DOI: 10.1002/ejoc.200901420

Simple Synthesis of Amides and Weinreb Amides Using PPh_3 or Polymer-Supported PPh_3 and Iodine

Amit Kumar,[a] Hari Kiran Akula,[a] and Mahesh K. Lakshman*[a]

Keywords: Amides / Phosphanes / Supported reagents / Iodine / Synthetic methods

The combination of PPh_3/I_2 has been shown to be effective for the conversion of a range of carboxylic acids into secondary, tertiary, and Weinreb amides. Simplification of the procedure was possible with the use of polymer-supported PPh_3/I_2. Weinreb amides produced with the use of polymer-supported PPh_3 could be filtered through a short silica gel plug and used in further transformations. Thus, the use of polymer-supported PPh_3 offers potential applicability to diversity-oriented reactions. Formal total syntheses of apocynin and pratosine, as well as syntheses of anhydrolychorinone and hippadine, have been achieved through the use of this amide-forming method. An attempt has been made to gain insight into this reaction.

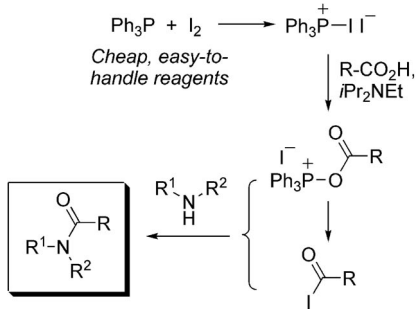
Introduction

Besides being a ubiquitous functionality, the amide linkage is prominent in functional group interconversions during multistep syntheses. This is reflected in a substantial amount of literature that continues to emanate on new methods for formation of the amide bond.[1,2] Halophosphonium salts derived from PPh_3/I_2 and $[(R_2N)_3]P/I_2$ have recently found applications in the activation of the amide linkages of hypoxanthine nucleosides for further transformations,[3–7] and dehydration of oximes by PPh_3/I_2 has been reported.[8] Direct activation of tautomerizable heterocycles for C–C bond-forming reactions by PyBroP has recently been demonstrated.[9] Thus, halophosphonium compounds enjoy wide applications in organic transformations. In the area of amide-bond formation, the combination of PPh_3 with halogen sources such as NCS,[10] NBS,[11] Br_2,[12] $BrCCl_3$,[13] CCl_4,[13,14] CBr_4,[14] and trichloroisocyanuric acid[15] have all been explored. In addition, polymer-supported PPh_3 (Pol–Ph_3P) has been utilized for amidation in combination with CCl_4[16] and Cl_3CCN.[17]

To our surprise, the combination of PPh_3 and I_2 for the generation of the amide linkage seems to have remained unstudied. The simplicity in handling these reagents, and the fact that they are inexpensive, renders them particularly attractive for this purpose. In this paper we have explored the utility of this reagent combination, as well as Pol–Ph_3P, for the synthesis of various amides and synthetically versatile Weinreb amides. We have applied this method en route to ketones, the formal synthesis of two natural products, and the total synthesis of two others, where amide formation is a key step.

Results and Discussion

By using $^{31}P\{^1H\}$ NMR spectroscopy, we previously observed that upon mixing PPh_3 and I_2 in a 1:1 ratio a new species is produced, presumably $(Ph_3P^+–I)I^-$. This entity was capable of reacting with the amide group of hypoxanthine nucleosides.[5] Therefore, our first question was whether such a species could react with carboxylic acids as well. Since BroP and PyBroP are well-known reagents for amidation,[18] this appeared feasible. For the reaction to occur, deprotonation of the carboxylic acid would be necessary and *i*Pr_2NEt was selected for this purpose. The overall reaction is depicted in Scheme 1. Here, either an acyl phosphonium species or an acyl iodide (produced by substitution of Ph_3PO with iodide) could undergo reaction with the amine, producing the amide.



Scheme 1. A plausible mechanism for the amidation reaction.

[a] Department of Chemistry, The City College and The City University of New York,
160 Convent Avenue, New York, NY 10031-9198, U.S.A
Fax: +1-212-650-6107
E-mail: lakshman@sci.ccny.cuny.edu

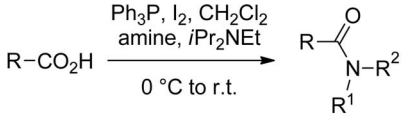
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.200901420.

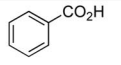
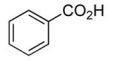
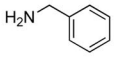
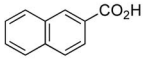
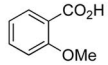
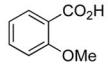
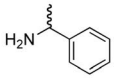
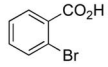
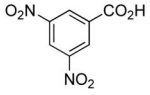
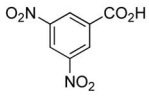
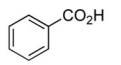
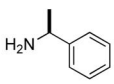
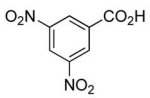
With this rationale we set about exploring the general versatility of the method by using a range of carboxylic acids and amines. The results from this analysis are presented in Table 1.

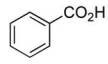
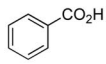
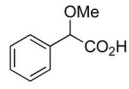
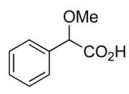
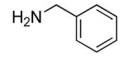
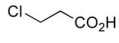
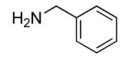
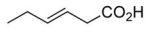
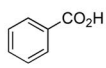
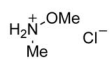
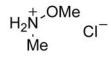
Results from Table 1 indicate that $(Ph_3P^+–I)I^–$ is suitably effective for the conversion of several carboxylic acids into the corresponding amides, and at a 1:1:1:1:1.5 stoichiometry of PPh_3/I_2/carboxylic acid/amine/iPr$_2$NEt, primary and secondary amines react well. Substitution α to the amine does not hinder the reaction (Table 1, Entries 5 and 9). Reaction of an *o*-substituted arylamine proceeded in acceptable yield (Table 1, Entry 10). 3-Furoic acid reacted efficiently, without complication (Table 1, Entry 11). Reaction of the highly hindered *tert*-butylamine with benzoic acid proceeded well (Table 1, Entry 13). α-Methoxyphenylacetic acid reacted reasonably with both *tert*-butylamine and benzylamine (Table 1, Entries 14 and 15). Acceptable reactions of 3-chloropropanoic acid with benzylamine (Table 1, Entry 16) and *trans*-3-hexenoic acid with piperidine (Table 1, Entry 17) were observed.

Although many reactions gave moderate to good product yields under the above-mentioned stoichiometry, some reactions could be improved with the use of 2 molar equivalents each of PPh_3 and I_2 (Table 1, Entries 10, 12, 14–17). Also of interest is the fact that *N*-methoxy-*N*-methyl (Weinreb[34]) amides could also be prepared by this route (Table 1, En-

Table 1. Amide and Weinreb amide synthesis using PPh_3/I_2.[a]



Entry	Acid	Amine	Time [h]	% Yield
1			4	77[2g]
2			1.5	77[19]
3			12	60[20]
4			1	74[21]
5			2	85[22]
6			2	77[23]
7			2	83[24]
8			1.5	83
9			0.5	78[25]
10			3 3	52[24] 72[b]

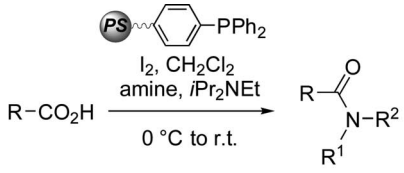
Entry	Acid	Amine	Time [h]	% Yield
11			0.5	83[26]
12			1 1	63[27] 72[c]
13			12	80[28]
14			1 1	56[29] 73[c]
15			2 2	45[29] 67[c]
16			13 13	44[30] 53[c]
17			3 1	48[31] 65[c]
18			1	70[d][32]
19			1	65[d][33]

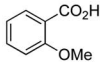
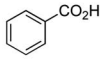
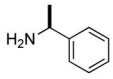
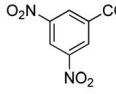
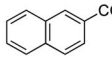
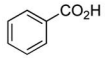
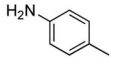
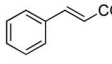
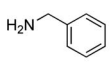
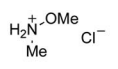
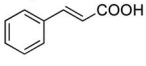
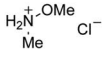
[a] Reactions were conducted by using 1 mmol each of PPh_3, I_2, carboxylic acid, amine, and 1.5 mmol of iPr$_2$NEt in 4 mL of CH_2Cl_2, unless noted otherwise. [b] Yield obtained by using 2 equiv. each of PPh_3 and I_2, and 1.5 equiv. of *o*-toluidine. [c] Yield obtained by using 2 equiv. each of PPh_3 and I_2. [d] 2.5 equiv. of iPr$_2$NEt was used.

tries 18 and 19). Owing to the synthetic versatility of Weinreb amides, methods for their facile preparation are of continued interest.[35–39]

Because Ph_3PO is a byproduct in this reaction, we next considered facilitating its easy removal. For this, polymer-supported PPh_3 (Pol–PPh_3) offered a simple solution. As indicated earlier, Pol–PPh_3 has been used for amidation,[16,17] and PPh_3/CBr_4 has been used in Weinreb amide synthesis.[40] However, to the best of our knowledge, Pol–PPh_3 has not been used in combination with I_2. Our results with Pol–PPh_3/I_2 are shown in Table 2.

Table 2. Use of Pol–PPh_3/I_2 for the synthesis of amides and Weinreb amides.[a]



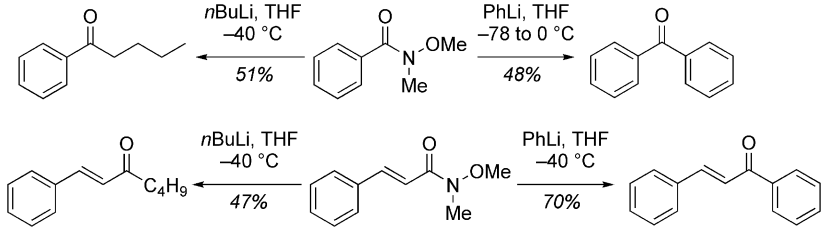
Entry	Acid	Amine	Time [h]	% Yield
1			2	75[21]
2			2	72[25]
3			1	65
4			11 4	57[20] 71[b]
5			6	53[41]
6			0.83 1	53[42] 78[b]
7			1	76[c][32]
8			1	79[c][39h]

[a] Reactions were conducted by using 1 mmol each of Pol–PPh_3 (2.28 mmol/g loading), I_2, carboxylic acid, amine, and 1.5 mmol of iPr_2NEt in 4 mL of CH_2Cl_2, unless noted otherwise. [b] Yield obtained by using 2 equiv. each of Pol–PPh_3 and I_2. [c] 2.5 equiv. of iPr_2NEt was used.

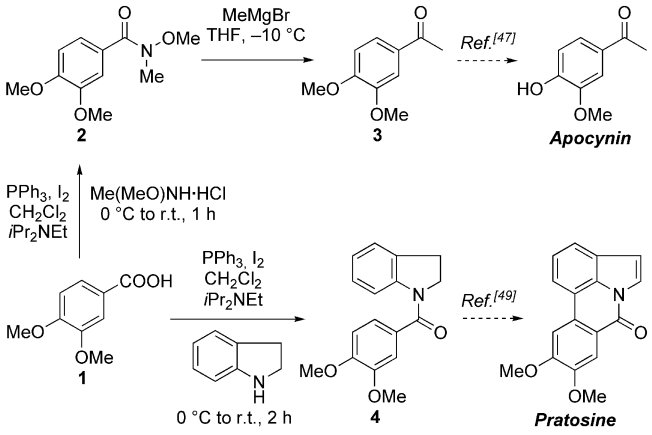
Results from Table 2 indicate that the use of (Pol–Ph_3P^+–I)I^- is just about as effective as solution chemistry and that this combination can be used for the synthesis of Weinreb amides as well. The operational simplicity is exemplified by the fact that the Weinreb amides obtained could be simply filtered through a short silica gel plug and then subjected to reactions with organometallics (Scheme 2, yields were not optimized but examples are to demonstrate utility for high-throughput synthesis). Thus, (*E*)-*N*-methoxy-*N*-methylbenzamide could be converted into benzophenone and *n*-butylphenyl ketone, whereas *N*-methoxy-*N*-methyl-3-phenylacrylamide was converted into chalcone and (*E*)-1-phenyl-1-hepten-3-one.

Next, we considered evaluating the use of the described methodology for the synthesis of natural products where a key step is amide formation. The first compound selected was apocynin (acetovanillin), which possesses interesting physiological activities. For example, it has been shown to have vasodialatory properties possibly through inhibition of Rho kinase activity,[43] antimetastatic activity against human lung cancer cells,[44] and inhibition of cartilage damage caused by inflammation.[45] This compound has previously been prepared by Grignard addition to vanillin acetate followed by oxidation with DDQ,[46a] and by $Yb(OTf)_3$-mediated Friedel–Crafts reaction/demethylation of aryl methyl ethers.[46b] As shown in Scheme 3, our formal synthesis of apocynin involved the conversion of veratric acid (**1**) into the corresponding Weinreb amide **2** by using 2 equiv. each of PPh_3 and I_2, 1 equiv. each of carboxylic acid and Me(MeO)NH·HCl, and 2.5 equiv. of iPr_2NEt (69% yield). Addition of MeMgBr to **2** then yielded 3′,4′-dimethoxyacetophenone (**3**, 97% yield). The conversion of **3** into apocynin by selective demethylation by using NaSEt is known in the literature.[47]

The second formal synthesis was that of pratosine, which belongs to the family of *Amaryllidaceae* alkaloids, and several members of this family possess high biological activity (e.g. reversible inhibition of fertility in male rats[48a] and antitumor activity[48b]). *N*-Acylindoline **4** has previously been prepared by a Pd-catalyzed amidation.[49] In our approach, starting from veratric acid (**1**), amide **4** was synthe-



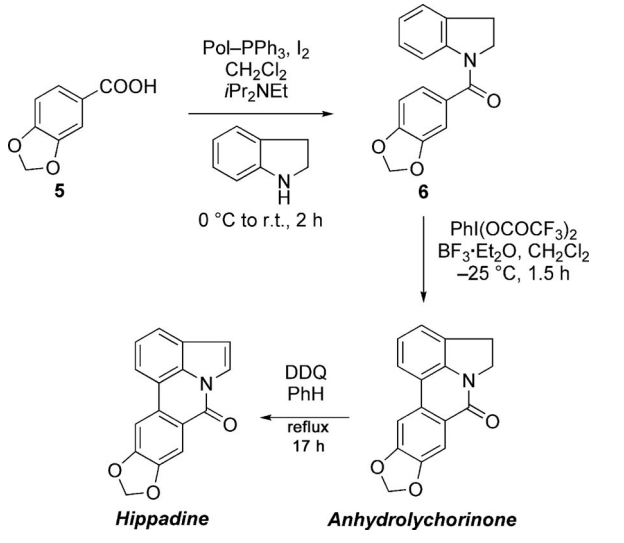
Scheme 2. Synthesis of ketones from Weinreb amides obtained through the use of Pol–PPh_3/I_2, followed by filtration through a silica gel plug.



Scheme 3. Formal total syntheses of apocynin and pratosine.

sized by using of 1 equiv. each of PPh_3/I_2/carboxylic acid/indoline and 1.5 equiv. of iPr_2NEt (83% yield). Conversion of **4** to pratosine has been reported.[49]

As a third example to showcase the amidation step, we completed the synthesis of anhydrolychorinone and hippadine (Scheme 4). Here again lynchpin *N*-acyl amide **6** was previously synthesized by Pd-catalyzed amidation.[49] We conducted amide formation by using 1 equiv. each of PPh_3/I_2/piperonylic acid/indoline and 1.5 equiv. iPr_2NEt, or with the use of Pol–PPh_3 in place of PPh_3 under otherwise identical conditions. Consistent with the results in Tables 1 and 2, yields from both methods were comparable: 70% from solution chemistry and 74% with Pol–PPh_3. Further conversions were conducted as reported.[49] Oxidation of **6** to anhydrolychorinone proceeded in 23% yield by using $PhI(OCOCF_3)_2$ and $BF_3{\cdot}Et_2O$ (83% reported in the literature[49]), and DDQ olefination proceeded in 78% yield (80% reported in the literature[49]) to yield hippadine.



Scheme 4. Syntheses of anhydrolychorinone and hippadine.

During the course of our investigations we encountered some unusual ^1H NMR spectroscopic characteristics of amides **4** and **6**. Although the ^1H NMR spectra of our products in $CDCl_3$ matched those in the literature, only six aromatic protons have been reported for each,[49] and this corresponded to our observations. We wanted to ensure that no undesired electrophilic reactions had occurred on the aromatic ring in our cases. Therefore, we sought additional data. When the ^1H NMR spectra of **4** and **6** were obtained in C_6D_6, an additional broad downfield proton resonance was observed in each case (ca. δ = 8.1 ppm, see spectra in the Supporting Information). Further, in the case of **4**, four distinct methoxy group resonances could be observed at δ = 3.31, 3.30, 3.28, and 3.27 ppm. Heating the C_6D_6 solutions to 70 °C resulted in a significant sharpening of the broad, downfield aromatic resonances in **4** and **6**. In the case of **4**, coalescence of the methoxy group resonances to two major ones was also seen. The COSY spectra for **4** and **6** in C_6D_6 at 70 °C are fully consistent with their respective structures, and in each case long-range coupling of the benzylic CH_2 group to the *ortho* aromatic proton was observed (see data in the Supporting Information).

Some of these properties are likely due to restricted rotation induced by the amide linkage. Although, this in itself is not surprising, it does raise a question about the efficiency of the cyclization reaction by hypervalent iodine reagents (e.g., **6** → anhydrolychorinone), which are conducted at subambient temperatures. That is, in such cases an unfavorably disposed rotamer could potentially influence the yield of the cyclization step.

Attempts at Understanding the Reaction Intermediates

As shown in Scheme 1, an acyl phosphonium species and/or an acyl iodide could be potential intermediates in this amidation. Acyl phosphonium intermediates have been invoked previously in the synthesis of esters, amides, and acyl azides.[10,14,40,50] On the other hand, acyl chlorides and acyl bromides have been prepared by reaction of acids with PPh_3/Cl_3CCN[51] and PPh_3/Br_3CCO_2Et,[52] respectively. Thus, we questioned whether acyl phosphonium intermediates could be directly observed by $^{31}P\{^1H\}$ NMR spectroscopy.

A solution of PPh_3 in CD_2Cl_2 at room temperature produced a sharp singlet at δ = –5.0 ppm. Addition of I_2 (1 equiv.) led to rapid disappearance of the phosphane signal and appearance of a new resonance at δ = –18.4 ppm, presumably due to the formation of $(Ph_3P^+–I)I^-$.[5] Addition of $PhCO_2H$ to this mixture led to no observable change in the ^{31}P resonance. However, upon addition of iPr_2NEt (1.5 equiv.), a new resonance was produced at δ = 30.1 ppm. Finally, addition of pyrrolidine (1 equiv.) to this mixture led to a very small upfield shift of the resonance (δ = 28.9 ppm). A similar result was obtained by using morpholine. Thus, it was not possible to establish exactly what type of intermediate is involved.

Therefore, in a second line of experimentation we exposed 3,5-dinitrobenzoic acid to the Pol–$PPh_3/I_2/iPr_2NEt$ combination in the absence of pyrrolidine. After 1 h, the polymer was filtered, pyrrolidine was added to the filtrate,

and the reaction was continued for an additional 1 h. The amide from this reaction was isolated in 11% yield, which is very low compared to that in Entry 3 in Table 2 (65% yield in a reaction time of 1 h). One possible explanation for the diminished yield could be the loss of the carboxylic acid as a polymer-bound acyl phosphonium species. Had acyl iodide been produced rapidly in the reaction, this should have remained in solution, leading to a better outcome. On the basis of this experiment, it is conceivable that the amidation reaction described herein proceeds largely via the intermediacy of an acyl phosphonium species, at least when Pol–PPh_3 is utilized.

Conclusions

In summary, we have demonstrated that the combination of PPh_3/I_2 or Pol–PPh_3/I_2 can be effectively utilized for the synthesis of a wide range of amides. The advantage of the PPh_3/I_2 combination is that the reagents are cheap and easy-to-handle, and the reactions are straightforward to conduct. In addition, the synthetically valuable *N*-methoxy-*N*-methyl (Weinreb) amides can also be synthesized by using this mild conversion, and simple purification allows for their rapid use in further transformations. The usefulness of this procedure has been demonstrated through the formal total synthesis of two natural products, apocynin and pratosine, as well as to the total synthesis of anhydrolychorinone and hippadine, where amide formation is an important step. No problems were evident in any of the cases reported.

Experimental Section

General Experimental Considerations: Thin-layer chromatography was performed on 200 μm silica gel plates and column chromatographic purifications were performed on 200–300 mesh silica gel. CH_2Cl_2 and *i*Pr_2NEt were distilled from CaH_2, and THF was distilled from $LiAlH_4$ and freshly distilled from Na prior to use. All other reagents were obtained from commercial sources and were used without further purification. Pol–PPh_3 (PS-triphenylphosphane, 2.28 mmol/g) was obtained from Biotage. ^1H NMR spectra were recorded at 500 MHz and are referenced to the residual protonated solvent. $^{31}P\{^1H\}$ NMR spectra were recorded at 202 MHz and are referenced to 85% H_3PO_4 as external standard. Some representative synthetic procedures are given below.

Synthesis of Amides by Using PPh_3/I_2: In a clean, dry, 10-mL round-bottomed flask equipped with a stirring bar were placed PPh_3 (1.0 mmol) and I_2 (1.0 mmol) in dry CH_2Cl_2 (4 mL). The reaction mixture was flushed with nitrogen gas and allowed to stir at 0 °C for 5 min. At this temperature, the carboxylic acid (1.0 mmol) was added, followed by the dropwise addition of *i*Pr_2NEt (1.5 mmol) and the appropriate amine (1.0 mmol). The reaction mixture was slowly brought to room temperature and allowed to stir until no starting material could be seen on TLC (see Table 1 for reaction times). The reaction mixture was diluted with water and extracted with CH_2Cl_2. The organic layer was dried with anhydrous Na_2SO_4 and evaporated under reduced pressure to afford the crude product, which was purified by chromatography on a silica gel column (EtOAc/hexanes). Any deviations from this procedure are noted in Table 1.

Synthesis of Amides by Using Pol–PPh_3/I_2: To a stirring solution of I_2 (1.0 mmol) in dry CH_2Cl_2 (5 mL) at 0 °C was added Pol–PPh_3 (1.0 mmol). The reaction mixture was flushed with nitrogen gas and allowed to stir at 0 °C for 5 min. At this temperature, the carboxylic acid (1.0 mmol) was added followed by the dropwise addition of *i*Pr_2NEt (1.5 mmol) and the appropriate amine (1.0 mmol). The reaction mixture was slowly brought to room temperature and allowed to stir until no starting material could be seen on TLC (see Table 2 for reaction times). The reaction mixture was filtered and evaporated to dryness. The crude product was purified through a short silica gel plug (EtOAc/hexanes). Any deviations from this procedure are noted in Table 2.

Synthesis of Weinreb Amides by Using Pol–PPh_3/I_2: To a stirring solution of I_2 (1.0 mmol) in dry CH_2Cl_2 (5 mL) at 0 °C was added Pol–PPh_3 (1.0 mmol). The reaction mixture was flushed with nitrogen gas and allowed to stir at 0 °C for 5 min. At this temperature, the carboxylic acid (1.0 mmol) was added followed by the dropwise addition of *i*Pr_2NEt (2.5 mmol) and *N*,*O*-dimethylhydroxylamine hydrochloride (1.0 mmol). The reaction mixture was slowly brought to room temperature and allowed to stir until no starting material could be seen on TLC (see Table 2 for reaction times). The reaction mixture was filtered and evaporated to dryness. The crude product was purified through a short silica gel plug (EtOAc/hexanes).

***N*-(3,5-Dinitrobenzoyl)pyrrolidine:** Purification of the crude product obtained by the procedure described above on a silica gel column (60% EtOAc in hexanes) afforded the title compound (84.3 mg, 83%) as a yellow foam. R_f (40% EtOAc in hexanes) = 0.35. ^1H NMR (500 MHz, $CDCl_3$, ambient temperature): δ = 9.13 (s, 1 H, Ar-H), 8.76 (s, 2 H, Ar-H), 3.74 (t, $^3J_{H,H}$ = 6.6 Hz, 2 H, pyrrolidinyl-H), 3.52 (t, $^3J_{H,H}$ = 6.6 Hz, 2 H, pyrrolidinyl-H), 2.09–2.01 (m, 4 H, pyrrolidinyl-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, ambient temperature): δ = 164.3, 148.3, 140.3, 127.5, 119.6, 49.5, 46.8, 26.4, 24.2 ppm. HRMS: calcd. for $C_{11}H_{12}N_3O_5$ $[M + H]^+$ 266.0771; found 266.0774.

3′,4′-Dimethoxyacetophenone (3)

Step1 – Preparation of Weinreb Amide 2: In a clean, dry, 10-mL round-bottomed flask equipped with a stirring bar were placed PPh_3 (526.0 mg, 2.0 mmol) and I_2 (507.6 mg, 2.0 mmol) in dry CH_2Cl_2 (6 mL). The reaction mixture was flushed with nitrogen gas and allowed to stir at 0 °C for 5 min. At this temperature, veratric acid (182.1 mg, 1.0 mmol) was added, followed by the dropwise addition of *i*Pr_2NEt (434 μL, 2.5 mmol) and *N*,*O*-dimethylhydroxylamine hydrochloride (97.5 mg, 1.0 mmol). The reaction mixture was slowly brought to room temperature and allowed to stir for 1 h. The reaction mixture was diluted with water and extracted with CH_2Cl_2. The organic layer was dried with anhydrous Na_2SO_4 and evaporated under reduced pressure to afford the crude product. Chromatographic purification on a silica gel column (40% EtOAc in hexanes) afforded **2** (155.2 mg, 69%) as a viscous liquid. R_f (40% EtOAc in hexanes) = 0.55. ^1H NMR (500 MHz, $CDCl_3$, ambient temperature): δ = 7.33 (d, $^3J_{H,H}$ = 8.4 Hz, 1 H, Ar-H), 7.22 (s, 1 H, Ar-H), 6.68 (d, $^3J_{H,H}$ = 8.4 Hz, 1 H, Ar-H), 3.86 (s, 3 H, OMe), 3.85 (s, 3 H, OMe), 3.52 (s, 3 H, *N*-OMe), 3.30 (s, 3 H, *N*-Me) ppm.

Step 2 – Addition of MeMgBr to 2: In a clean, dry, 10-mL round-bottomed flask equipped with a stirring bar was placed **2** (125.0 mg, 0.554 mmol) in dry THF (5.0 mL) under nitrogen gas, and the mixture was cooled to –10 °C. At this temperature, MeMgBr (554 μL, 1.66 mmol) was added dropwise, with stirring.

The reaction mixture was slowly brought to 0 °C and allowed to stir for 1 h. The reaction was quenched with saturated aqueous NH_4Cl (5 mL) and extracted with EtOAc (20 mL). The organic layer was separated, dried with Na_2SO_4, and concentrated. Chromatographic purification on a silica gel column (35% EtOAc in hexanes) afforded **3** (96.2 mg, 97%) as a colorless, viscous liquid. R_f (40% EtOAc in hexanes) = 0.62. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.49 (d, $^3J_{H,H}$ = 8.3 Hz, 1 H, Ar-H), 7.44 (s, 1 H, Ar-H), 6.81 (d, $^3J_{H,H}$ = 8.3 Hz, 1 H, Ar-H), 3.86 (s, 3 H, OMe), 3.85 (s, 3 H, OMe), 2.48 (s, 3 H, $COCH_3$) ppm. This compound is commercially available.

***N*-(3,4-Dimethoxybenzoyl)indoline (4):**[49] ^{1}H NMR (500 MHz, $CDCl_3$, ambient temperature): δ = 7.21 (d, $^3J_{H,H}$ = 7.4 Hz, 1 H, Ar-H), 7.16 (dd, $^3J_{H,H}$ = 1.8, 8.2 Hz, 1 H, Ar-H), 7.14 (s, 1 H, Ar-H), 7.11 (br. s, 1 H, Ar-H), 7.00 (t, $^3J_{H,H}$ = 7.1 Hz, 1 H, Ar-H), 6.89 (d, $^3J_{H,H}$ = 8.2 Hz, 1 H, Ar-H), 3.66 (t, $^3J_{H,H}$ = 8.3 Hz, 2 H, *N*CH_2), 3.41 (s, 3 H, OCH_3), 3.38 (s, 3 H, OCH_3), 2.51 (t, $^3J_{H,H}$ = 8.3 Hz, 2 H, CH_2) ppm. ^{1}H NMR (500 MHz, C_6D_6, 70 °C): δ = 7.94 (br. s, 1 H, Ar-H), 7.09 (s, 1 H, Ar-H), 7.04 (d, $^3J_{H,H}$ = 7.8 Hz, 1 H, Ar-H), 7.00 (t, $^3J_{H,H}$ = 7.8 Hz, 1 H, Ar-H), 6.91 (d, $^3J_{H,H}$ = 7.3 Hz, 1 H, Ar-H), 6.83 (t, $^3J_{H,H}$ = 7.3 Hz, 1 H, Ar-H), 3.66 (t, $^3J_{H,H}$ = 8.3 Hz, 2 H, *N*CH_2), 3.41 (s, 3 H, OCH_3), 3.38 (s, 3 H, OCH_3), 2.51 (t, $^3J_{H,H}$ = 8.3 Hz, 2 H, CH_2) ppm.

***N*-(Piperonoyl)indoline (6):**[49] To a stirring solution of I_2 (253.8 mg, 1.0 mmol) in dry CH_2Cl_2 (5 mL) at 0 °C was added Pol–PPh_3 (438.0 mg, 1.0 mmol). The reaction mixture was flushed with nitrogen gas and allowed to stir at 0 °C for 5 min. At this temperature, piperonylic acid (166.1 mg, 1.0 mmol) was added, followed by the dropwise addition of *i*Pr_2NEt (260.0 μL, 1.5 mmol) and indoline (112 μL, 1.0 mmol). The reaction mixture was slowly brought to room temperature and allowed to stir for 2 h. The mixture was filtered and evaporated to dryness. Chromatographic purification on a silica gel column (30% EtOAc in hexanes) afforded **6** (199.2 mg, 74%) as a colorless solid. R_f (40% EtOAc in hexanes) = 0.60. ^{1}H NMR (500 MHz, $CDCl_3$, ambient temperature): δ = 7.21 (d, $^3J_{H,H}$ = 7.4 Hz, 1 H, Ar-H), 7.18–7.09 (br. s, 1 H, Ar-H), 7.09 (dd, $^3J_{H,H}$ = 1.5, 8.0 Hz, 1 H, Ar-H), 7.04 (s, 1 H, Ar-H), 7.01 (t, $^3J_{H,H}$ = 7.4 Hz, 1 H, Ar-H), 6.85 (d, $^3J_{H,H}$ = 8.0 Hz, 1 H, Ar-H), 6.03 (s, 2 H, OCH_2), 4.10 (t, $^3J_{H,H}$ = 7.9 Hz, 2 H, indolinyl-H), 3.11 (t, $^3J_{H,H}$ = 7.9 Hz, 2 H, indolinyl-H) ppm. ^{1}H NMR (500 MHz, C_6D_6, 70 °C): δ = 7.93 (br. s, 1 H, Ar-H), 6.99 (t, $^3J_{H,H}$ = 8.0 Hz, 1 H, Ar-H), 6.96 (s, 1 H, Ar-H), 6.89 (d, $^3J_{H,H}$ = 7.8 Hz, 1 H, Ar-H), 6.82 (t, $^3J_{H,H}$ = 7.3 Hz, 1 H, Ar-H), 6.51 (d, $^3J_{H,H}$ = 7.8 Hz, 1 H, Ar-H), 5.29 (s, 2 H, OCH_2), 3.51 (t, $^3J_{H,H}$ = 8.0 Hz, 2 H, *N*CH_2), 2.45 (t, $^3J_{H,H}$ = 8.0 Hz, 2 H, CH_2) ppm.

Supporting Information (see footnote on the first page of this article): Copies of the ^{1}H NMR spectra of all amides and Weinreb amides shown in Tables 1 and 2; ^{13}C NMR spectrum of *N*-(3,5-dinitro)benzoylpyrrolidine; ^{1}H NMR spectra of **3**, **4**, **6**, anhydrolychorinonine and hippadine; ^{1}H–^{1}H COSY spectra of **4** and **6**.

Acknowledgments

Partial support of this work by the National Science Foundation (NSF) (Grant CHE-0640417), the National Institutes of Health (NIH) (Grant 5S06 GM008168-30), and a PSC CUNY award to M. K. L. is acknowledged. Mr. Tom Melninkaitis and Mr. Scott Klepfer (Biotage) are thanked for a sample of Pol–PPh_3 (PS-triphenylphosphane) used in this work, and Dr. Padmanava Pradhan is thanked for his assistance with some NMR experiments. Infrastructural support was provided by Research Centers at Minority Institutions (Grant NIH/NCRR/RCMI – G12 RR03060).

[1] R. C. Larock, *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, New York, **1999**.
[2] a) Y. Rao, X. Li, S. J. Danishefsky, *J. Am. Chem. Soc.* **2009**, *131*, 12924–12926; b) L. J. Gooßen, D. M. Ohlmann, P. P. Lange, *Synthesis* **2009**, 160–164; c) J. Burés, M. Martín, F. Urpí, J. Vilarrasa, *J. Org. Chem.* **2009**, *74*, 2203–2206; d) L. U. Nordstrøm, H. Vogt, R. Madsen, *J. Am. Chem. Soc.* **2008**, *130*, 17672–17673; e) G. E. Veitch, K. L. Bridgwood, S. V. Ley, *Org. Lett.* **2008**, *10*, 3623–3625; f) S. Y. Seo, T. J. Marks, *Org. Lett.* **2008**, *10*, 317–319; g) K. R. Reddy, C. U. Maheswari, M. Venkateshwar, M. L. Kantam, *Eur. J. Org. Chem.* **2008**, 3619–3622; h) C. Gunanathan, Y. Ben-David, D. Milstein, *Science* **2007**, *317*, 790–792; i) T. Maki, K. Ishihara, H. Yamamoto, *Tetrahedron* **2007**, *63*, 8645–8657; j) M. Matsugi, M. Hasegawa, D. Sadachika, S. Okamoto, M. Tomioka, Y. Ikeya, A. Masuyama, Y. Mori, *Tetrahedron Lett.* **2007**, *48*, 4147–4150; k) E. Valeur, M. Bradley, *Tetrahedron* **2007**, *63*, 8855–8871; l) A. Novak, L. D. Humphreys, M. D. Walker, S. Woodward, *Tetrahedron Lett.* **2006**, *47*, 5767–5769; m) M. Zhang, P. Vedantham, D. L. Flynn, P. R. Hanson, *J. Org. Chem.* **2004**, *69*, 8340–8344; n) M. S. Nery, R. P. Ribeiro, C. C. Lopes, R. S. C. Lopes, *Synthesis* **2003**, 272–276; o) P. Li, J.-C. Xu, *Tetrahedron* **2000**, *56*, 4437–4445; p) A. R. Katritzky, H.-Y. He, K. Suzuki, *J. Org. Chem.* **2000**, *65*, 8210–8213.
[3] X. Lin, M. J. Robins, *Org. Lett.* **2000**, *2*, 3497–3499.
[4] J. Zlatko, X. Lin, M. J. Robins, *Nucleosides Nucleotides Nucleic Acids* **2004**, *23*, 137–147.
[5] S. Bae, M. K. Lakshman, *J. Org. Chem.* **2008**, *73*, 1311–1319.
[6] S. Bae, M. K. Lakshman, *J. Org. Chem.* **2008**, *73*, 3707–3713.
[7] M. K. Lakshman, A. Choudhury, S. Bae, E. Rochttis, P. Pradhan, A. Kumar, *Eur. J. Org. Chem.* **2009**, 152–159.
[8] A. V. Narasaiah, D. Sreenu, K. Nagaiah, *Synth. Commun.* **2006**, *36*, 137–140.
[9] a) F.-A. Kang, Z. Sui, W. V. Murray, *Eur. J. Org. Chem.* **2009**, 461–479; b) F.-A. Kang, Z. Sui, W. V. Murray, *J. Am. Chem. Soc.* **2008**, *130*, 11300–11302.
[10] P. Frøyen, *Synth. Commun.* **1995**, *25*, 959–968.
[11] B. P. Bandgar, S. V. Bettigeri, *Synth. Commun.* **2004**, *34*, 2917–2924.
[12] J. Garcia, F. Urpí, J. Vilarrasa, *Tetrahedron Lett.* **1984**, *25*, 4841–4844.
[13] L. E. Barstow, V. J. Hruby, *J. Org. Chem.* **1971**, *36*, 1305–1306.
[14] S.-i. Yamada, Y. Takeuchi, *Tetrahedron Lett.* **1971**, *12*, 3595–3598.
[15] R. d. C. Rodriguez, I. M. A. Barros, E. L. S. Lima, *Tetrahedron Lett.* **2005**, *46*, 5945–5947.
[16] C. R. Harrison, P. Hodge, B. J. Hunt, E. Koshdel, G. Richardson, *J. Org. Chem.* **1983**, *48*, 3721–3728.
[17] H.-P. Buchstaller, H. M. Ebert, U. Anlauf, *Synth. Commun.* **2001**, *31*, 1001–1005.
[18] S.-Y. Han, Y.-A. Kim, *Tetrahedron* **2004**, *60*, 2447–2467.
[19] X. Yang, V. B. Birman, *Org. Lett.* **2009**, *11*, 1499–1502.
[20] R. Salvio, L. Moisan, D. Ajami, J. Rebek Jr., *Eur. J. Org. Chem.* **2007**, 2722–2728.
[21] M. Lysen, S. Kelleher, M. Begtrup, J. L. Kristensen, *J. Org. Chem.* **2005**, *70*, 5342–5343.
[22] A. Tetsuaki, F. Xie, A. Tsutomu, U. Shuji, I. Toshimasa, I. Yasuko, I. Chuzo, M. Naoyoshi, *J. Chin. Chem. Soc. (Taipei)* **2000**, *47*, 865–868.
[23] S. L. MacNeil, M. Gray, D. G. Gusev, L. E. Briggs, V. Snieckus, *J. Org. Chem.* **2008**, *73*, 9710–9719.
[24] I. Mohammadpoor-Baltork, M. M. Sadeghi, K. Esmayilpour, *Synth. Commun.* **2003**, *33*, 953–959.
[25] A. V. Karnik, S. S. Kamath, *Tetrahedron: Asymmetry* **2008**, *19*, 45–48.
[26] N. Zanatta, D. Faoro, S. C. Silva, H. G. Bonacorso, M. A. P. Martins, *Tetrahedron Lett.* **2004**, *45*, 5689–5691.
[27] P. A. Grieco, D. S. Clark, G. P. Withers, *J. Org. Chem.* **1979**, *44*, 2945–2947.

[28] L. D. Luca, G. Giacomelli, A. Porcheddu, *J. Org. Chem.* **2002**, *67*, 6272–6274.
[29] R. V. Hoffman, N. K. Nayyar, *J. Org. Chem.* **1995**, *60*, 7043–7046.
[30] T. Okawara, T. Matsuda, M. Furukawa, *Chem. Pharm. Bull.* **1982**, *30*, 1225–1233.
[31] S. Kafka, J. Kytner, A. Šilhánková, M. Ferles, *Collect. Czech. Chem. Commun.* **1987**, *52*, 2035–2046.
[32] D. Glynn, D. Bernier, S. Woodward, *Tetrahedron Lett.* **2008**, *49*, 5687–5688.
[33] T. Kinoshita, D. Ichinari, J. Sinya, *J. Heterocycl. Chem.* **1996**, *33*, 1313–1317.
[34] S. Nahm, S. M. Weinreb, *Tetrahedron Lett.* **1981**, *22*, 3815–3818.
[35] a) S. Balasubramaniam, I. S. Aidhen, *Synthesis* **2008**, 3707–3738; b) J. Singh, N. Satyamurthi, I. S. Aidhen, *J. Prakt. Chem.* **2000**, *342*, 340–347.
[36] M. Mentzel, H. M. R. Hoffmann, *J. Prakt. Chem.* **1997**, *339*, 517–524.
[37] V. K. Khlestkin, D. G. Mazhukin, *Curr. Org. Chem.* **2003**, *7*, 967–993.
[38] M. P. Sibi, *Org. Prep. Proc. Int.* **1993**, *25*, 15–40.
[39] One-pot methods: a) T. Niu, W. Zhang, D. Huang, C. Xu, H. Wang, Y. Hu, *Org. Lett.* **2009**, *11*, 4474–4477; b) A. Deagostino, P. Larini, E. G. Occhiato, L. Pizzuto, C. Prandi, P. Venturello, *J. Org. Chem.* **2008**, *73*, 1941–1945; c) I. J. Lee, *Bull. Korean Chem. Soc.* **2007**, *28*, 695–697; d) K.-J. Han, M. Kim, *Lett. Org. Chem.* **2007**, *4*, 20–22; e) J. R. Martnelli, D. M. M. Freckmann, S. L. Buchwald, *Org. Lett.* **2006**, *8*, 4843–4846; f) J. C. S. Woo, E. Fenster, G. R. Dake, *J. Org. Chem.* **2004**, *69*, 8984–8986; g) L. De Luca, G. Giacomelli, M. Taddei, *J. Org. Chem.* **2001**, *66*, 2534–2537; h) M. Banwell, J. Smith, *Synth. Commun.* **2001**, *31*, 2011–2019; i) A. R. Tunoori, J. M. White, G. I. Georg, *Org. Lett.* **2000**, *2*, 4091–4093.
[40] J. Einhorn, C. Einhorn, J.-L. Luche, *Synth. Commun.* **1990**, *20*, 1105–1112.
[41] Z. Zhang, Y. Yu, L. S. Liebeskind, *Org. Lett.* **2008**, *10*, 3005–3008.
[42] Y. Saito, H. Ouchi, H. Takahata, *Tetrahedron* **2008**, *64*, 11129–11135.
[43] T. Schlüter, A. C. Steinbach, A. Steffen, R. Rettig, O. Grisk, *Cardiovasc. Res.* **2008**, *80*, 271–279.
[44] K. Lirdprapamongkol, J.-P. Kramb, T. Suthiphongchai, R. Surarit, C. Srisomsap, G. Dannhardt, J. Svasti, *J. Agric. Food Chem.* **2009**, *57*, 3055–3063.
[45] F. P. J. G. Lafeber, C. J. Beukelman, E. van den Worm, J. L. A. M. van Roy, M. E. Vianen, J. A. G. van Roon, H. van Dijk, J. W. J. Bijlsma, *Rheumatology* **1999**, *38*, 1088–1093.
[46] a) O. P. Suri, R. S. Bindra, N. K. Katti, R. K. Khajuria, *Indian J. Chem. Sect. B* **1987**, *26B*, 587–588; b) S. Weike, C. Jin, *Synth. Commun.* **2004**, *34*, 4199–4205.
[47] J. A. Dodge, M. G. Stocksdale, K. J. Fahey, C. D. Jones, *J. Org. Chem.* **1995**, *60*, 739–741.
[48] a) S. Chattopadhyaya, U. Chattopadhyaya, P. P. Mathur, K. S. Saini, S. Ghosal, *Planta Med.* **1983**, *49*, 252–254; b) S. Ghosal, R. R. Lochan, A. Y. Kumar, R. S. Srivastava, *Phytochemistry* **1985**, *24*, 1825–1828.
[49] M. D. Ganton, M. A. Kerr, *Org. Lett.* **2005**, *7*, 4777–4779.
[50] a) P. Frøyen, *Phosphorus Sulfur Silicon Relat. Elem.* **1994**, *91*, 145–151; b) P. Frøyen, *Phosphorus Sulfur Silicon Relat. Elem.* **1994**, *89*, 57–61.
[51] D. O. Jang, D. J. Park, J. Kim, *Tetrahedron Lett.* **1999**, *40*, 5323–5326.
[52] D. H. Kang, T. Y. Joo, E. H. Lee, S. Chaysripongkul, W. Chavasiri, D. O. Jang, *Tetrahedron Lett.* **2006**, *47*, 5693–5696.

Received: December 7, 2009
Published Online: April 7, 2010

