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Synthetic Communications

An International Journal for Rapid Communication of Synthetic Organic Chemistry

ISSN: 0039-7911 (Print) 1532-2432 (Online) Journal homepage: https://www.tandfonline.com/loi/lsyc20

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To cite this article: Fathima Pilathottathil, Doppalapudi Vineet Kumar & Alagiri Kaliyamoorthy (2020): Synthesis of various acylating agents directly from carboxylic acids, Synthetic Communications, DOI: 10.1080/00397911.2020.1747631

To link to this article: https://doi.org/10.1080/00397911.2020.1747631

SYNTHETIC COMMUNICATIONS®
https://doi.org/10.1080/00397911.2020.1747631

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Synthesis of various acylating agents directly from carboxylic acids

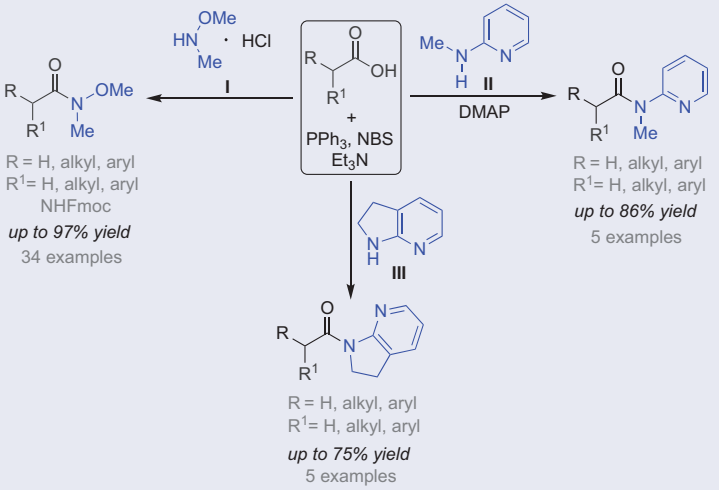
Fathima Pilathottathil*, Doppalapudi Vineet Kumar*, and Alagiri Kaliyamoorthy

School of Chemistry, Indian Institute of Science Education and Research, Thiruvananthapuram, India

ABSTRACT

A straightforward synthesis of acylating reagents such as Weinreb and MAP amides from aromatic, aliphatic carboxylic acids, and amino acids using PPh_3/NBS combination is described. A chemo-selective modification of the carboxylic acid group into Weinreb amide in the presence of more reactive aldehydes and ketones is presented. All reactions were performed at ambient temperature under air using undried commercial grade solvent. Furthermore, the present methodology could be performed at a gram scale under inert-free reaction conditions. In addition, 7-azaindoline amide auxiliary (used for catalytic asymmetric aldol- and Mannich-type reactions), which behaves like Weinreb amide is also synthesized under similar reaction conditions.

GRAPHICAL ABSTRACT



ARTICLE HISTORY
Received 13 February 2020

KEYWORDS
MAP amide; Meyers and Comins amide; N-methoxy-N-methylamide; N-methylaminopyridine amide; Weinreb amide

Introduction

Carbonyl functionality such as aldehyde and ketone is of the highest importance and pervasive in several natural products and biologically active compounds. Also, they are

CONTACT Alagiri Kaliyamoorthy alagiri@iisertvm.ac.in School of Chemistry, Indian Institute of Science Education and Research, Thiruvananthapuram, Kerala 695551, India.
*These authors contributed equally to this work.

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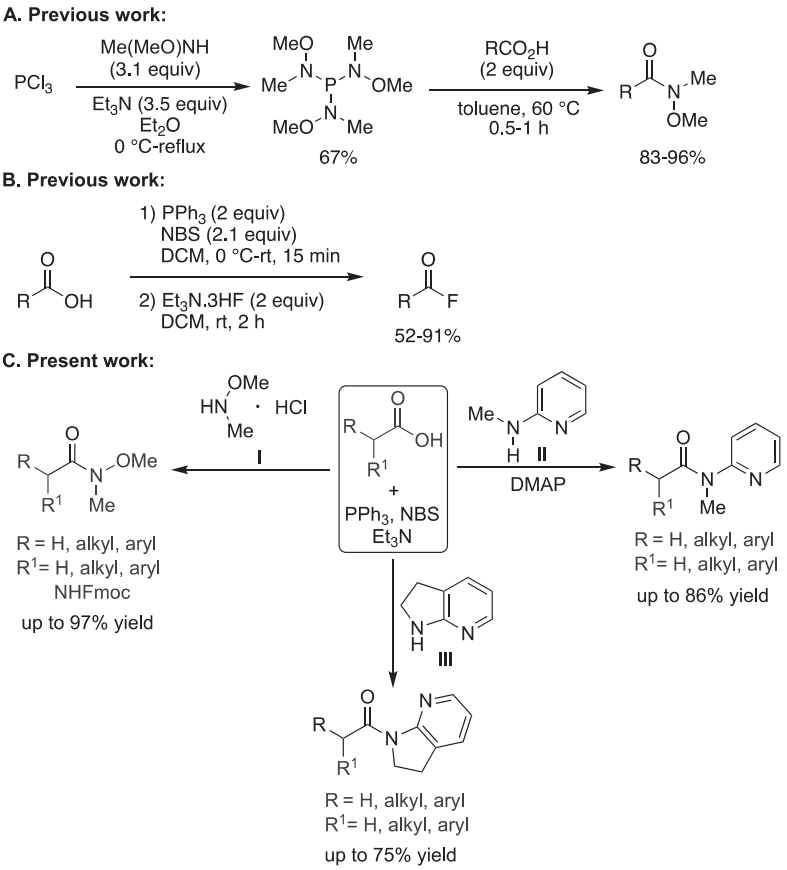
the central functionality in numerous organic synthesis due to their ease of chemical manipulations to various functional groups. The realization of carbonyl compounds directly from carboxylic acid derivatives through the addition of organometallic reagents or metal-hydrides is a highly demanding task and it often leads to over-addition of such reagents. To circumvent the excessive addition of organometallic reagents during the selective acylation process, Nahm and Weinreb devised the specific class of acylating reagents such as *N*-methoxy-*N*-methylamide (also termed as Weinreb amide),[1] which provides an easy access to a wide range of carbonyl compounds. Organometallic reagents like Grignard and organolithium reagents and metal-hydrides react with Weinreb amide to furnish ketones and aldehydes, respectively. Alternatively, aldehydes and ketones were accomplished through the Wittig reaction between phosphoranes and Weinreb amides.[2] Commonly, Weinreb amides are synthesized from acid chlorides,[1,3] anhydrides,[4] lactones,[5] esters,[6] amides,[7] and aryl halides/triflates.[8] Besides, plenty of efforts have been invested toward the synthesis of Weinreb amides directly from carboxylic acids in the presence of peptide coupling reagents,[9] CBr_4/PPh_3/pyridine,[10a] $Cl_3CCN/PPh_3/Et_3N$,[10b] $SOCl_2$,[10c] $TiCl_4$,[10d] 1-methylpyridinium iodide derivatives,[11] methanesulfonyl chloride,[12] and Deoxo-Fluor reagent.[13] Furthermore, a straightforward conversion of carboxylic acids to *N*-methoxy-*N*-methylamides was reported using $P[NMe(OMe)]_3$ as the stoichiometric amidating agent (Scheme 1A).[14]

Meyers and Comins amide, also called MAP (*N*-methylamino)pyridine amide is one the important acylating reagents among the plethora of reagents developed for the introduction of carbonyl functionality.[15] The characteristic feature of MAP amide is that the presence of pyridine nitrogen makes the MAP amides to display reactivity similar to Weinreb amides. Besides, MAP amide holds multifaceted utility over Weinreb amide, and offers an easy access to unsymmetrical secondary/tertiary alcohols via the successive addition of two different metallo-nucleophiles to the MAP amide.[15a] In 2010, Odell and coworkers reported the synthesis of MAP aryl amides through microwave-assisted Heck-aminocarbonylation reaction using $Mo(CO)_6$ as a solid CO source at 120 °C.[8a] Recently, Shibasaki and coworkers have demonstrated the use of 7-azaindoline amide as the auxiliary for various catalytic asymmetric reactions such as aldol- and Mannich-type reactions.[16] The specific feature of this auxiliary is that it exhibits reactivity similar to the Weinreb amide toward organometallic reagents (like organolithium, Grignard reagents, and metal-hydrides) due to its stabilizing chelation with the metal ion in the tetrahedral intermediate.

However, most of the reactions mentioned above are performed at either low temperature or reflux condition under rigorous dry reaction conditions. Therefore, the development of complementary methods using commercial grade solvent without preclusion of air and moisture under ambient reaction conditions are highly desirable. Recently, Prakash and coworkers[17a] documented a one-pot synthesis of acyl fluorides directly from carboxylic acids using PPh_3/*N*-bromosuccinimide (NBS) combination,[17a,b] this strategy involves the activation of carboxylic acids to acyloxyphosphonium ion, which is a crucial intermediate in this reaction and was corroborated by ^{31}P NMR study. Then, subsequent treatment of fluoride ion source with acyloxyphosphonium ion furnishes the acyl fluorides. Intrigued by this report, and also by the high synthetic importance of Weinreb and MAP amides in organic synthesis, we envisaged a



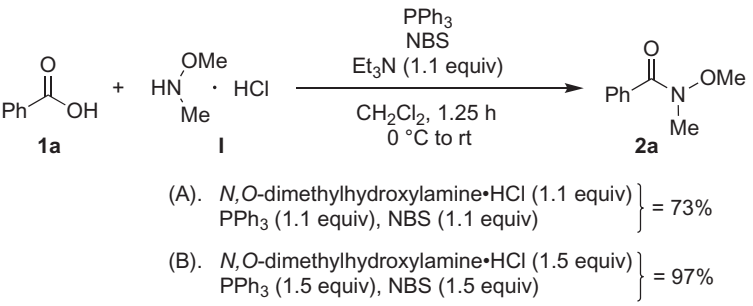
Scheme 1. (A) synthesis of Weinreb amides directly from carboxylic acids and P[NMe(OMe)]$_3$. (B) Synthesis of acyl fluorides from carboxylic acids. (C) A strategy for straightforward synthesis of Weinreb amides, MAP amides and 7-azaindoline amides from various carboxylic acids.

straightforward, one-pot, and viable synthesis of Weinreb and MAP amides from carboxylic acids.

Results and discussion

The use of 1.1 equivalent of each PPh_3 and NBS for the Appel type[17] in situ activation of benzoic acid using undried commercial grade dichloromethane solvent (under inert-free conditions) followed by addition of *N,O*-dimethylhydroxylamine hydrochloride (**I**) and Et_3N (1.1 equiv. of each) afforded the desired Weinreb amide (**2a**) in 73% yield in 1.25 h (Scheme 2A). Gratifyingly, increasing the equivalents of PPh_3/NBS/*N,O*-dimethylhydroxylamine combination to 1.5 equivalents furnished the requisite product **2a** in excellent yield (97%, Scheme 2B), and hence, this condition was used for further studies.

To investigate the synthetic prospect of this method, a variety of aromatic carboxylic acids were explored under the reaction conditions given in Scheme 2B, and the results are summarized in Table 1. Both 1-naphthoic acid (**1b**) and 2-naphthoic acid (**1c**) underwent a smooth amidation reaction to give the corresponding Weinreb amides in

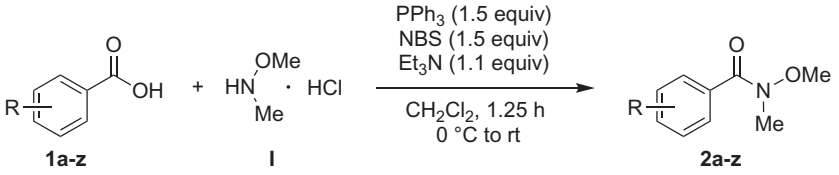


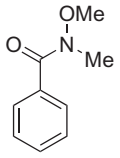
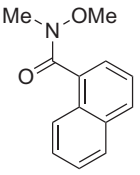
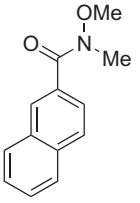
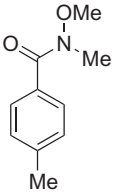
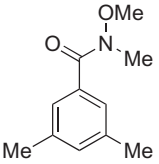
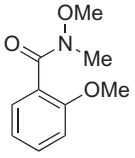
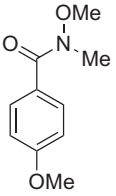
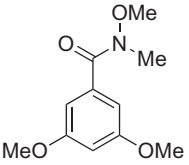
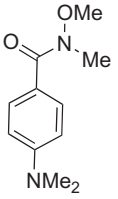
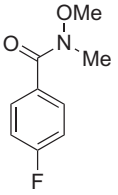
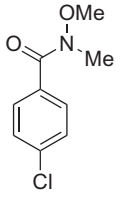
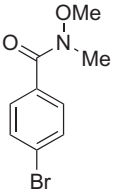
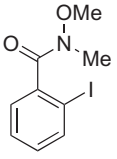
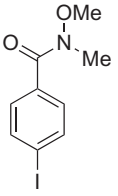
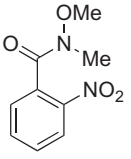
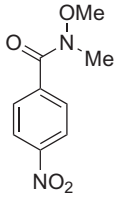
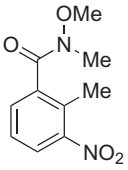
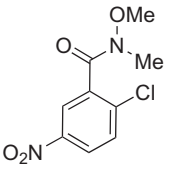
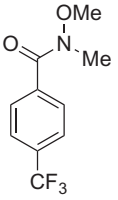
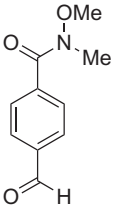
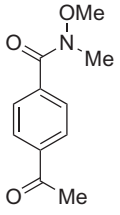
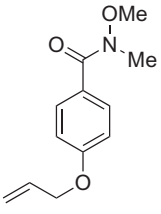
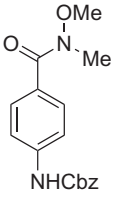
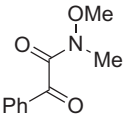
Scheme 2. Direct synthesis of Weinreb amide from carboxylic acid.

93% yield (entries **2b** and **2c**, Table 1). Besides, aromatic carboxylic acids bearing electron-donating substituents such as methyl (**1d, 1e**), methoxy (**1f–h**), dimethylamino (**1i**) groups afforded the ensuing products in good to excellent yields (entries **2d–2i**, Table 1). The amidation reaction was very proficient in the case of diversely halo-substituted benzoic acids (**1j–1n**) and provided the associate products (**2j–2n**) in significant yields. The presence of electron-withdrawing nitro-group at the *ortho*, *meta,* and *para*- position of benzoic acids (**1o–1r**), and 4-trifluoromethyl benzoic acid (**1s**) afforded the related Weinreb amides (entries **2o–2s,** Table 1) in 74–97% yields. Interestingly, the chemoselective conversion of carboxylic acids to *N*-methoxy-*N*-methylamides can be achieved in the presence of more reactive functional groups like aldehyde and ketones (entries **2t** and **2u**, Table 1). We surmise that the high reactivity of in situ generated acyloxyphosphonium ion over carbonyl groups could be the possible reason for this excellent chemoselectivity. Besides, benzoic acid tethered with allylic ether functionality (**1v**) and benzoic acid bearing Cbz-protected amino group (**1w**) underwent smooth amidation reaction to render the corresponding target amides in 67% and 83% yields, respectively (entries **2v** and **2w**, Table 1). Besides, this method can be extended to chemoselective conversion of carboxylic acid functionality of α-keto acids, such as phenyl glyoxylic acid to the corresponding Weinreb amide without affecting the activated keto-group in appreciable yield (entry **2x**, Table 1).

Next, we shifted our focus toward the synthesis of Weinreb amides from aliphatic carboxylic acids and amino acids (Table 2). Along these lines, phenylacetic acid and its substituted congeners were subjected for the amidation reaction under the present reaction conditions, and the requisite Weinreb amides were obtained in good to excellent yields (entries **3a–3d**, Table 2). Further, sterically hindered carboxylic acid such as adamantane-1-carboxylic acid was converted to the corresponding Weinreb amide in appreciable yield (entry **3e**, Table 2). A variety of Fmoc-protected amino acids (such as L-alanine, L-leucine, L-norvaline, glycine, and *O*-benzyl-L-serine) were converted into corresponding Weinreb amides in good to excellent yields without erosion in the optical purity (entries **3f–3j**; The observed optical purity of Fmoc-alanine $\{[\alpha]_D^{25} = +1.9$ (*c* 0.68, $CHCl_3)\}$ is similar to the reported literature value $\{[\alpha]_D^{20} = +2.1$ (*c* 0.68, $CHCl_3)\}$, and suggests that the optically pure substrates do not undergo racemization under the present reaction conditions).[18] However, the decomposition of starting

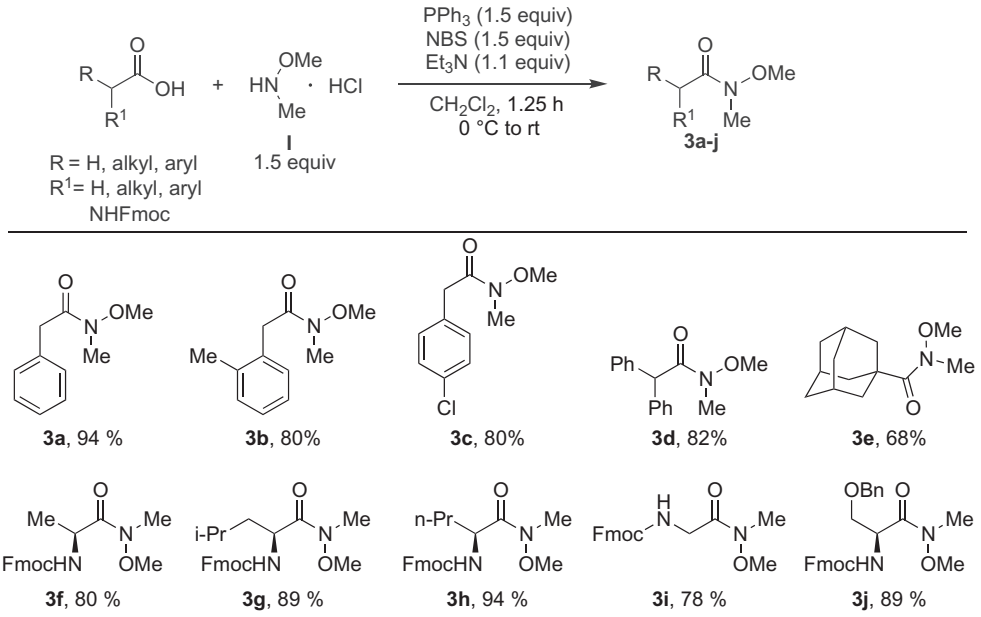
Table 1. Direct synthesis of aromatic Weinreb amides from various aromatic carboxylic acids.[a]



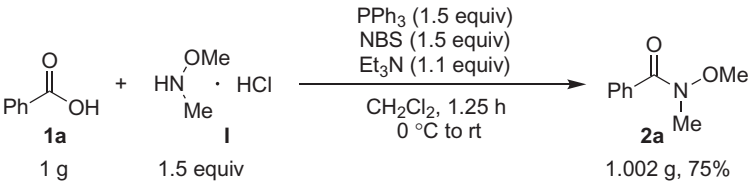
 **2a**, 97%	 **2b**, 93%	 **2c**, 93%	 **2d**, 81%	 **2e**, 62%
 **2f**, 86%	 **2g**, 82%	 **2h**, 87%	 **2i**, 77%	 **2j**, 75%
 **2k**, 85%	 **2l**, 83%	 **2m**, 97%	 **2n**, 81%	 **2o**, 78%
 **2p**, 97%	 **2q**, 74%	 **2r**, 94%	 **2s**, 95%	 **2t**, 82%
 **2u**, 81%	 **2v**, 67%	 **2w**, 83%	 **2x**, 75%	

[a]Isolated yields.

Table 2. Synthesis of Weinreb amides directly from various aliphatic carboxylic acids and aminoacids.[a]



[a]Isolated yields

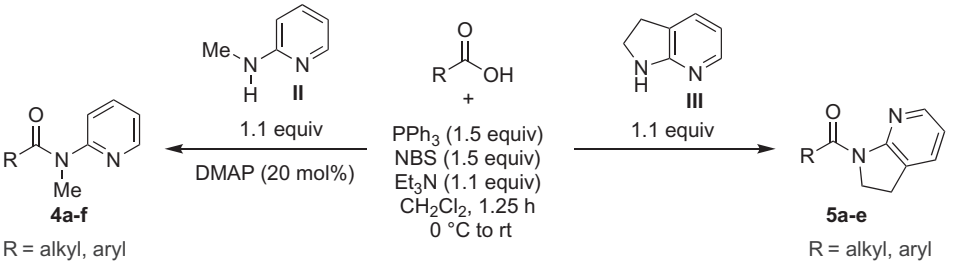


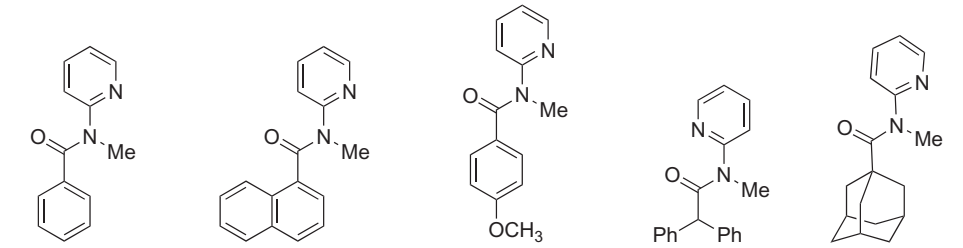
Scheme 3. Gram scale synthesis of Weinreb amide.

material was observed in the case of Boc- and Cbz-protected amino acids. A gram scale synthesis of Weinreb amide derived from benzoic acid was performed using commercial grade solvent, and the target amide (**2a**) was obtained in 75% yield (Scheme 3).

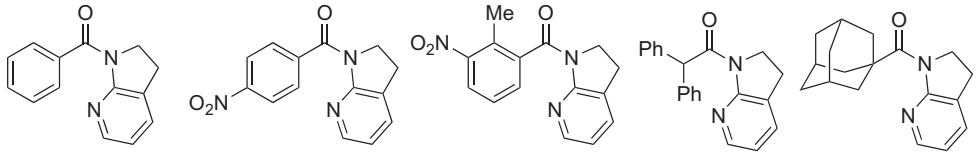
After a successful demonstration of direct synthesis of a series of Weinreb amides from carboxylic acids, we envisioned a straightforward synthesis of MAP amides and 7-azaindoline amides from carboxylic acids under the same reaction conditions outlined for the synthesis of Weinreb amides (Tables 1 and 2). In the case of MAP amide synthesis, 20 mol% DMAP was employed as a nucleophilic catalyst to facilitate the acyl transfer reaction. The treatment of aromatic carboxylic acids, such as benzoic acid and 1-naphthoic acid with PPh_3/NBS/DMAP combination followed by the addition of 2-(methylamino)pyridine (**II**) gave the corresponding MAP amides in 86% and 74%, respectively (Table 3, entries **4a** and **4b**). Aromatic carboxylic acid bearing electron-donating methoxy group, aliphatic carboxylic acids such as diphenylacetic acid and sterically hindered adamantane-1-carboxylic acid furnished the requisite amides in good to excellent yields (Table 3, entries **4c–4e**). Next, we explored the synthesis of a diverse

Table 3. Direct synthesis of MAP amides and 7-azaindoline amides from various carboxylic acids[a].





4a, 86% **4b**, 74% **4c**, 68% **4d**, 58 % **4e**, 81%



5a, 73% **5b**, 71% **5c**, 75% **5d**, 62% **5e**, 75%

[a]Isolated yields.

range of 7-azaindoline amide derivatives with the reaction conditions used for the synthesis of Weinreb amides. Several aromatic and aliphatic carboxylic acids were subjected for the amidation reaction using 7-azaindoline (**III**) as the nucleophile in the presence of PPh_3/NBS combination, and the respective 7-azaindoline amides were obtained in high yields (Table 3, entries **5a–5e**).

Conclusion

In summary, we have demonstrated a direct conversion of various aromatic and aliphatic carboxylic acids to the corresponding Weinreb amides in the company of PPh_3, NBS, and *N,O*-dimethylhydroxylamine hydrochloride (**I**) using commercial grade solvent under open-air atmosphere. The carboxylic acid functionality was chemoselectively transformed into Weinreb amide in the presence of more reactive carbonyl groups such as aldehyde and ketone. Besides, the present protocol was used for the synthesis of Weinreb amides of various amino acids without loss in the optical purity. The manifestation of gram scale synthesis of Weinreb amide of benzoic acid exhibits the viability of the present protocol for further scale-up. Further, we extended this strategy for the synthesis of a number of MAP amides and 7-azaindoline amides directly from aromatic and aliphatic carboxylic acids under identical reaction conditions.

Experimental section

General procedure for the synthesis of Weinreb amides

To a mixture of benzoic acid (50 mg, 0.41 mmol, 1 equiv.), PPh_3 (160 mg, 0.61 mmol, 1.5 equiv.), and NBS (108.5 mg, 0.61 mmol, 1.5 equiv.), CH_2Cl_2 (2 mL) was added and the reaction was stirred at 0 °C for 15 min. The reaction was brought to room temperature and *N,O*-dimethylhydroxylamine hydrochloride (59.5 mg, 0.61 mmol, 1.5 equiv.) and Et_3N (45.5 mg, 63 µL, 0.45 mmol, 1.1 equiv.) were added and the reaction mixture was stirred for 1 h at room temperature. The reaction mixture was quenched with aqueous sodium bicarbonate solution and diluted with CH_2Cl_2. The bicarbonate washings were again extracted with CH_2Cl_2 and the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Column chromatography was performed using EtOAc/Petroleum ether (1:5).

N-methoxy-N-methylbenzamide (2a)

Prepared according to the general procedure using benzoic acid (50 mg, 0.41 mmol). Yield: 97% (66 mg).[14a] The title compound was obtained as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.60–7.58 (m, 2H), 7.39–7.31 (m, 3H), 3.47 (s, 3H), 3.28 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 170.1, 134.2, 130.6, 128.2, 128.1, 61.1, 33.9. HRMS (*m*/*z*): calculated for $C_9H_{11}NO_2$ (M + H): 166.0860, found (M + H) 166.0825. The data is in accordance with reported literature.

General procedure for synthesis of 2-(methylamino)pyridine amides

To a mixture of benzoic acid (50 mg, 0.41 mmol, 1 equiv.), PPh_3 (160 mg, 0.61 mmol, 1.5 equiv.), and NBS (108.5 mg, 0.61 mmol, 1.5 equiv.), CH_2Cl_2 (2 mL) was added and the reaction was stirred at 0 °C for 15 min. The reaction was brought to room temperature, then, DMAP (10 mg, 0.082 mmol, 20 mol%), 2-(methylamino)pyridine (59.5 mg, 0.61 mmol, 1.5 equiv.), and Et_3N (45.5 mg, 63 µL, 0.45 mmol, 1.1 equiv.) were added and the reaction mixture was stirred for 1 h at room temperature. The reaction mixture was quenched with aqueous sodium bicarbonate solution and diluted with CH_2Cl_2. The bicarbonate washings were again extracted with CH_2Cl_2 and the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Column chromatography was performed using EtOAc/Petroleum ether (1:5).

N-methyl-N-(pyridin-2-yl)benzamide (4a)

Prepared according to the general procedure using benzoic acid (50 mg, 0.41 mmol).[8] Yield: 86% (75 mg). The title compound was obtained as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.37–8.36 (m, 1H), 7.37–7.34 (m, 1H), 7.27–7.22 (m, 3H), 7.16–7.13 (m, 2H), 6.97–6.95 (m, 1H), 6.73 (d, $J = 8.0$ Hz, 1H), 3.51 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 171.1, 156.9, 148.8, 137.4, 136.1, 130.2, 128.6, 128.1, 121.7, 121.0, 36.1. HRMS (*m*/*z*): calculated for $C_{13}H_{12}N_2O$ (M + H): 213.1022, found (M + H) 213.1023. The data is in accordance with reported literature.

General procedure for the synthesis of 2,3-dihydro-7-azaindole amides

A reaction tube with a teflon coated magnetic stir bar was charged with benzoic acid (50 mg, 0.41 mmol, 1 equiv.), PPh_3 (160 mg, 0.61 mmol, 1.5 equiv.), and NBS (108.5 mg, 0.61 mmol, 1.5 equiv.). CH_2Cl_2 (2 mL) was added and the reaction was stirred at 0 °C for 15 min. The reaction was brought to room temperature and 2,3-dihydro-7-azaindole (54 mg, 0.45 mmol, 1.1 equiv.) and Et_3N (45.5 mg, 63 µL, 0.45 mmol, 1.1 equiv.) were added and the reaction mixture was stirred for 1 h at room temperature. The reaction mixture was diluted with EtOAc and washed with aqueous sodium bicarbonate solution. The bicarbonate washings were again extracted with EtOAc and the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Column chromatography was performed using EtOAc/Petroleum ether (1:5).

(2,3-Dihydro-1H-pyrrolo[2,3-b]pyridin-1-yl)(phenyl)methanone (5a)

Prepared according to the general procedure using benzoic acid (50 mg, 0.41 mmol). Yield: 73% (66.8 mg). The title compound was obtained as a white solid, mp = 114 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.85 (d, J = 5.0 Hz, 1H), 7.59 (d, J = 7.0 Hz, 2H), 7.48–7.45 (m, 2H), 7.38 (t, J = 7.5 Hz, 2H), 6.81 (dd, J = 7.5, 5 Hz, 1H), 4.22 (t, J = 8.0 Hz, 2H), 3.11 (t, J = 8.5 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 169.3, 156.2, 146.3, 136.1, 133.3, 130.7, 128.5, 127.8, 125.8, 118.5, 47.9, 25.1. IR (ATR, cm^{-1}): 1643, 1593, 1420, 1379, 1347, 1245, 790, 712. HRMS (m/z): Calculated for $C_{14}H_{12}N_2O$ (M + H) 225.1022, found (M + H) 225.1022.

Full experimental details, characterization data for compounds with copies of ^{1}H and ^{13}C NMR spectra and HRMS of all new compounds. This material can be found via the "Supporting Information" section of this article's webpage.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

The authors thank IISER Thiruvananthapuram for financial support. One of the authors (F.P) thank UGC, New-Delhi for senior research fellowship.

ORCID

Alagiri Kaliyamoorthy http://orcid.org/0000-0002-5183-8191

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