Organic Process Research & Development **2010,** *14,* 579–584

Substituents Effect on the Erlenmeyer–Plöchl Reaction: Understanding an Observed Process Reaction Time

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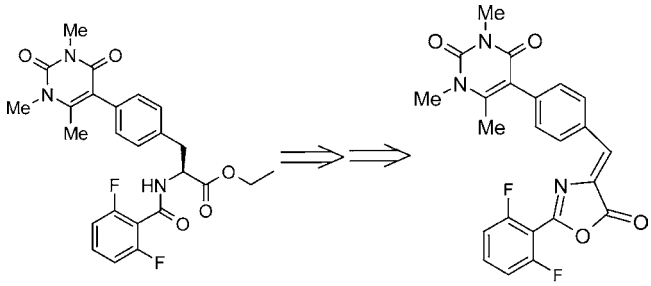
Abstract:

A systematic study on hippuric acid substituents was performed in order to better understand the influence of stereoelectronic factors on the Erlenmeyer reaction rate. In addition, two reaction systems were evaluated: Hünig's base solvent free conditions and catalytic sodium acetate in 2-methyl-THF. The effect on reaction rate of electron withdrawing and electron donating groups are reported. Specifically, the study led to the conclusion that stereoelectronic factors have significant influence in one of our key Erlenmeyer reaction by affecting its reaction rate.

Introduction

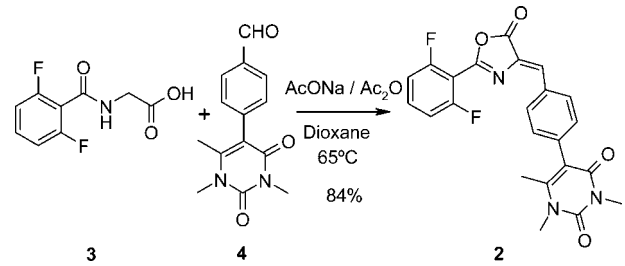
The Integrin VLA-4 ($\alpha 4\beta 1$) is expressed on a variety of leucocytes, including β-cells, T-cells, basophiles, and eosinophils, and is involved in the recruitment, activation and survival of these cell types.[1] Data supporting a role for VLA-4 in a number of inflammatory diseases including asthma, rheumatoid arthritis, inflammatory bowel diseases, multiple sclerosis, atherosclerosis, and diabetes have been summarized in recent reviews.[2] Integrin antagonist **1** was identified as an interesting compound on the basis of its potency in our ELISA- and cell-based assays, and is currently being evaluated as a clinical candidate for the treatment of rheumatoid arthritis (RA) and multiple sclerosis (MS). Rheumatoid arthritis, an aggressive autoimmune disease, affects about 3.3 million adults worldwide and is an area of high medical need.



1 **2**

The synthesis of **1** is carried out in five steps, and one of the key intermediate is the oxazolone **2** which is obtained by an Erlenmeyer–Plöchl reaction,[3,4] wherein 1,6-difluoro-hippuric acid **3**, aldehyde **4** and acetic anhydride are reacted in dioxane

Scheme 1. **Synthesis of intermediate 2 via Erlenmeyer reaction**



3 **4** **2**

in the presence of a stoichiometric amount of sodium acetate (Scheme 1). Under these reaction conditions, the desired product **2** was obtained with adequate yield; however, several technical issues such as a heavy slurry causing initial reactor agitation problems and an extended process reaction time (~80 h) were observed during the first pilot-plant campaign. The agitation problems were relatively easy to solve, and the process reaction time was reduced to 24 h; however, all attempts to minimize the reaction time further were unsuccessful. In order to better understand this reaction, a systematic study of hippuric acid substituent effects on the Erlenmeyer reaction rate was undertaken, and the results from this study are reported herein.

Results and Discussion

Attempts to minimize the process reaction time for the formation of intermediate **2** included screening several reaction base [(triethylamine, pyridine, dimethylamino pyridine),[5] diammonium hydrogen phosphate,[6] zinc oxide,[7] and bismuth acetate[8]], reaction solvents (toluene, tetrahydrofuran, 1,2-dichloroethane, ethyl acetate, and 2-methyl-tetrahydrofuran),[5] and reaction temperatures (even under pressure). Unfortunately, all of these attempts were unsuccessful. We turned our attention to evaluating the effect of hippuric acid substituents on the Erlenmeyer reaction to better understand the transformation; in this context, evaluation of substituents of hippuric acid was performed[5] as follows: (a) reaction with an aldehyde containing an electron-withdrawing group such as **6a**, (b) reaction with an aldehyde containing an electron-donating group such as **6b**, (c) evaluation of Hünig's base and sodium acetate as reaction base. The general reaction strategy for this study is shown in Scheme 2.

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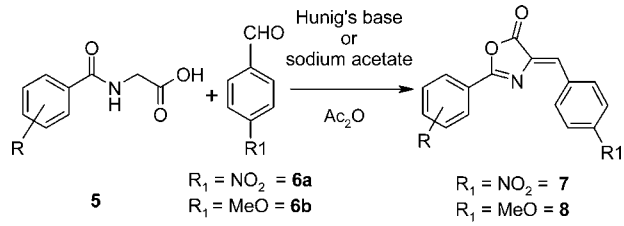
10.1021/op100032s
Published on Web 04/07/2010

Scheme 2. **General reaction for substituted hippuric acids evaluation**



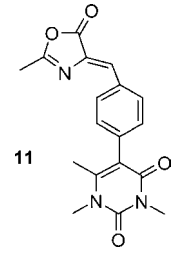
Substituted Hippuric Acids Syntheses. 4-Arylidene-2-phenyl-5(4)-oxazolones are important intermediates for the synthesis of several fine chemicals[9] which are usually obtained via an Erlenmeyer reaction. This classical method affords a potential mixture of *Z*- and *E*-stereoisomers; however, in most of the cases the thermodynamically more stable *Z*-isomer[10] is observed as the main product. Numerous papers have been published in the recent past evaluating different bases for the Erlenmeyer reaction.[6−8,11−19] Most of the recent reports involved reactions of hippuric acid with a variety of aromatic aldehydes, but a detailed study of substituent effects was lacking. To this end, we undertook studies of both the substituent effects on the aromatic aldehyde, reported elsewhere,[5] and on the hippuric acid partner. The substituted hippuric acids **3** and **5a**−**k** were synthesized *via* a modified Schotten−Baumann[20] reaction with the appropriate acid chloride **9** and glycine ethyl ester hydrochloride, **10**, as shown in Scheme 3.

Stereoelectronic Effects in the Hünig's Base-Catalyzed Reaction. It was recently reported by our group[5] that, compared to all other bases, Hünig's base provides fast Erlenmeyer reaction conversion; nevertheless, the reaction time could be limited by substituents on the benzaldehyde. Benzaldehydes containing electron-withdrawing groups (EWGs) were shown to react faster; meanwhile, electron-donating groups (EDGs) afforded slower reactions. Taking into account these facts, the strategy was to react substituted hippuric acids with a highly reactive aldehyde in order to nullify the effect of aldehyde on the reaction. If the hippuric acid substituent was affecting the reaction conversion, this could be detected and then compared with reaction conversions using the reference substrate **5** (Table 1, entry 1). Thus, the first step of our study was to evaluate the effect of substituents on the hippuric acids in the presence of the highly reactive aldehyde 4-nitrobenzaldehyde **6a** using Hünig's base and acetic anhydride under solvent-free reaction conditions[5] (Table 1).

It was apparent that the presence of an *o*-substituent influenced the reaction rate. The observed reactivity was in the order $NO_2 \ll Cl, Br < F, Me$ (Table 1, entries 2−6). The same order was observed for *p*-substitution but with less impact. In addition, electronic effects seem to have greater influence on the reaction rate than those from steric factors (Table 1, entries 2−3). Clear examples of these observations are *o*-fluoro- and *o*-nitro-hippuric acids, which require longer reaction times as compared with their *p*-analogues (Table 1, entries 3, 13 vs 8, and 6 vs 7, see Figure 1). Following these observations, it was expected that 2,6-disubstitution would have the largest effect on the reaction rate, especially if it is an electron-withdrawing substituent, and this proved to be the case (Table 1, entries 9, 12, 13).

Knowing the net effect with an activated aldehyde, the next step was the evaluation of substituted hippuric acids with the deactivated 4-methoxybenzaldehyde, **6b** (Table 1, entries 14−18). The introduction of an extra deactivating group on the system produced longer reaction times in most of the examples. A comparison of the relative reaction rate of substituted hippuric acids with aldehyde **6a** versus **6b** is shown in Figure 2.

Hünig's base reaction conditions were subsequently assessed with the substrates of interest: **3** and **4** (Scheme 1). Taking into account the observed effects of substituents, slow conversion was hypothesized because of two main factors: the deactivating effect of the *o*-difluoro groups on **3** and the deactivating characteristics of aldehyde **4**. Consequently, when this reaction was performed under Hünig's base reaction conditions, only 35% conversion to **2** was observed by HPLC after 12 h. In addition to the slow conversion, the transacylation byproduct **11** was observed in approximately 17%.[21,22] This byproduct became a significant problem during product isolation, and the product quality was adversely affected.



Efforts were made to optimize the Hünig's base reaction conditions by using elevated temperature (80 °C). Although a 30 °C increase in reaction temperature successfully decreased the reaction time for hippuric acids containing electron-donating

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(22) Large amounts of transacetylation were also observed in reactions using other bases: NaOAc, $Bi(AcO)_3$, and $(NH_4)_2H(PO)_4$. When using ZnO_2 at room temperature, transacetylation was not detected, but conversion was also minimal.

Scheme 3. **General reaction for preparing substituted hippuric acids**

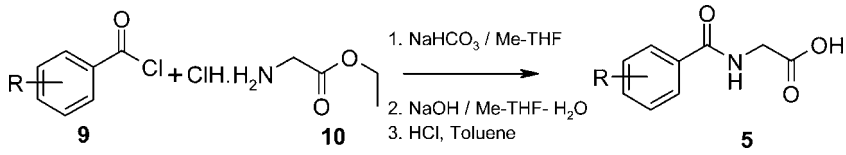
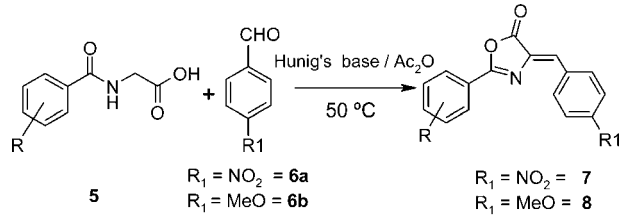


Table 1. **Substituted hippuric acids reacted with aldehydes 6a and 6b under Hünig's base reaction conditions**



entry	hippuric acid substituent	aromatic aldehyde	reaction time[a] (h)	conversion (area %)[b,c]	oxazolone
1	none	**6a**	0.5	98	**7**
2	2-methyl-	**6a**	7	87	**7a**
3	2-fluoro-	**6a**	24	76	**7b**
4	2-chloro-	**6a**	24	60	**7c**
5	2-bromo-	**6a**	24	62	**7d**
6	2-nitro-	**6a**	24	12	**7e**
7	4-nitro-	**6a**	7	62	**7f**
8	4-fluoro-	**6a**	2	81	**7g**
9	2-chloro-6-methyl-	**6a**	24	30	**7h**
10	2,6-dimethyl-	**6a**	24	77	**7i**
11	2,6-dimethoxy-	**6a**	24	67	**7j**
12	2,6-dichloro-	**6a**	24	20	**7k**
13	2,6-difluoro-	**6a**	24	72	**7l**
14	none	**6b**	24	82	**8**
15	2-methyl-	**6b**	24	74	**8a**
16	2-fluoro-	**6b**	24	59	**8b**
17	2-chloro-	**6b**	24	52	**8c**
18	2,6-difluoro-	**6b**	24	35	**8l**

[a] Reaction at 50 °C except entry 1 at 25 °C. [b] Geometries of the alkylidene residues have not been determined. [c] Areas have not been normalized for comparison, unlike those for the substrates.

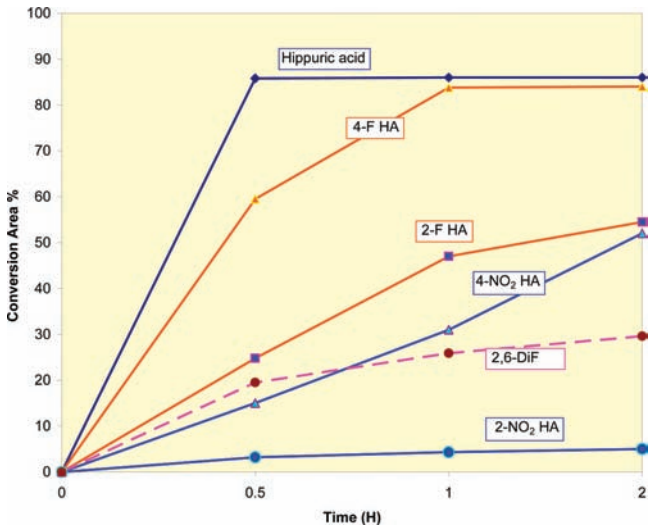


Figure 1. **Hippuric acid *o*- vs *p*-substituent effect. The substituted hippuric acids were reacted with aldehyde 6a in the presence of Hünig's base and acetic anhydride at 25 °C for 30 min and then kept at 50 °C.**

groups, the modification was detrimental for those containing electron-withdrawing groups. In these last cases, the reaction conversion was affected by increased occurrence of side reactions, such as transacylation and condensation side products.

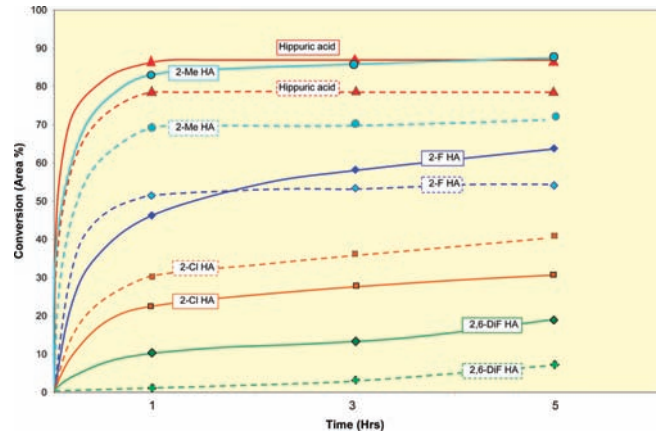


Figure 2. **Comparison of reaction conversion for hippuric acids reacted with aldehyde 6a (solid line) vs aldehyde 6b (broken line). HA = hippuric acid.**

It is clear that substituents in the aromatic ring of hippuric acid play an important role in the reaction. Furthermore, the effect on the reaction rate by hippuric acid substituents also led to several byproduct such as **11**, **14**, and **15**. We strongly believe that **14** and **15** are produced from the proposed intermediate **13** (Scheme 4).[23] On the basis of reference 23 and

(23) Chandrasekhar, S.; Karri, P. *Tetrahedron Lett.* **2006**, *47*, 5763–5766.

Scheme 4. **Erlenmeyer reaction intermediates and byproducts under Hünig's base reaction conditions**

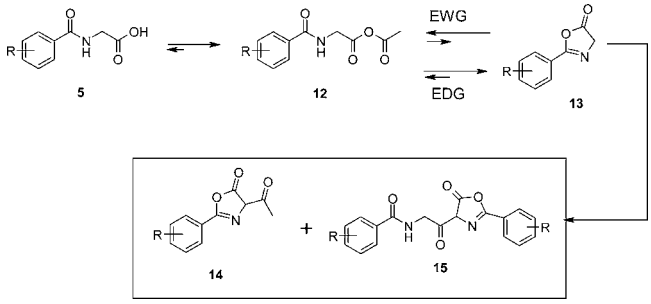
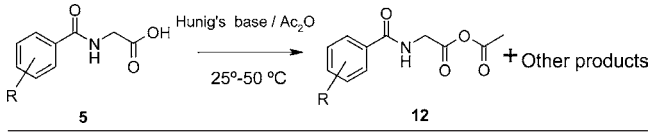


Table 2. **Mixed anhydride (12) conversion under Hünig's base conditions**[a]



entry	hippuric acid substituent	temp/time °C/h	conversion (area %)[b]	mixed anhydride
1	none	25/1	42	**12**
2	2-methyl-	25/1	59	**12a**
3	2-fluoro-	25/2	57	**12b**
4	2-chloro-	25/2	65	**12c**
5	2-bromo-	25/2	71	**12d**
6	2-nitro-	25/1	90	**12e**
7	4-nitro-	25/1	68	**12f**
8	2-chloro-6-methyl-	50/2	81	**12h**
9	2,6-dichloro-	50/2	84	**12k**
10	2,6-difluoro-	50/2	84	**12l**

[a] To a mixture of hippuric acid (10 mmol) and acetic anhydride (30 mmol), Hünig's base was added (10 mmol) and the reaction monitored by HPLC. [b] Areas have not been normalized for comparison, unlike those for the substrates.

from the above results, the formation of the proposed intermediate **13** was thought to be affected by hippuric acid substituents. The presence of EWGs seems to drive the equilibrium towards intermediate **12**; meanwhile, EDGs drive the equilibrium towards the proposed intermediate **13**. To gain a better understanding of this equilibrium phenomenon, experiments were conducted with several hippuric acid derivatives in the absence of aldehyde, and the reactions were monitored by HPLC (Table 2).[24] On the basis of the observed results, it was evident that groups such as H- and Me- (Table 2, entries 1−2) afforded higher amounts of **14** and **15**, and therefore, a low percentage of **12** was detected. On the other hand, as the strength of the deactivating effect of the *o*-substituent increased, a higher percentage of intermediate **12** was observed; consequently, decreased amounts of byproducts **14** and **15** were detected (Table 2, entries 3−6). In these series, F-group was the exception. By switching the *o*-substituent to the *p*-position, a decreased amount of **12** was detected (Table 2, entries 6−7) showing that *o*-substitution has a greater effect on the **12**−**13** equilibrium. Finally, 2,6-disubstitution afforded a high percentage of **12** (Table 2, entries 8−10) because of the EWG's influence. As a result of these observations, we conclude that both the nature and the isomeric position of substituents on the hippuric acid dictate the equilibrium position between **12** and proposed intermediate **13**.

Stereoelectronic Effects in the Sodium Acetate-Catalyzed Reaction. To access the stereoelectronic effects on the reaction rate using the sodium acetate base, an additional study with sodium acetate was undertaken. This process utilizes only 10−20 mol % of sodium acetate, rather than the original stoichiometric amount. In addition, Me-THF proved to be a superior solvent compared to dioxane for this reaction. The sodium acetate/Me-THF conditions (SAMT Process) successfully minimized the transacylation side reaction. It was expected that, even with these improvements, the stereoelectronic effects would show the same trend as in the Hünig's base.

Substituted hippuric acids, **3** and **5a**−**k,** were reacted with aldehydes **6a** and **6b**, acetic anhydride, sodium acetate, and Me-THF at reflux (Table 3). Analogous to Hünig's base experiments, the aldehyde substituents significantly affected reaction rate. Reactions with electron-deficient **6a** were considerably faster than those with the electron-rich **6b**. In all cases, low-to-moderate conversion was achieved in 24 h. The trend for the substituted hippuric acids under the SAMT process conditions was also similar to that seen under the Hünig's base conditions. The strong deactivating effect of the *o*-nitro group reduced the reaction conversion compared with that of its *p*-nitro analogue (Table 3, entries 6 vs 7 and 19 vs 20). Again, 2,6-disubstitution had a more pronounced effect than *o*-substitution on the reaction conversion.

Even though the SAMT process in general showed longer reaction times, lower quantities of byproduct were observed compared with those from reactions with the Hünig's base conditions. In this case, we hypothesize that the proposed intermediate **13** (Scheme 4) was gradually generated, and because the overall basicity of the reaction media was relatively low as compared to Hünig's base conditions, the competitive side reactions were inhibited. Therefore, the desired reaction pathway prevailed in most cases, leading to higher yields.

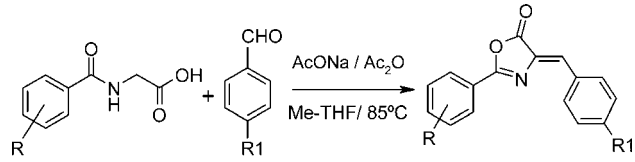
In general terms, the effect of hippuric acid substituents on the Erlenmeyer reaction rate was similar under both Hünig's base and SAMT process conditions. Hünig's base conditions (1 equiv of base) resulted in faster reactions but generated side reactions such as condensation and transacylation. On the other hand, the SAMT process (catalytic amount of base) was slower, but undesired side reactions were minimized.

Conclusion

We demonstrated the effects of stereoelectronic factors of substituents in the aromatic ring of hippuric acid on the progression of the Erlenmeyer−Plöchl reaction. Substituents in the *o*-position had more impact on reaction conversion compared with those in the *p*-position. In general, electron-withdrawing substituents resulted in longer reaction times and lower conversions than electron-donating substituents with some exceptions (Table 3, entry 26). These substituents affected both the reactivity of the hippuric acid and the reactivity of the proposed oxazolone intermediate **13**, not only the reaction time, but also the prevalence of condensation and/or transacylation side reactions. The occurrence of side reactions was also related

(24) The proposed intermediate **13** was not detected in our reactions maybe because the HPLC conditions reverted the species **13** back to the probable, more stable intermediate **12**. We confirmed the reversibility process of oxazolone **13** by injecting a purchased sample from Aldrich (R = H).

Table 3. **Substituted hippuric acids reacted with aldehydes 6a and 6b under sodium acetate/Me-THF reaction conditions**



5 $R_1 = NO_2$ = **6a**; R_1 = MeO = **6b**

$R_1 = NO_2$ = **7**; R_1 = MeO = **8**

entry	hippuric acid substituent	aromatic aldehyde	reaction time[a] (h)	conversion (area %)[b,c]	oxazolone
1	none	**6a**	1	93	**7**
2	2-methyl-	**6a**	3	92	**7a**
3	2-fluoro-	**6a**	4	94	**7b**
4	2-chloro-	**6a**	3	90	**7c**
5	2-bromo-	**6a**	4	93	**7d**
6	2-nitro-	**6a**	24	82	**7e**
7	4-nitro-	**6a**	4	83	**7f**
8	4-fluoro-	**6a**	3	86	**7g**
9	2-chloro-6-methyl-	**6a**	24	83	**7h**
10	2,6-dimethyl-	**6a**	24	93	**7i**
11	2,6-dimethoxy-	**6a**	24	91	**7j**
12	2,6-dichloro-	**6a**	24	58	**7k**
13	2,6-difluoro-	**6a**	24	87	**7l**
14	none	**6b**	24	85	**8**
15	2-methyl-	**6b**	24	88	**8a**
16	2-fluoro-	**6b**	24	83	**8b**
17	2-chloro-	**6b**	24	80	**8c**
18	2-bromo-	**6b**	24	78	**8d**
19	2-nitro-	**6b**	24	61	**8e**
20	4-nitro-	**6b**	24	67	**8f**
21	4-fluoro-	**6b**	24	83	**8g**
22	2-chloro-6-methyl-	**6b**	24	23	**8h**
23	2,6-dimethyl-	**6b**	24	37	**8i**
24	2,6-dimethoxy-	**6b**	24	28	**8j**
25	2,6-dichloro-	**6b**	24	18	**8k**
26	2,6-difluoro-	**6b**	24	67	**8l**

[a] Reaction at reflux temperature. [b] Geometries of the alkylidene residues have not been determined. [c] Areas have not been normalized for comparison, unlike those for for the substrates.

to the kind of base used in the system. Furthermore, substituents in the aromatic ring of the aldehyde had an additional effect on the reaction rate. Overall, substituents in both the hippuric acid and the benzaldehyde had profound effect on the reaction rate. The SAMT process conditions were deemed superior, due to the advantage of minimizing side reactions even at the cost of extended reaction times and higher temperatures. The effect of substitutions led us to conclude that the observed reaction time for the formation of intermediate **2** was a result of stereoelectronic factors rather than process parameters. The SAMT process was selected for our subsequent chemistry to produce intermediate **2** at 70-g scale, affording acceptable quality and yield.

Experimental Section

General. *HPLC analytical procedure:* Agilent 1100; UV 260 nm; Eclipse XDB-C8 Column (100 mm ×3.0 mm, 3.5 μm, Part No. 961967-306); 40 °C; 0.5 mL/min flow rate; 2 μL injection; Phase A: 0.1% TFA in DI H_2O; Phase B: 0.1% TFA in ACN; 15 min run time (isocratic) and 5 min post time.

Area % was calculated as follows: $A_i \times 100/\Sigma A =$ Area %

where A_i = Area of oxazolone; ΣA = Area of all peaks in sample (excluding blank peaks).

*General Procedure for the Preparation of Substituted Hippuric Acids **3** and **5a**−**k.*** A mixture of glycine ethyl ester hydrochloride (**10**) (42.9 g, 0.307 mol), sodium bicarbonate (60.8 g, 0.723 mol), and methyl-THF (180 mL) was cooled to 0−5 °C, and water (80 mL) was added. The mixture was stirred 30 min at 0°−5 °C. A solution of respective acyl chloride (**9**) (0.228 mol) in methyl-THF was added over 2 h. The mixture was held at 10 °C for 60 min and then diluted with water (180 mL). The phases were separated, and the aqueous phase was removed; the organic phase was washed with water (86 mL) and treated with 15% sodium hydroxide solution (74 g) for 1 h at 25−28 °C to complete hydrolysis. Finally, the mixture was treated with 31% hydrochloric acid enough to bring pH <2. The phases were separated, the aqueous phase was removed, and the organic phase was washed with water (22 mL). Crystallization was performed by replacing methyl-THF with toluene via vacuum distillation. The solid was collected by vacuum filtration which, after drying under vacuum for about 8 h, afforded the substituted hippuric acids **3**, and **5a**−**k**. Yield: **3** (95%); **5a** (95%); **5b** (83%); **5c** (96%); **5d** (93%); **5e** (97%); **5f** (86%); **5g** (87%); **5h** (93%); **5i** (85%); **5j** (92%); **5k** (98%). Yields are from the respective acyl chloride except for compounds **3**, **5i** and **5j** which are from the free acid.

General Procedure using Hünig's base. 2-Bromo-hippuric acid **5d** (1.44 g, 6 mmol), aldehyde **6a** (0.703 g, 5 mmol), and

acetic anhydride (1.71 g, 17 mmol) were combined. Hünig's base (0.65 g, 5 mmol) was added and stirred 30 min at room temperature. The mixture was heated to 50 °C, and samples were taken accordingly as shown in Table 1. Alternatively, oxazolone isolation was performed by cooling the reaction mixture to 35−40 °C and then adding an ethanol−water mixture, 1:1 v/v (10 mL). The oxazolone (**7d**) was collected by vacuum filtration followed by washing with 1:1 ethanol/water (5 mL), warm water (5 mL), and ethanol (5 mL). After drying at 50−60 °C under vacuum for 12 h, the oxazolone was characterized by HPLC, ^{1}HNMR, and melting point.

Oxazolones General Procedure using Sodium Acetate. A mixture of **6a** (0.5 g, 3.3 mmol), sodium acetate (0.06 g, 0.73 mmol), 2-fluoro-hippuric acid **5b** (0.78 g, 4.0 mmol), and acetic anhydride (0.7 g, 6.85 mmol) in 2-methyl-tetrahydrofuran (6.4 mL) was stirred and heated to reflux. Samples were taken accordingly for the specified time (Table 3). Alternatively for oxazolone isolation, the reaction mixture was cooled to room temperature, ethanol/water 1:1 v/v (10 mL) was added, and the slurry was cooled overnight (≤10 °C). The oxazolone **7b** was collected by vacuum filtration followed by washing with 1:1 ethanol/water (5 mL), warm water (5 mL), and ethanol (10 mL). After drying at 50−60 °C under vacuum for 12 h, the oxazolone was characterized by HPLC, ^{1}H NMR, ^{13}C NMR, and melting point.

SAMT Process for Compound 2. A mixture of **3** (70 g, 0.33 mol), aldehyde **4** (70 g, 0.27 mol, sodium acetate (5.3 g, 0.065 mol) in methyl-THF (500 mL) was heated to 55 °C for 30 min. To the slurry was added acetic anhydride (72.4 g, 0.71 mol). The mixture was heated to reflux for 3 h and then ∼100 mL of methyl-THF was removed by distillation. The yellow slurry was held at reflux for 21 h. After reaction completion by HPLC (<4% aldehyde **4**), the reaction mixture was cooled to room temperature and diluted with water (196 mL). The slurry was stirred overnight at room temperature. The solid was collected by vacuum filtration followed by washing with warm water (250 mL) and warm ethanol (250 mL). The yellow solid was dried at 50−60 °C under vacuum for 12 h to afford oxazolone **2** (100.7 g) in 85% yield. Mp 261 °C; ^{1}H NMR (400 MHz, DMSO-d_6) 8.29 (dd, J = 6.7, 1.6 Hz, 2H), 7.80 (tt, J = 8.5, 6.3 Hz, 1H), 7.53 (s, 1H), 7.39 (m, 2H), 7.37 (d, J = 8.3 Hz, 2H), 3.43 (s, 3H), 3.23 (s, 3H), 2.17 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.24, 161.03, 160.83 (dd, J = 259.7, 5.2 Hz), 156.50 (t, J = 4.3 Hz), 151.30 (s), 150.22 (s), 138.28 (s), 135.64 (t, J = 11.0 Hz), 132.61 (s), 132.06 (s, J = 11.3 Hz), 131.94 (s), 131.70 (s, J = 8.8 Hz), 131.61 (s), 113.17 (dd, J = 21.5, 3.5 Hz), 111.44 (s), 104.45 (t, J = 14.5 Hz), 32.03 (s), 27.97 (s), 17.91 (s).

Acknowledgment

We thank Dr. Stephan Chan for the valuable HPLC/MS data and Dr. Jodie Brice for her useful comments.

Supporting Information Available

Supplementary ^{1}H NMR and ^{13}C NMR data for compounds **2**, **5a**−**k**, **7**, **7a**−**l**, **8**, **8a**−**l** and complete NMR study data and spectra for compound **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

Received for review January 20, 2010.

OP100032S