200 or 400 MHz on a Varian Gemini and Varian Mercury plus 2000 FT NMR spectrometers; the chemical shifts were reported in δ ppm. The mass spectrum (70 eV) was recorded on HP 5989 A LC/MS spectrometer. The melting points were determined by using the capillary method on Polmon (model MP-96) melting point apparatus. The solvents and reagents were used without further purification.

Preparation of 1-Methylpyrrole-2-oxo-2-yl Acetic Acid (3). To a solution of oxalyl chloride (78.4 g, 0.617 mol) in dichloromethane (250 mL) at −10 °C was slowly added a solution of *N*-methylpyrrole (50 g, 0.617 mol) in dichloromethane (500 mL) at −10 to 0 °C. After stirring for 1 h at 0 °C, the pH was adjusted to 10 with the dropwise addition of 25% aq KOH solution at −10 to 0 °C. The reaction mass was stirred for an additional 30 min, and the layers were separated. The aqueous layer was again washed with dichloromethane (250 mL). The pH of the aqueous layer was adjusted to 1−2 with 20% H_2SO_4 and stirred for 30 min; the solid was filtered and washed with chilled water (25 mL). The compound was dried under vacuum at 50 °C to give **3** (88 g, 93% yield and 98.5% GC purity). Mass (M + 1): 154; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28 (dd, J = 4.3 Hz, 1.4 Hz, 1H), 7.17 (t, J = 1.9 Hz, 1H), 6.22 (dd, J = 3.9 Hz, 2.4 Hz, 1H), 3.95 (s, 3H).

Preparation of 1-Methylpyrrole-2-yl Acetic Acid (4). Hydrazine hydrate (43.1 g, 0.862 mol) was added to 1-methylpyrrole-2-oxo-2-yl acetic acid **3** (80 g, 0.522 mol). To this reaction mixture was slowly added 20% KOH solution (900 mL). It was slowly heated to reflux and stirred at same temperature for 5 h. Thereafter, the reaction mixture was cooled to 30 °C. The pH of the mass was slowly adjusted to 2 with 50% HCl at below 30 °C. Subsequently, the reaction mixture was extracted with dichloromethane (3 × 300 mL). The organic layer was washed with water, dried over sodium sulphate, and evaporated to give 60 g of **4** (82.5% yield and 98% purity by GC). Mass (M + 1): 140; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.58 (t, J = 2.4 Hz, 1H), 6.07 (d, J = 3.4 Hz, 1H), 6.05 (d, J = 3.4 Hz, 1H), 3.62 (s, 2H), 3.57 (s, 3H).

Preparation of Methyl-1-methylpyrrole-2-acetate (5). To a solution of 1-methylpyrrole-2-yl acetic acid **4** (50 g, 0.35 mol) in dichloromethane (500 mL) was added potassium carbonate (74.4 g, 0.539 mol) and dimethylsulphate (49.8 g, 0.39 mol). The resulting mixture was stirred at 30 °C for 3 h. Thereafter, the reaction mixture was washed with 5% aq ammonia solution (250 mL) followed by brine solution (250 mL). The organic layer was separated, dried over sodium sulphate, and concentrated below 35 °C under vacuum to afford 50.1 g of **5** (91% yield and 97% HPLC purity). Mass (M + 1): 154; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.58 (t, J = 1.9 Hz, 1H), 6.06 (d, J = 3.4 Hz, 1H), 6.05 (d, J = 2.9 Hz, 1H), 3.69 (s, 3H), 3.61 (s, 2H), 3.56 (s, 3H).

Preparation of 1-Methyl-5-*p*-tolylpyrrole-2-acetate (6). To a solution of methyl-1-methylpyrrole-2-acetate **5** (20 g, 0.13 mol) in *o*-xylene (200 mL) was added *p*-toluoyl chloride (40.4 g, 0.26 mol). The resulting mixture was heated to reflux for 24 h. After completing the reaction, the solvent was evaporated, and the resulted residue was

dissolved in dichloromethane (200 mL). Thereafter *N*,*N*-dimethylaminopropylamine (40 mL) was added and stirred for 30 min. The resulting mixture was washed with water (200 mL), 10% HCl (200 mL), 10% potassium carbonate (200 mL), and finally with brine solution (200 mL). The organic layer, was separated, dried over sodium sulphate, and evaporated to give 34 g of **6** (95% yield and 80% purity by HPLC). Mass (M + 1): 272; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.71 (d, J = 8.2 Hz, 2H), 7.25 (d, J = 7.8 Hz, 2H), 6.67(d, J = 4.3 Hz, 1H), 6.11 (d, J = 3.9 Hz, 1H), 3.94 (s, 3H), 3.75 (s, 3H), 3.72 (s, 2H), 2.42 (s, 3H).

Preparation of 1-Methyl-5-*p*-tolylpyrrole-2-acetic Acid (2). To a solution of 1-methyl-5-*p*-tolylpyrrole-2-acetate **6** (34 g, 0.125 mol) in methanol (170 mL) was added a solution of NaOH (11 g, 0.276 mol) in water (170 mL). The resulting mixture was stirred for 2 h at 30 °C. Organic solvent was evaporated from the reaction mixture to which was added water (340 mL) and dichloromethane (340 mL). After stirring for 10 min, the organic layer was separated; the aqueous layer was again washed with dichloromethane (170 mL). The pH of the aqueous layer was adjusted to 2 with 50% HCl. The resulting mass was stirred for 30 min and filtered; the solid was washed with water (200 mL) and recrystallized in methanol to give 16.8 g of **2** (52% yield and 99% HPLC purity). Melting point: 155−158 °C; Mass (M + 1): 258; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.63 (d, J = 7.8 Hz, 2H), 7.27 (d, J = 7.8 Hz, 2H), 6.63 (d, J = 3.9 Hz, 1H), 6.11 (d, J = 4.3 Hz, 1H), 3.91 (s, 3H), 3.76 (s, 2H), 2.40 (s, 3H).

***tert*-Butyloxycarbonylamino Acetic Acid (9).**[12] To a solution of 3.8 N NaOH (400 mL) was added glycine (50 g, 0.66 mol) and tetrahydrofuran (500 mL). The reaction mixture was cooled to 0−5 °C, and Boc-anhydride (145 g, 0.66 mol) was added slowly dropwise. The reaction mixture was warmed to 30 °C and stirred for 15 h. Thereafter, it was cooled to 0−5 °C, and the pH was adjusted to 3 with 2 N hydrochloric acid and extracted with dichloromethane (750 mL); the solvent was evaporated to afford **9** (105 g, 90% yield).[12]

***tert*-Butyloxycarbonylamino Acetic Acid-2-guacil Ester (10).** To a solution of Boc-glycine **9** (50 g, 0.28 mol) in dichloromethane (400 mL) was added 1-hydroxybenzotriazole (7.57 g, 0.056 mol) and triethylamine (8 mL, 0.056 mol). Thereafter, a solution of guaiacol (23.1 mL, 0.28 mol) in dichloromethane (100 mL) was added to it. Subsequently was slowly added dropwise a solution of dicyclohexylcarbodiimide (70.6 g, 0.34 mol) in dichloromethane (150 mL). The resulting reaction mixture was stirred for 4 h at 30 °C. Thereafter, it was cooled to 0−5 °C and stirred for 30 min. The unwanted solid was filtered (DCU), and the filter bed was washed with dichloromethane (100 mL). The filtrate was washed with 2% sodium carbonate solution (150 mL) followed by water (100 mL). Solvent was evaporated at below 40 °C to obtain the title compound **10** (76.3 g, 95% yield). Mass (M + 1): 282; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.26 (m, 1H), 7.05 (m, 1H), 6.96 (m, 1H), 4.22 (d, J = 5.5 Hz, 2H), 3.82 (s, 3H), 1.60 (s, 9H).

Amino Acetic Acid-2-guacil Ester Hydrochloride (11). To a solution of **10** (76.3 g, 0.27 mol) in dichloromethane (400 mL) was passed dry hydrochloric acid gas for 4 h at 25−30 °C. Thereafter, the product was filtered and washed with dichloromethane (100 mL), and the solid was dried to afford **11** (47.3 g, 80% yield). Filtrate was distilled completely under vacuum to afford another 7.1 g of **11** (12% yield), total 92% yield. Mass (M + 1): 182; ^{1}H NMR ($CDCl_3$, + DMSO, 400 MHz): δ 7.25 (m, 1H), 7.09 (m, 1H), 7.03 (m, 1H), 6.96 (m, 1H), 4.01 (s, 2H), 3.83 (s, 3H).

Preparation of 1-Methyl-5-*p*-toluoylpyrrole-2-acetamidoacetic Acid Guacil Ester (1). To a solution of **11** (20 g, 0.091 mol) in acetone (500 mL) at 0−5 °C, was added 1-methyl-5-*p*-toluoylpyrrole-2-acetic acid **2** [tolmetin] (23.5 g, 0.09 mol) and 1-hydroxybenzotriazole (2.5 g, 0.018 mol) followed by potassium carbonate (15.2 g, 0.11 mol). To this reaction mixture was slowly added dropwise a solution of dicyclohexylcarbodiimide (22.3 g, 0.108 mol) in acetone (100 mL) at −5 °C. Thereafter, the reaction mass was slowly warmed to 25−30 °C and stirred for 5 h. After that it was cooled to 0 °C and stirred for 30 min. The unwanted solid was filtered (DCU) and washed with acetone (40 mL). The filtrate was distilled completely, and the obtained residue was dissolved in dichloromethane (200 mL) and washed with 2% sodium carbonate followed by water. The solvent was evaporated, and the product was crystallized in isopropyl alcohol (200 mL) to provide 23.1 g of the title compound **1** (amtolmetin) (60% yield, 98% purity by HPLC).

An Alternate Process for 1-Methyl-5-*p*-toluoylpyrrole-2-acetamidoacetic Acid Guacil Ester (1). To a solution of **11** (20 g, 0.091 mol) in dichloromethane (200 mL) at 0−5 °C, was added 1-methyl-5-*p*-toluoylpyrrole-2-acetic acid **2** [tolmetin] (23.5 g, 0.09 mol) and 1-hydroxybenzotriazole (2.5 g, 0.018 mol). Subsequently *N*-methylmorpholine (10.1 g, 0.10 mol) was added slowly dropwise. To the resulting reaction mixture was slowly added dropwise a solution of dicyclohexylcarbodiimide (22.3 g, 0.108 mol) in dichloromethane (100 mL) at −5 °C. After that, the reaction mass was warmed slowly to 25−30 °C and stirred for 5 h. After that, it was cooled to 0 °C and stirred for 30 min. The unwanted solid was filtered (DCU) and washed with dichloromethane (40 mL). The filtrate was washed with 2% sodium carbonate followed by water. The organic layer was separated, treated with silica (10 g), and distilled off completely below 40 °C under vacuum; the resulting residue was dissolved in isopropyl alcohol (240 mL) at 80 °C. Carbon (4 g) was charged to it and stirred for 30 min at the same temperature. After that it was filtered in hot condition on a Celite bed, and the bed was washed with hot isopropyl alcohol (40 mL). The filtrate was slowly cooled to 25−30 °C and stirred for 3 h. The solid was filtered and washed with isopropyl alcohol (60 mL). The compound was dried at 60 °C under vacuum for 6 h to provide the title compound **1** (21.2 g, 55.2% yield, 98% purity by HPLC).

Preparation of (2-{2-[1-Methyl-5-(4-methyl-benzoyl)-1H-pyrrol-2-yl]acetylamino}-acetylamino)acetic Acid 2-Methoxy-phenyl Ester (12). To a heterogeneous solution of **8** (50 g, 0.159 mol) in dichloromethane (200 mL) at 0 °C was sequentially added 1-hydroxybenzotriazole (4.3 g, 0.031 mol), triethylamine (3.2 g, 0.031 mol) and **11** (34.63 g, 0.159 mol). After stirring for 15 min, a solution of dicyclohexylcarbodiimide (39.5 g, 0.191 mol) in dichloromethane (150 mL) was added slowly in 50 min at 30 °C; the reaction mixture was stirred for 3 h. Thereafter, it was cooled to 0 °C and stirred for 30 min. The unwanted solid was filtered (DCU) and washed with chilled dichloromethane (100 mL). The filtrate was washed with 2% Na_2CO_3 solution (100 mL) followed by water (100 mL). The organic layer was separated, and distilled off completely below 40 °C under vacuum, and the residue was dissolved in isopropyl alcohol (600 mL) at 80 °C and cooled to 25−30 °C. The solid stirred for 3 h and was filtered and washed with isopropyl alcohol (150 mL). The compound was dried at 60 °C under vacuum for 6 h to provide the title compound **12** (34.2 g, 45% yield). Mass (M + 1): 478; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.71(d, J = 7.8 Hz, 2H), 7.24 (m, 3H), 7.04 (dd, J = 1.8 Hz, 7.8 Hz, 1H), 6.95 (m, 2H), 6.68 (d, J = 4.1 Hz, 1H), 6.54 (bs, 1H), 6.37 (bs, 1H), 6.14 (d, J = 3.7 Hz, 1H),4.34 (d, J = 5.5 Hz, 2H), 3.99 (d, J = 5.1 Hz, 2H) 3.91 (s, 3H), 3.81 (s, 3H), 3.70 (s, 2H), 2.42 (s, 3H).

Preparation of 1-Methyl-5-*p*-toluoylpyrrole-2-acetamidoacetic Acid Isopropyl Alcohol Ester (13). To a heterogeneous solution of **8** (50 g, 0.159 mol) in dichloromethane (200 mL) at 0 °C was sequentially added 1-hydroxybenzotriazole (4.3 g, 0.031 mol), triethylamine (3.2 g, 0.031 mol), and isopropyl alcohol (20 mL) at 0 °C. After stirring for 15 min, a solution of dicyclohexylcarbodiimide (39.5 g, 0.191 mol) in (150 mL) was added slowly dropwise in 50 min at 25−35 °C. After stirring for 3 h, the reaction mixture was cooled to 0 °C and stirred additionally for 30 min. The unwanted solid was filtered (DCU) and washed with chilled dichloromethane (100 mL). Filtrate was washed with 2% Na_2CO_3 solution (100 mL) followed by water (100 mL). The organic layer was separated and distilled off completely below 40 °C under vacuum, and the residue was dissolved in isopropyl alcohol (600 mL) at 80 °C. The solution was cooled to 25−30 °C and stirred for 3 h. The solid was filtered and washed with isopropyl alcohol (150 mL). The compound was dried at 60 °C under vacuum for 6 h to provide the title compound **13** (34.0 g, 60% yield). Mass (M + 1): 357; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.72(d, J = 7.9 Hz, 2H), 7.26 (d, J = 9.4 Hz, 2H), 6.70 (d, J = 3.9 Hz, 1H), 6.16 (d, J = 3.9 Hz, 1H), 6.00 (bs, 1H), 5.04 (m, 1H), 3.99 (d, J = 5.4 Hz, 2H) 3.94 (s, 3H), 3.70 (s, 2H), 2.42 (s, 3H), 1.25 (s, 3H), 1.24 (s, 3H).

Preparation of 1-Methyl-5-*p*-toluoylpyrrole-2-acetic Acid Guacil Ester (14). To a heterogeneous solution of tolmetin **2** (50 g, 0.194 mol) in dichloromethane (200 mL) was sequentially added 1-hydroxybenzotriazole (5.3 g, 0.039 mol), triethylamine (3.9 g, 0.039 mol), and a solution of *o*-methoxyphenol (24.1 g, 0.194 mol) in dichloromethane (50 mL). After stirring for 15 min, a solution of dicyclohexylcarbodiimide (39.5 g, 0.191 mol) in dichloromethane (150 mL) was added slowly dropwise in 50 min at 30 °C. After stirring for 3 h, it was cooled to 0 °C and stirred for additionally 30 min. The unwanted solid was filtered (DCU) and washed with chilled dichloromethane (100 mL). Filtrate was washed with 2% Na_2CO_3 solution (100 mL) followed by water (100 mL). Organic layer was separated and distilled off completely below 40 °C under vacuum and the residue was dissolved in isopropyl alcohol (600 mL) at 80 °C. It was slowly cooled to 25−30 °C and stirred for 3 h. Filtered the solid and washed with isopropyl alcohol (150 mL). Dried the compound at 60 °C under vacuum for 6 h to provide the title compound **14** (49.5 g, 70% yield, and >99.5% HPLC purity). Mass (M + 1): 364; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.73(d, J = 7.8 Hz, 2H), 7.25 (d, J = 8.2 Hz, 2H), 7.20 (m, 1H), 7.04 (dd, J = 1.4 Hz, 7.8 Hz, 1H), 6.95 (m, 2H), 6.70 (d, J = 3.9 Hz, 1H), 6.23 (d, J = 3.9 Hz, 1H), 4.03 (s, 3H), 3.97 (s, 2H), 3.80 (s, 3H), 2.41 (s, 3H).

Preparation of 1-Methyl-5-*p*-toluoyl-2-acetamidoacetic Acid (8). Glycine methyl ester hydrochloride (5.86 kg, 46.7 mol) and dichloromethane (50 L) were charged into a flask. To this heterogeneous mass, was slowly added a solution of triethylamine (4.72 kg, 46.7 mol) in dichloromethane (10 L) at 30 °C in 20 min. After stirring for 30 min, 1-methyl-5-*p*-toluoylpyrrole-2-acetic acid **2** (tolmetin) (10 kg, 38.91 mol) and 1-hydroxybenzotriazole were charged. Thereafter a solution of dicyclohexyl carbodiimide (8.8 kg, 42.7 mol) in dichloromethane (40 L) was added slowly during 45−60 min at 30 °C. After stirring for 3 h at 30 °C, it was cooled to 0 °C and stirred for 30 min at 0−5 °C. The unwanted solid was filtered (DCU) and washed with dichloromethane (10 L). The filtrate was washed with 2% Na_2CO_3 solution (20 L). Organic layer was distilled off completely below 40 °C under vacuum. To the obtained residue was added a solution of NaOH (23.4 kg, 58.5 mol) in water (50 L) and stirred for 3 h at 30 °C. Thereafter, ethylacetate (40 L) was added to the reaction mixture and stirred for 15 min. The aqueous layer was separated and washed with ethylacetate (30 L). Water (200 L) was charged to the aqueous layer, and the pH was slowly adjusted to 1.0−2.0 with 50% of 12 N hydrochloric acid and stirred for an additional 60 min. The compound was filtered and washed with water (20 L). The wet compound was again slurried in water (140 L) to reach the neutral pH of the compound. The compound was dried to a constant weight at 60−70 °C under vacuum to give 10.76 kg of **8** (88.2% yield, 99.3% HPLC). Melting point: 200°−202 °C. Mass (M + 1): 315; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.64 (dd, J = 6.3 Hz, 1.9 Hz, 2H), 7.28 (d, J = 7.8 Hz, 2H), 6.65 (d, J = 3.9 Hz, 1H), 6.17 (d, J = 3.9 Hz, 1H), 3.92 (s, 3H), 3.73 (s, 2H), 3.30 (t, J = 1.4 Hz, 2H), 2.41(s, 3H).

Preparation of 1-Methyl-5-*p*-toluoylpyrrole-2-acetamidoacetic Acid Guacil Ester (1). To a solution of **8** (10 kg, 31.8 mol) in dichloromethane (40 L) was sequentially added 1-hydroxybenzotriazole (0.86 kg, 6.2 mol), triethylamine (0.64 kg, 6.2 mol), and a solution of *o*-methoxyphenol (3.95 kg, 31.8 mol) in dichloromethane (10 L). After stirring the reaction

mixture for 15 min, a solution of dicyclohexylcarbodiimide (7.9 kg, 38.2 mol) in dichloromethane (30 L) was added slowly dropwise in 50 min at 25−35 °C. After stirring for 3 h, it was cooled to 0 °C and stirred for additional 30 min. The unwanted solid was filtered (DCU) and washed with chilled dichloromethane (20 L). The filtrate was washed with 2% Na_2CO_3 solution (20 L) followed by water (20 L). The organic layer was separated, treated with silica (7.5 kg), and distilled off completely below 40 °C under vacuum; the residue was dissolved in isopropyl alcohol (120 L) at 80 °C. Carbon (2 kg) was charged and stirred for 30 min at the same temperature. Thereafter, it was filtered in hot conditions on a Celite bed, and the bed was washed with hot isopropyl alcohol (20 L). Filtrate was slowly cooled to 25−30 °C and stirred for 3 h, and the solid was filtered and washed with isopropyl alcohol (30 L). The compound was dried at 60 °C under vacuum for 6 h to provide the title compound **1** (10 kg, 74.8% yield, and >99.5% HPLC purity). Melting point: 116°−119 °C. Mass (M + 1): 421; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.63 (dd, J = 6.3 Hz, 1.9 Hz, 2H), 7.28 (d, J = 8.2 Hz, 2H), 7.23(m, 1H), 7.19 (m, 2H), 6.94 (m, 1H), 6.64 (d, J = 3.9 Hz, 1H), 6.18 (d, J = 3.9 Hz, 1H), 4.23 (s, 2H), 3.92 (s, 3H), 3.78 (s, 3H), 3.76 (s, 2H), 2.40 (s, 3H).

Received for review November 2, 2009.

OP900284W