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Copper catalyzed aryl amidation between N^{α}-Fmoc-protected amino-acid azides and aryl boronic acids

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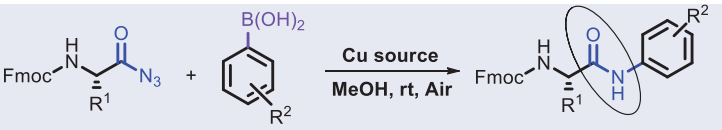
ABSTRACT

A simple and efficient method for the synthesis of aryl amides *via* oxidative copper-catalyzed coupling of commercially available aryl boronic acids and bench stable N^{α}-protected amino-acid azides is reported. The potential utility of this protocol is demonstrated through a survey of diversely substituted aryl boronic acids and several side-chain functionalized amino-acid azides, leading to the preparation of the desired amidated products in good to excellent yields. This amide synthesis is suitable for the preparation of amides (such as peptide aryl amides and sterically hindered amino acids) that are not or hardly accessible via classical approaches.

GRAPHICAL ABSTRACT



R^1 = Amino acid side chain, R^2 = aryl substitutions

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KEYWORDS
Amide bond; aryl boronic acid; copper(I) bromide dimethyl sulfide; N^{α}-Fmoc-amino-acid azides

Introduction

The amide bond is the most abundant functional group in organic chemistry.[1] It is an important component in peptides, proteins, natural products, and pharmaceuticals.[2] The classical means of preparing amides are the dehydrative coupling of carboxylic acids with amines by the use of coupling reagents (Route 1 in chemical toolbox).[3] This method often possesses various drawbacks such as long duration, expensive reagents, the formation of byproduct and several others.[4] Thus, a universal method for the formation of amides is not feasible. Over the past few years, chemists have extensively investigated new methods to construct the amide linkage, aiming at a more efficient and environmentally benign pathway.[5] Interesting approaches include the reaction of

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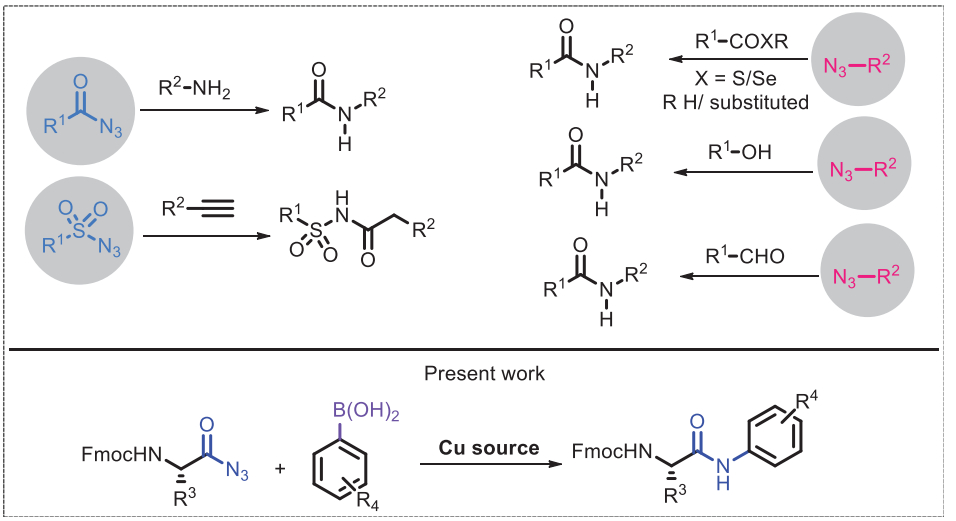
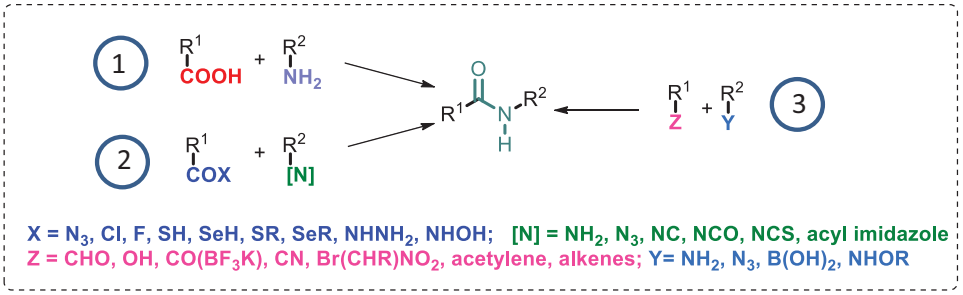


Figure 1. Amidations from various azides.

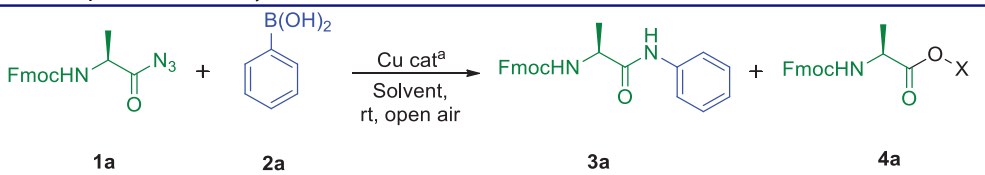
either activated carboxylic acid derivatives or activated amino derivatives (Route 2 in chemical toolbox).[6] The potential utility of this route has been well established for the synthesis of a variety of complex amides, peptides and natural products. Several of these methods have been effectively transformed as chemoselective ligation reactions for the protein chemical synthesis.[7] Many amide-containing pharmaceuticals and active drugs are small molecules and thus require large scale preparation.[8] In this context, unnatural substrates other than acid and amine as coupling agents, are useful to transform into amides (Route 3 in chemical toolbox). However, these processes often work at high temperature and requirement of metal catalysts.[9]



Chemical toolbox. Amidation reactions in literature.

Route 2 in the chemical toolbox for amide bond formation also includes azides which have been shown to exhibit advantages in certain amidation reactions, for example, acid azide-amine reaction,[10] Staudinger ligation,[11] thio acid-azide amidation,[12] seleno acid-azide amidation,[13] alkyne-sulfonylazide coupling,[14] alcohol-azide amide synthesis,[15] and azide-aldehyde amidation (Figure 1).[16] Most of these amidation reactions are redox neutral and involving only the release of volatile side products (toxic HN_3 in case of acid azide-amine coupling, sulfur in thio acid-azide amidation reaction and all other reactions involve the release of N_2 as the sole byproduct). Therefore, the use of an acid azide and boronic acids as substrates for amide formation is an attractive process.

Table 1. Optimization of aryl amidation reaction.



1a **2a** **3a** **4a**

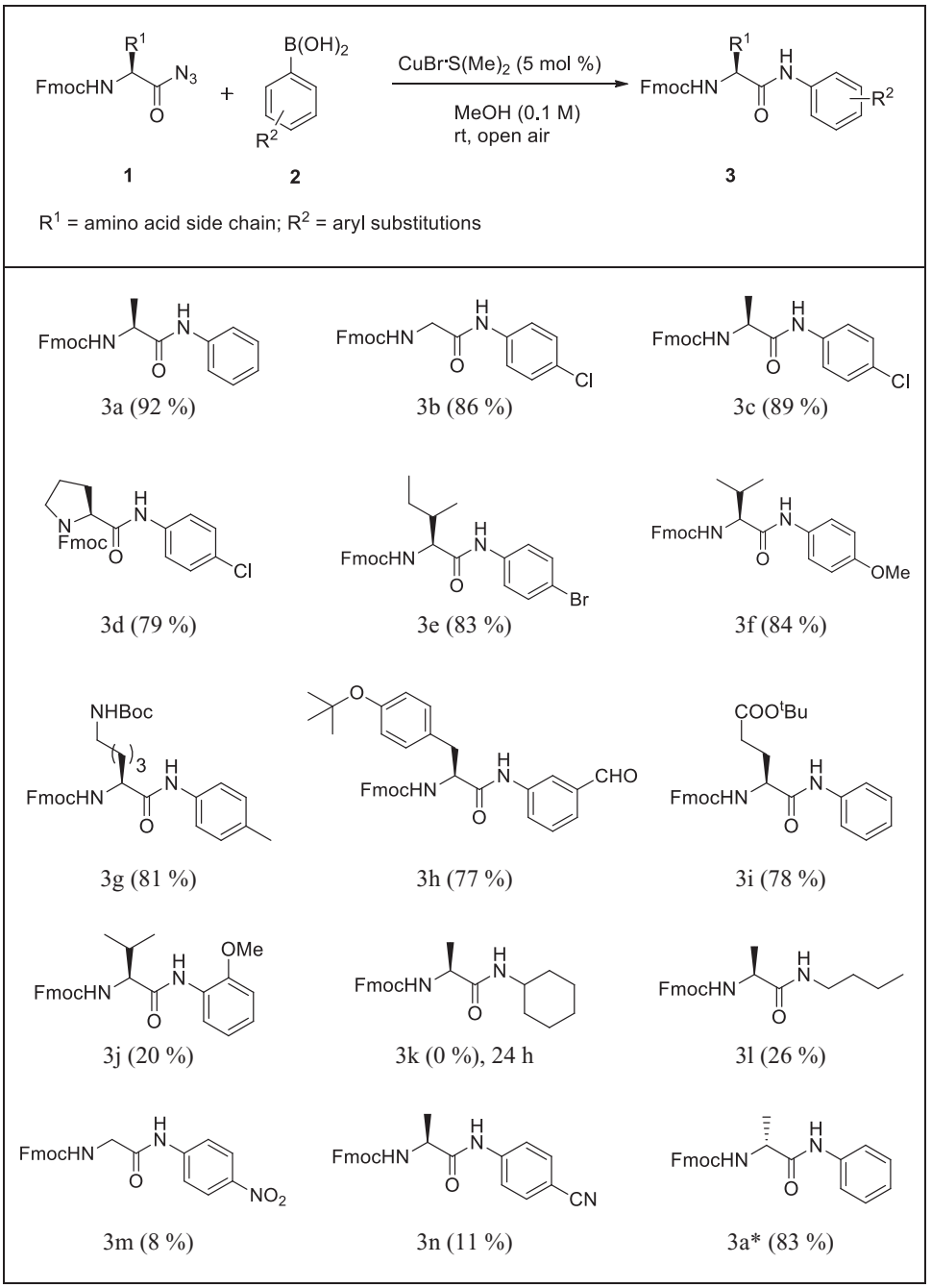
Entry	Catalyst	Solvent (0.1 M)	Time (h)	Yield **3a**[h] (%)	Yield **4a** (%)
1[a]	CuCl	MeOH	4	70	5[e]
2[b]	CuCl	MeOH	5	68	18[e]
3[c]	CuCl	MeOH	5	52	28[e]
4[d]	CuCl	MeOH	5	62	15[e]
5[b]	$CuBr{\cdot}S(Me)_2$	MeOH	1	81	–
6[d]	$CuBr{\cdot}S(Me)_2$	MeOH	1	92	–
7[c]	CuBr	MeOH	2	60	–
8[d]	$CuBr_2$	MeOH	5	71	5[e]
9[d]	$Cu(OAc)_2$	MeOH	4	45	22[e]
10[d]	CuI	MeOH	4	53	30[e]
11[d]	none	MeOH	24	6	80[e]
12[d]	$CuSO_4$	MeOH	24	65	–
13[d]	$CuBr{\cdot}S(Me)_2$	EtOH	24	60	30[f]
14[d]	$CuBr{\cdot}S(Me)_2$	Trifluoroethanol	24	45	25[g]
15[d]	$CuBr{\cdot}S(Me)_2$	THF	24	35	–
16[d]	$CuBr{\cdot}S(Me)_2$	CH_3CN	24	39	–
17[c,i]	$CuBr{\cdot}S(Me)_2$	MeOH	3	81	–
18[b]	$Cu(OAc)_2{\cdot}H_2O$	MeOH	4	51	20[e]
19[d]	$CuSO_4{\cdot}5H_2O$	MeOH	24	69	–

[a]1.0 eq. of **1a**, **2a** and 10 mol % of catalyst;
[b]1.0 eq. of **1a**, 1.5 eq. **2a** and 10 mol % of catalyst;
[c]1.0 eq. of **1a**, 2.0 eq. **2a** and 10 mol % of catalyst;
[d]1.0 eq. of **1a**, 1.5 eq. **2a** and 5 mol % of catalyst;
[e]X = Me;
[f]X = Et;
[g]$X = CH_2CF_3$;
[h]= Isolated yield;
[i]= control reaction under argon atmosphere (without O_2).

Boronic acid, which is thermally and air-stable, is one of the important coupling partners in the Suzuki cross-couplings.[17] In the context, of industrial applications and large scale preparations, aryl amines are difficult to form amide under classical approaches because of the less nucleophilicity of aryl amines. Thus, numerous non-classical substrates are found to be highly inviable for the aryl-amidation process.[18]

Results and discussion

Recently, the copper-catalyzed Chan-Lam coupling has been discovered as a promising greener alternative employed for the synthesis of aryl ethers,[19] carbamates or ureas[20] and aryl sulfonyl amides.[21] In 2013, Watson and coworkers reported the first example of the Chan-Lam coupling of alkyl boronic acids and primary amides catalyzed by a copper(I) source.[22] It should be noted that high temperature and use of di-tert-butyl peroxide as oxidant are not tolerable to stereochemically labile amino acids. Kim and coworkers reported the synthesis of N-aryl carbamates via copper-catalyzed Chan-Lam coupling of azidoformate and arylboronic acids.[20] We, therefore, targeted an oxidative Chan-Lam coupling procedure that would form amide bond under mild conditions with the use of alternative and reactive acid azides (Table 1 and Scheme 1). Herein, we



Scheme 1. Scope of N$^{\alpha}$-Fmoc amino-acid azides in the aryl amidation.

report a copper-catalyzed N-protected α-amino-acid azide-aryl boronic acid amidation reaction which could be carried out under mild conditions to afford aryl amides in excellent yields.

Our laboratory had reported the synthesis of N$^{\alpha}$-Fmoc-amino-acid azides and a wide range of applications in the construction of novel peptidomimetics.[23] Thus, our plan

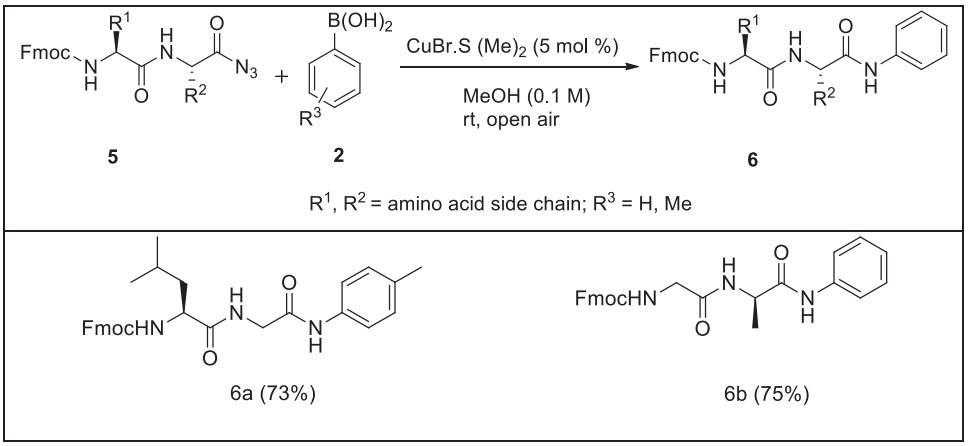
was to evaluate the use of acid azides as an alternative to a primary amide source in Chan-Lam couplings.

Our initial studies focused on the copper-catalyzed coupling between of N^{α}-Fmoc-Ala-CON_3 (**1a**) [The Fmoc-protected amino-acid azide was prepared by activating the amino acid using $SOCl_2$ to the corresponding acid chloride in CH_2Cl_2. When 0.1 eq of DMF as a catalyst was added, the reaction was completed within an hour at room temperature. To this acid chloride, NaN_3 was added to afford the corresponding Fmoc amino-acid azide] and phenyl boronic acid (**2a**) at room temperature. An equimolar amount of **1a** and **2a** in presence of 10 mol % of CuCl gave only a moderate yield of **3a** along with the trace amount of methyl ester **4a** derived from the esterification of **1a** with MeOH (Table 1, entry 1). The use of increased stoichiometry of boronic acid **2a** such as 1.5, and 2.0 equivalents afford corresponding amide **3a** in 68% and 52% yield respectively along with methyl ester **4a** (Table 1, entries 2 and 3). The yield of amide **3a** was similar when the catalyst loading was reduced to 5 mol % (Table 1, entry 4). We further investigated various copper(I) catalysts (Table 1, entries 5–12, 18 and 19). Interestingly, 5 mol % of $CuBr{\cdot}S(Me)_2$ gave 92% of amide **3a** without any methyl ester **4a** at room temperature (Table 1, entry 6). Further screening of copper catalysts CuBr, CuI, CuCl, $CuSO_4$, $Cu(OAc)_2$, $CuBr_2$, $Cu(OAc)_2{\cdot}H_2O$ and $CuSO_4{\cdot}5H_2O$ was found less efficient than $CuBr{\cdot}S(Me)_2$ in terms of catalyst loading and yield. Other solvent systems such as THF, CH_3CN, trifluoroethanol and ethanol gave only poor yields of **3a** (Table 1, entries 13–16). Additionally, the controlled reaction under an argon atmosphere (without O_2) afforded the desired product in a lower yield of 81% in **3h** (Table 1, entry 17 and page 5).

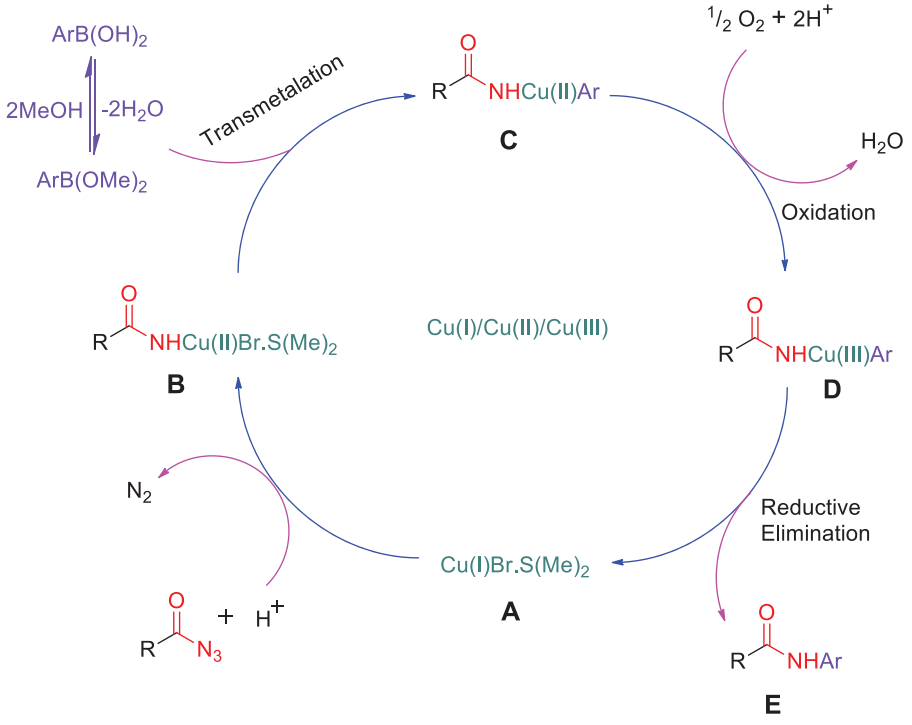
The scope of the reaction is illustrated with respect to various N^{α}-protected amino-acid azides and aryl boronic acids as well. In general, electron-donating phenyl boronic acids furnished the desired products in good yields ranging from 78% to 92%. When electron-withdrawing groups were employed as coupling partners, particularly, phenyl boronic acids bearing chloro or bromo group, we obtained the desired amide in lesser yields. When phenyl boronic acid bearing nitro (NO_2) and cyano (CN) are used, we observed expected amide in poor yields along with methyl ester **4a**. On the other hand, the *ortho*-substituted methoxy phenyl boronic acids gave the product in poor yield. This is due to the steric hindrance by the ortho methoxy group (Scheme 1, **3j**). Use of alkyl boronic acid such as n-butyl boronic acid, afforded the desired product **3l** in poor yield. However, cyclohexylboronic acid was found to be unsuitable as the desired product was not formed even after 24 hr. The sterically hindered amino acids and bifunctional amino-acid azides readily engaged in the amidation process without compromising the overall yield. All the desired amides were furnished in good yields at room temperature (Scheme 1).

Test for racemization

The HPLC analysis of enantiomeric amides **3a** and **3a*** showed the retention times of **16.178** min and **12.197** min, respectively. However, the equimolar mixture of the isomers showed distinct retention times of **16.180** min and **12.191** min which confirms that the present protocol is racemization free and the isomers are optically pure (method: gradient 0.1% TFA water-acetonitrile; flow rate: 0.5 mL/min, 20 min).



Scheme 2. Coupling of dipeptide acid azide and aryl boronic acid.



Scheme 3. Putative mechanism for the amidation reaction.

With the optimized reaction conditions in hand, the scope of peptide acid azides was investigated next. N-Protected amino-peptide acid azide is coupled with substituted phenyl boronic acid, obtained the desired products in good yields (Scheme 2).

Based on the literature precedents[20,21(a)], [24], a plausible mechanism for amidation reaction between acid azide and boronic acid has been presented in Scheme 3. The first step proceeds through the reaction of Cu(I) salt **A** and an acid azide which yields

Cu(II) complex **B** via copper nitrene formation with the elimination of N_2. Methyl boronate ester (arylboronic acid and methyl boronate ester are in equilibrium)[25] undergoes transmetalation with **B** to afford Cu(II) complex **C**. **C** undergoes oxidation to afford Cu(III) complex **D**, and finally target amide **E** as a stable molecule is obtained by the reductive elimination of **D**, regenerating Cu(I) catalyst **A** in the process. In the absence of O_2, the reductive elimination route from **C** occurs to give amide **E**, which is a slow step (Scheme 3).[26]

Conclusion

In summary, we have developed a facile copper-catalyzed aryl amidation of aryl boronic acids with acid azides to obtain *N*-aryl amides. The efficiency and functional group tolerance was examined with respect to both acid azide and boronic acid which is satisfactory, allowing for the preparation of a series of functionalized aryl amides in good yields. This transformation is economical, as it can be carried out effectively in an open atmosphere at room temperature in the presence of only catalytic amount of CuBr·S(Me)$_2$.

Experimental section

General procedure for the amidation reaction

To a solution of N^{α}-Fmoc amino-acid azide[23] (1.0 mmol) in MeOH (10 ml) was added CuBr·S(Me)$_2$ (5 mol %) and arylboronic acid (1.5 mmol). The mixture was stirred at room temperature until the reaction was complete (TLC). The solution was filtered through a pad of Celite and washed with EtOAc (10 mL). The filtrate was diluted with H_2O (10 mL) and the mixture was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed thrice with 10% Na_2CO_3 (3 × 10 mL), 1 N HCl (3 × 10 mL) and H_2O (3 × 10 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvent under *vacuo* followed by column chromatography on silica gel (mesh 100–200) using ethyl acetate and hexane as the eluents [Ethyl acetate/Hexane = 3:7], gave the product in good yields.

Fmoc-Ala-[CONH]-C_6H_5 [3a]

White solid, yield (92%, 0.355 g), m.p. = 190–192 °C (Lit. 191–193 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.20 (s, 1 H), 7.60–7.00 (m, 13 H), 6.28 (d, J = 5.2 Hz, 1 H), 4.95-4.82 (m, 1 H), 4.35 (d, J = 5.2 Hz, 2 H), 4.07 (t, J = 5.2 Hz, 1 H), 1.3 (d, J = 5.6 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.0, 155.8, 143.5, 140.9, 138.1, 130.8, 128.5, 127.4, 126.8, 124.9, 123.7, 119.6, 66.4, 50.9, 46.8, 18.7. HRMS: m/z Calculated for $C_{24}H_{23}N_2O_3$ $[M+H]^+$ 387.1709; found: 387.1706.[27]

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 "Supplementary Content" section of this article's webpage.

Acknowledgements

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