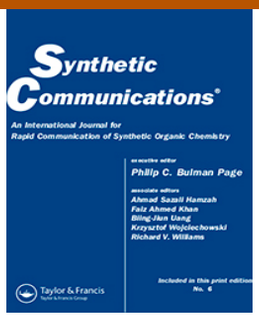

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One-pot synthesis of Weinreb amides employing 3,3-dichloro-1,2-diphenylcyclopropene (CPI-Cl) as a chlorinating agent

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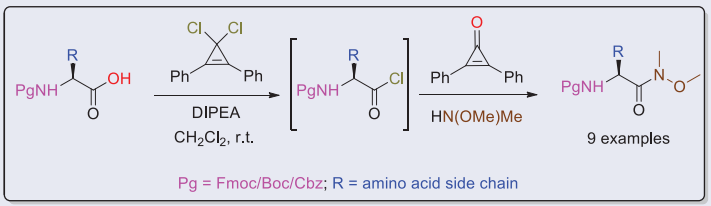
ABSTRACT

The synthesis of N$^{\alpha}$-protected amino alkyl Weinreb amides starting from the corresponding α-amino acids as well as carboxylic acids has been delineated through the in situ generation of acid chlorides using CPI-Cl as a chlorinating agent. The protocol is simple; the reaction conditions employed were mild, and compatible with all the three commonly used urethane protecting groups namely, Boc, Cbz and Fmoc groups. The resulting Weinreb amides are obtained in good yields as optically pure products.

GRAPHICAL ABSTRACT



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KEYWORDS
Acid chloride; CPI-Cl; N$^{\alpha}$-protected amino alkyl Weinreb amides; N,O-dimethylhydroxylamine

Introduction

Since Nahm and Weinreb first reported on the use of *N*-methoxy-*N*-methylamides as carbonyl equivalents,[1] this functional group has rapidly become popular in organic synthesis.[2] These amides react with organometallics, hydride reducing agents or Wittig reagent to give aldehydes or ketones.[3] They are used in the preparation of an array of compounds with functional groups such as ynones,[4] heterocycle[5] and in the total synthesis of natural products.[6] Weinreb amides can be synthesized from a plethora of functional groups such as carboxylic acids or its derivatives acid chlorides,[7] esters,[8] amides,[9] anhydrides,[10] alcohols,[11] amino carbonylative coupling[12] and Stille cross-coupling reactions.[13] Among the several approaches, direct conversion of carboxylic acids into the corresponding Weinreb amides is most outstanding and attractive because

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Supplemental data for this article can be accessed here.

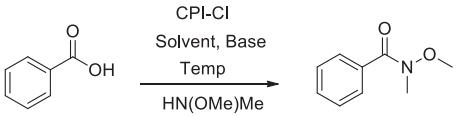
of the easy availability of the precursors.[14] The reported methods for the synthesis of Weinreb amides through in situ generation of acid halides using phosphorous trichloride (PCl_3),[15] PPh_3/Cl_3CCN,[16] PPh3/I_2,[17] PPh3/CBr4,[18] and [bis(2-methoxyethyl)amino]sulfur trifluoride (Deoxo-Fluor).[19] However, PCl_3, PPh_3/Cl_3CCN are not compatible with acid-labile protecting groups. PPh_3/CBr_4 is expected to result in racemization. The protocol using Deoxo-Fluor requires longer reaction duration (3–8 h). Weinreb amides from the corresponding N^{α}-Fmoc amino/peptide acid chlorides generated using $SOCl_2$ has been reported by our group. Due to the instability of acid chlorides, the protocol could not be extended to N^{α}-Boc/Cbz amino acids.[20] Vilsmeier reagent is an efficient chlorinating agent employed for the acid chloride formation, which can be prepared by the combination of $(COCl)_2$ and DMF with the formation of HCl as by-product, which cleaves acid sensitive Boc group.[21] Katritzky developed a method for the synthesis of different Weinreb amides including Boc-protected amino Weinreb amides from corresponding carboxylic acids. N-Acyl benzotriazole was refluxed with N,O-dimethylhydroxylamine hydrochloride, for 6–12 h.[22] Peptide coupling reagents such as BOP,[23] DCC,[24] DEPC,[25] HBTU,[26] CDMT[27] and DMTMM[28] are also employed. Furthermore, CDI,[29] COMU,[30] T3P/DBU[31] and mixed anhydride[32] method have been utilized for the synthesis of the title compounds. These protocols suffer from many disadvantages *viz*, longer reaction time, side reactions due to elevated temperature, poor yields, racemization, *etc*. In this paper, we delineate an efficient method for the synthesis of *N*-methoxy-*N*-methyl amides of α-amino acids through in situ generation of acid chlorides employing 3,3-dichloro-1,2-diphenylcyclopropene (CPI-Cl).

The cyclopropenium cation is the smallest member of the Hückel aromatic system. There are several investigations on this cation ever since the first synthesis of triphenylcyclopropenylium perchlorate by Breslow.[33] Lambert et al., employed the reactions involving cyclopropenium intermediates, for the rapid conversion of alcohols and carboxylic acids into the corresponding alkyl chlorides and acid chlorides respectively.[34] A similar strategy was applied for the dehydrative cyclization of diols to cyclic ethers.[35] Nucleophilic substitution of alcohols by methane sulfonate ion with inversion of configuration is also known.[36] The conversion of ketoximes to amides/ketones by Beckmann rearrangement is also known.[37] Recently our group reported CPI-Cl mediated synthesis of amino acid azides and their conversion to α-ureidopeptides.[38] In continuation of our interest in using CPI-Cl as a useful reagent for functional group conversions, herein we report our results on the synthesis of Weinreb amides from the corresponding carboxylic acids.

Results and discussions

Initially, we have chosen benzoic acid **1a** as a model substrate to establish the optimal reaction conditions. In a typical experiment to the in situ generated CPI-Cl (generated by the treatment of 2,3-diphenylcyclopropenone with oxalyl chloride in CH_2Cl_2), a solution of benzoic acid (1.0 equiv.) and diisopropylethylamine (DIPEA, 1.2 equiv.) in dry CH_2Cl_2 was added at room temperature under an argon atmosphere. After 5 min, a solution of *N,O*-dimethylhydroxylamine (1.2 equiv.) in CH_2Cl_2 was added to the above in situ

Table 1. Optimization of Weinreb amidation reaction.



1a 2a

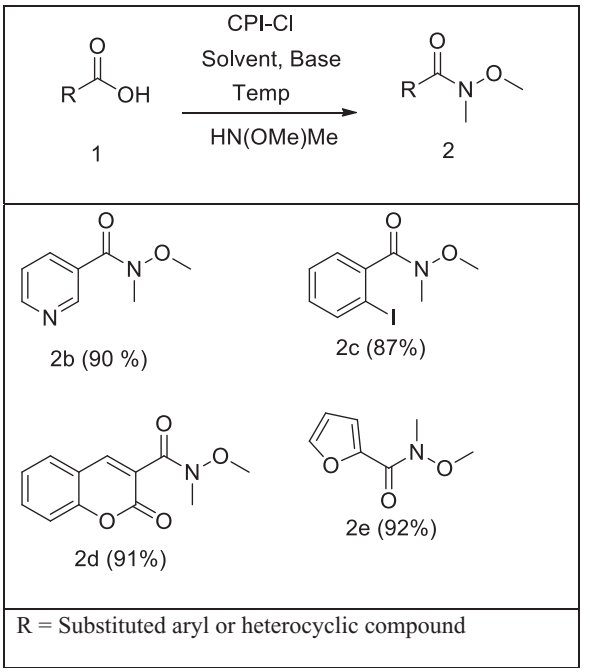
Entry	Solvent	Base (equiv)	HN(OMe)Me	Time(min)	Yield (%)
1	CH_2Cl_2	DIPEA (1.2)	1.2[a]	90	55
2	CH_2Cl_2	DIPEA (1.2)	1.2[b]	90	53
3	CH_2Cl_2	DIPEA (1.5)	1.5[a]	35	79
4	CH_2Cl_2	DIPEA (2.0)	2.0[a]	20	93
5	CH_2Cl_2	DIPEA (2.2)	2.2[a]	20	93
6	THF	DIPEA (2.2)	2.0[a]	40	75
7	Acetonitrile	DIPEA (2.2)	2.0[a]	40	68
8	Dioxane	DIPEA (2.2)	2.0[a]	40	65
9	CH_2Cl_2	TEA (2.2)	2.0[a]	40	80
10	CH_2Cl_2	NEM (2.2)	2.0[a]	40	78
11	CH_2Cl_2	Pyridine (2.2)	2.0[a]	40	74
12	CH_2Cl_2	NMM (2.2)	2.0[a]	40	79

[a]reaction was carried out at r.t.; [b]reaction was carried out at 0 °C.

generated acid chloride. As monitored by TLC analysis, the desired Weinreb amide **2a** was obtained in 55% after 90 min along with unreacted benzoic acid (entry 1). The yield of **2a** was 53% when the same reaction was performed at 0 °C (entry 2). In order to improve the yield of **2a**, the amount of DIPEA and *N,O*-dimethylhydroxylamine was increased to 1.5 equiv., the yield of **2a** increased to 79%. We obtained a 93% yield of desired product **2a**, using the DIPEA (2.0 equiv.) and *N,O*-dimethylhydroxylamine (2.0 equiv.) in 20 min duration of the reaction (TLC analysis). It is evident that among the screened solvents (CH_2Cl_2, THF, acetonitrile and dioxane) and bases (DIPEA, TEA, NEM, pyridine and NMM), CH_2Cl_2 and DIPEA were found to be more efficient (Table 1). After a simple work-up, the crude compound was purified by column chromatography using hexane and ethyl acetate [hexane:EtOAc; (70:30)] as eluents to afford pure Weinreb amide **2a**. Further 2,3-diphenylcyclopropenone was also recovered quantitatively through column chromatography and reused. Benzoyl Weinreb amide to substituted and heterocyclic weinreb amides have been synthesized in good yields (Scheme 1).

After the optimized reaction conditions were established, we tested the methodology with an array of N^{α}-Fmoc/Boc/Cbz protected amino acids including bifunctional as well as sterically hindered amino acids. Furthermore, side-chain-modified Weinreb amide of the N and C terminally protected aspartic acid (5g) is also synthesized in good yield (Scheme 2).

The Fmoc-L-Phe-N(Me)O(Me) and Fmoc-D-Phe-N(Me)O(Me), 5a and 5a* made using the optimized conditions were chosen as model compounds to study racemization. The RP-HPLC analysis was carried out. The chromatograms had peaks at $R_t = 8.241$ min (5a) and $R_t = 7.187$ min (5a*), respectively. Also, intentionally prepared equimolar mixture of L- and D-Phe-N(Me)O(Me) had distinct peaks at $R_t = 8.213$ and 7.228 min (5a and 5a*). These observations inferred that the protocol is free from racemization and the amino Weinreb amides were obtained as optically pure compounds (method: gradient 0.1% TFA water-methanol (60-40); flow rate: 0.5 mL/min, 10 min).



Scheme 1. Synthesis of aryl/heterocyclic Weinreb amides.

The putative mechanism for Weinreb amidation reaction is now presented in Scheme 3. Cyclopropene **i** bearing two geminal chlorides may exist in equilibrium with cyclopropenium salt **ii**. Addition of carboxylate to **ii** resulting in cyclopropenium activated carboxylate **iv** [**iii** dissociates to **iv** by reionization]. Nucleophilic addition [NH(OMe)Me] to **iv** to give expected product **v**.

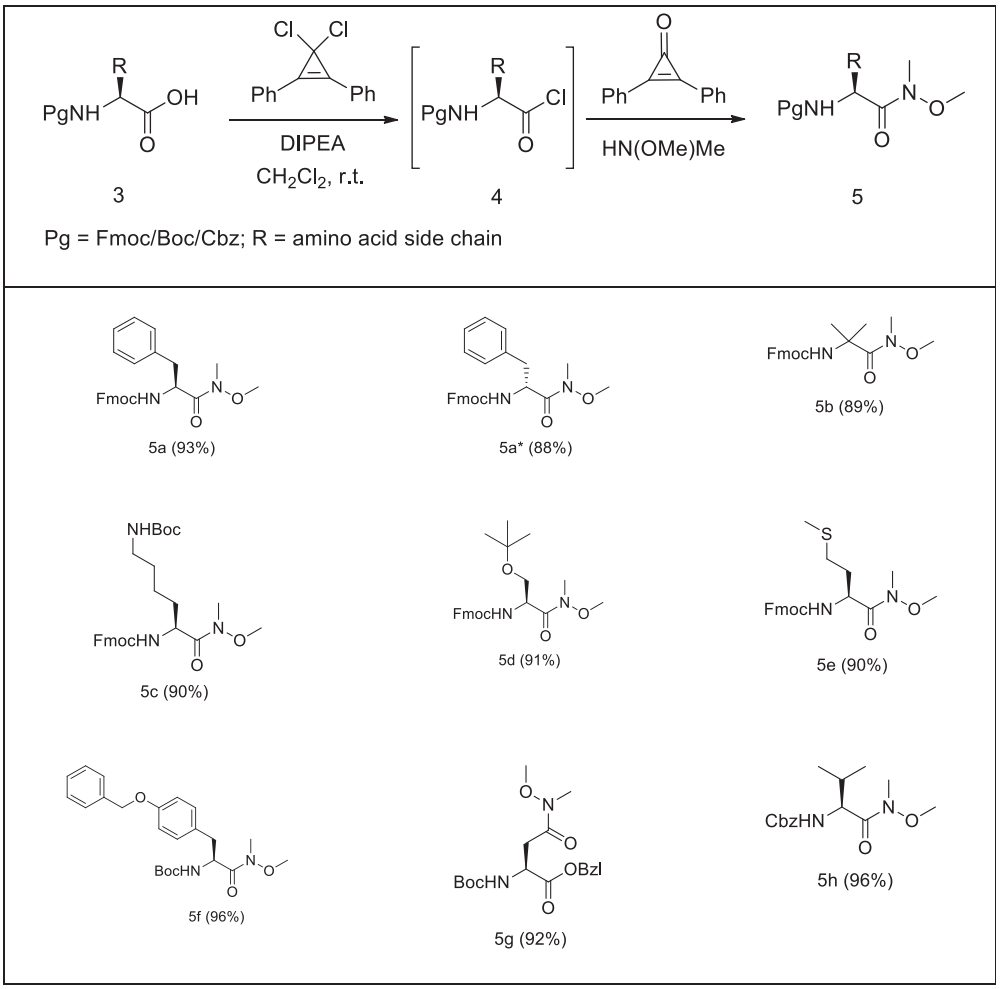
Conclusion

A simple and efficient strategy for the construction of Weinreb amides through in situ generation of acid chlorides using CPI-Cl as a useful chlorinating agent from the corresponding carboxylic acid is reported. The advantage that the protocol offers is the use of in situ generated CPI-Cl in chlorinating the carboxyl acid of Boc-protected amino acids. Generally, other chlorinating agents cleaves the Boc-group. Therefore, in terms of compatibility offered by present chlorinating reagent to obtain Weinreb amides bearing acid labile moieties is advantageous. Furthermore, diphenylcyclopropenone is recovered quantitatively at the end of the reaction through column chromatography and reused.

Experimental section

General procedure for the preparation of Weinreb amides

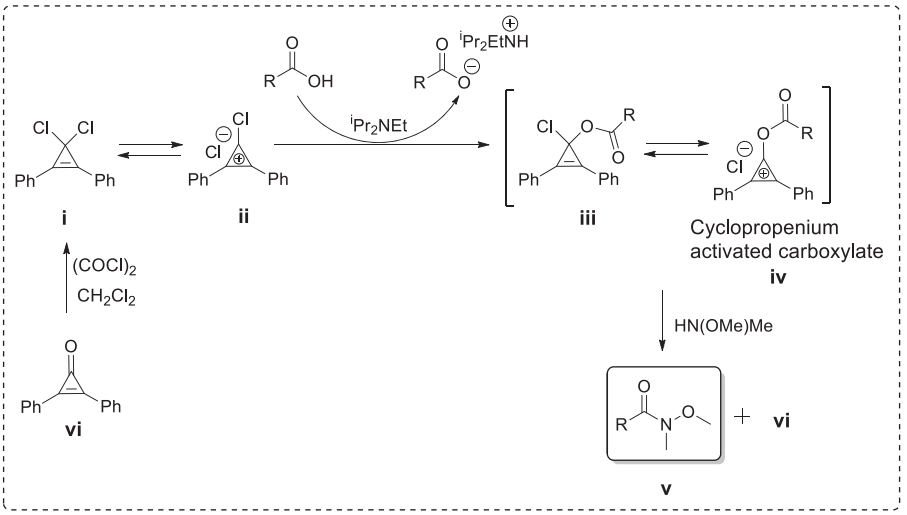
To a solution of in situ generated CPI-Cl (generated by the treatment of 2,3 diphenylcyclopropenone with oxalyl chloride in CH_2Cl_2) was added aryl/heterocyclic/N^{α}-protected



Scheme 2. Synthesis of N^{α}-protected amino Weinreb amides.

amino acid (1 mmol), DIPEA (2 mmol) stirring at room temperature. After the formation of acid chloride solution of *N,O*-dimethylhydroxylamine (2 mmol) in CH_2Cl_2 was added. After the completion of the reaction (determined by TLC), solvent was evaporated under vacuo and diluted with EtOAc, washed with 5% citric acid and Na_2CO_3 (10 mL ×2), water, brine and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated and purified by column chromatography using hexane and EtOAc as eluents.

Fmoc-Phe-N(OMe)Me [5a]: White solid, yield 90%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85–7.16 (m, 13 H), 5.69 (d, $J = 7.2$ Hz, 1 H), 4.4 (d, $J = 7.2$ Hz, 2 H), 4.28 (q, $J = 6.8$ Hz, 1 H), 4.17 (t, $J = 6.8$ Hz, 1 H), 3.67 (s, 3 H), 3.19 (s, 3 H), 3.06–2.91 (m, 2 H). 13 C NMR (100 MHz, $CDCl_3$) δ 160.83, 156.51, 143.57, 141.36, 136.36, 129.15, 127.70, 126.99, 125.97, 125.57, 125.20, 120.17, 67.31, 63.63, 51.39, 47.17, 37.40, 31.26. HRMS: m/z calculated for $C_{26}H_{27}N_2O_4$ $[M+H]^+$ 431.1971; found: 431.1966.



Scheme 3. Putative mechanism for Weinreb amidation.

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