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A Reaction of *N*-Substituted Succinimides with Hydroxylamine as a Novel Approach to the Synthesis of Hydroxamic Acids

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Abstract: We describe a novel two-step approach for the synthesis of compounds with a hydroxylamide group (hydroxamic acids), which are widely known for their biological activity (histone deacetylase inhibitors, matrix metalloproteinases inhibitors and others). The first stage is the synthesis of *N*-substituted succinimide via the reaction of aromatic amine or carboxylic acid hydrazide with succinic anhydride. The second step involves the imide ring opening reaction by hydroxylamine. For both stages, universal synthetic methods are developed to exclude additional purification procedures for the target compounds. Sixteen hydroxamic acids are synthesized using the developed approach. Most of the compounds are obtained for the first time.

Keywords: *N*-substituted succinimides; hydroxylamine; hydroxamic acids; imide ring opening; HDAC inhibitors; MMP inhibitors

1. Introduction

Hydroxamic acids belong to a very important class of compounds for anticancer drug development [1] because of their ability to inhibit metalloenzymes [2] such as histone deacetylase (HDAC) [3,4] or matrix metalloproteinase (MMP) [5,6]. Additionally, these compounds are of great interest for the development of such a modern field of organic chemistry as oxidative coupling reactions [7–9]. There are several well-known reactions for the synthesis of hydroxamic acids (see Figure 1) that involve carboxylic acids, esters, amides and aldehydes as starting compounds with different reaction activation additives (*N*,*N*-dimethylchloromethaniminium chloride, ethyl chloroformate, 1-methanesulfonyl-1*H*-benzotriazole MSBT, cyclic phosphonic anhydride PPAA, etc.) or catalysts (KCN, Fe^{3+}, MgO, etc.) [2,10,11]. One more reaction that we believe can expand the possibilities for the synthesis of a broad number of new compounds with hydroxamic acid group is the five-membered imide cycle opening by ammonia derivatives [12–14]. Recently [15], based on the reaction of *N*-substituted succinimides with hydroxylamine, we developed a novel approach that features simple and mild conditions. Here, we report a detailed description of the developed approach, which consists of two steps: (i) the synthesis of *N*-substituted succinimides by the reaction of succinic anhydride with amines in chloroform in the presence of polyphosphate ester and (ii) the treatment of *N*-substituted succinimides by hydroxylamine aquatic solution.

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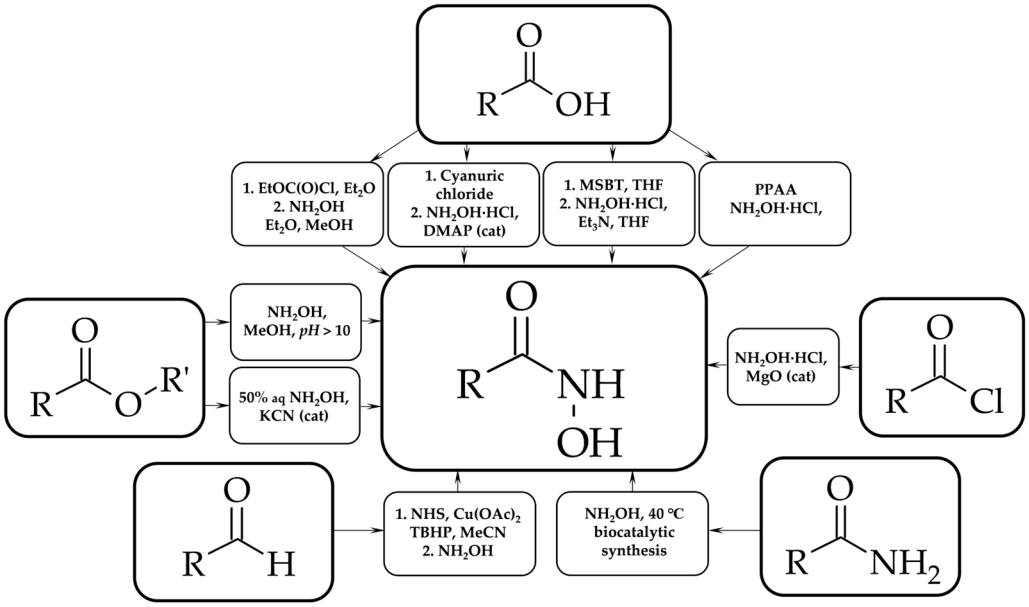


Figure 1. General approaches to the synthesis of hydroxamic acids [2,10,11].

2. Materials and Methods

Mass spectra were recorded on a Finnigan MAT INCOS 50 mass spectrometer with direct sample injection (EI ionization, 70 eV). IR spectra were acquired on a Bruker Alpha FT-IR spectrometer (all samples were analyzed directly without dilution in KBr). ^{1}H and ^{13}C NMR spectra were acquired on a Bruker DRX-500 (and DRX-600) in $CDCl_3$ or DMSO-d_6 with TMS as the internal standard.

Polyphosphate ester (PPE) was synthesized according to the described method [16]. Hydrazides were synthesized using a general approach described in [17]. Succinic anhydride was purified from succinic acid residues by Soxhlet extraction using chloroform (TCM) as a solvent (anhydride was collected as extract).

Synthesis of compounds **1**. General method (one-pot approach): an amount of 10 mmol of amine (or hydrazide) R-NH_2 (or R-C(O)-$NHNH_2$) was added to refluxing solution of 10 mmol succinic anhydride in 50 mL of TCM. Resulted mixture was refluxed for 6 h, then the PPE (1 g for **1a**; 2 g for **1b**–**f**; 3 g for **1h**–**p**; 5 g for **1g**) was added, and reaction continued for 6 h at the same temperature. General method (two-step approach): An amount of 10 mmol of amine (or hydrazide) R-NH_2 (or R-C(O)-$NHNH_2$) was added to refluxing solution of 10 mmol succinic anhydride in 50 mL of TCM. Resulted mixture was refluxed for 6 h. Formed precipitate IM (intermediate amido acid) was filtered, washed by 30 mL of TCM, and suspended in 50 mL of TCM in 100 mL flask. To the resulting suspension, the PPE (1.5 g for **1a**–**f**; 2.5 g for **1h**–**p**; 5 g for **1g**) was added, and reaction mixture was refluxed for 6 h. For both approaches, the reaction can be monitored by TLC (TCM as eluent for **1a**–**f** and TCM with isopropanol (with a volume ratio of 90:10) for **1g**–**p**). At the completion of the imidization reaction, the reaction mixture turned homogenous (except for **1g** that precipitates out of the reaction mixture). Isolation of **1a**–**f** and **1h**–**p**. Reaction mixture was treated with 35 mL of $NaHCO_3$ hot saturated solution, then organic fraction was separated and dried with Na_2SO_4. TCM was removed on rotary evaporator and resulted precipitate was washed by 30 mL of hot methanol. Isolation of **1g**. The precipitate was filtered off and washed by TCM (3 × 30 mL) and dried in desiccator with phosphorus pentoxide.

Synthesis of compounds **2** (general method): an amount of 1.11 g (16 mmol) of hydroxylamine hydrochloride was dissolved in 6.8 mL of 20% ammonia water solution. Then, the excess ammonia was removed under vacuum (10 torr, during 30 min) followed by argon bubbling within 3 h (until the smell of ammonia disappears). The hydroxylamine water solution was added to a suspension of 1 (4 mmol) in 1 mL of methanol. Resulted

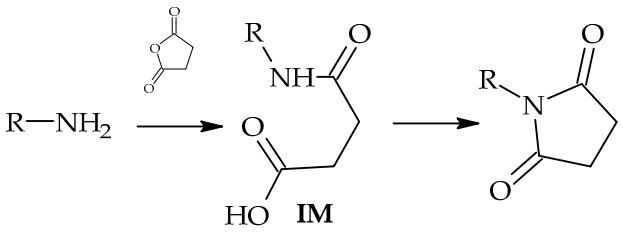
reaction mixture was stirred at 30 °C for 1 h (except for 2b that was stirred at 40 °C for 8 h); the precipitate structure changing (from crystalline to amorphous) was observed during the reaction. Resulted precipitate was filtered, washed by water (3 × 30 mL) and TCM (3 × 30 mL), and dried in desiccator with phosphorus pentoxide.

Synthesis of 2-phenyl-1*H*-isoindole-1,3(2*H*)-dione: an amount of 0.93 g (10 mmol) of aniline was added to refluxing solution of 1.66 g (10 mmol) benzene-1,2-dicarboxylic acid with 17 g of PPE in TCM (40 mL). Resulted mixture was refluxed for 6 h, then treated with 100 mL of $NaHCO_3$ hot saturated solution. Organic fraction was separated and dried with Na_2SO_4. TCM was removed on rotary evaporator and resulted precipitate was washed by hot methanol (3 × 25 mL). Yield 0.96 g (43%) of colorless crystals.

Compounds **1f**, **1h**–**p** and **2b**–**p** were synthesized for the first time. Compounds **1a**–**e**, **1g** and **2a** are also described in [18–23]. All spectral data are available in Supporting Materials. Most of the ^{1}H NMR (and some of ^{13}C NMR) spectra of the synthesized hydroxamic acids 2 (see Supplementary Materials) have additional signals or broad peaks related to cis-trans isomerization [24].

3. Results and Discussion

For our work, a universal method for the synthesis of *N*-substituted succinimides had to be developed. The simplest way to obtain *N*-substituted succinimides is the acylation reaction of amine by succinic anhydride, followed by a cyclodehydration process to a target imide (Scheme 1).

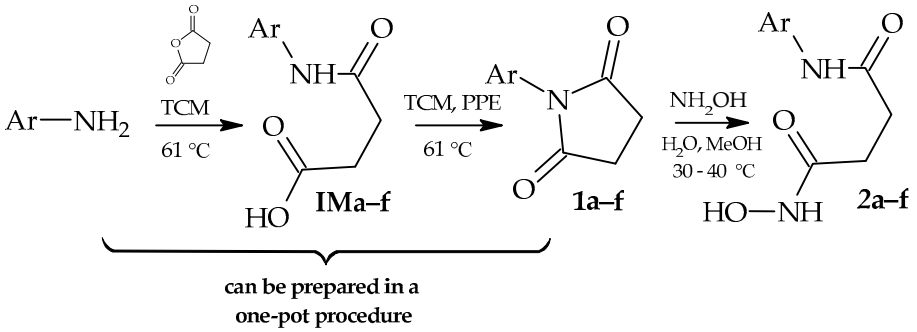


Scheme 1. Synthesis of *N*-substituted succinimides.

The first step of the reaction depicted in Scheme 1 usually undergoes with high yields under mild conditions in diethyl ether, toluene, 1,2-dimethoxyethane [25], polyethylene glycol [26], etc. The cyclodehydration reaction (step 2 in Scheme 1) can be provided by heating (120 °C) [26–29] or acetic anhydride addition [25,30,31]. At first, we synthesized *N*-phenylsuccinimide by thermal imidization and found some side-product formation, which might be caused by the partial thermal degradation of the intermediate amido acid (IM). Therefore, we hypothesize that thermal imidization is not universal for *N*-substituted succinimides synthesis, especially for compounds with less thermal stability than 4-anilino-4-oxobutanoic acid. Using acetic anhydride can result in a side acetylation reaction (e.g., the reaction with phenol groups [32,33]).

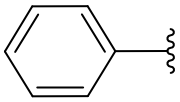
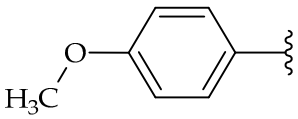
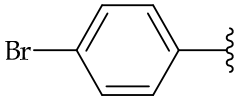
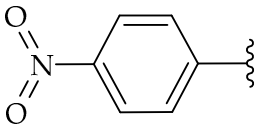
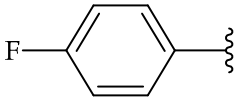
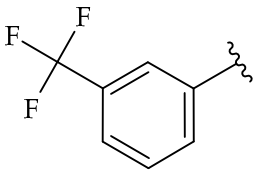
Polyphosphate ester (PPE) is a known mild reagent for cyclodehydration reactions [34,35] and it can be used even without additional protection of the phenol groups [34]. Here, we report for the first time the usage of PPE as the dehydration additive for imidization reaction. We have found that an addition of 1–5 g of PPE per 10 mmol of formed acylation product (amidoacid) leads to its conversion into succinimide. This finding provides a two-step reaction (Scheme 1) in chloroform (TCM) in a one-pot manner (Scheme 2, synthesis of **1a**–**f**). The first step in Scheme 2 can be controlled by visually observing the reaction mixture: the acylation product IMa–f precipitates from TCM following a dissolving process after PPE addition. It should be noted that using colorless amine Ar-NH_2 is an absolute prerequisite for the one-pot approach (the coloration of Ar-NH_2 indicates the presence of impurities which significantly decrease the yield of **1**). This limitation can be circumvented by separating of the intermediate amido acid IMa–f precipitate from impurities dissolved in TCM, hence the subsequent imidization stage can be carried out in pure solvent. The

yield difference between "one-pot" (without separation of IMa–f) and "two step" (with separation of IMa–f) syntheses of **1a–f** is clearly seen in Table 1. The main feature of the proposed method of **1** synthesis is the simplicity of product separation (no additional purification procedures are required, the product is only washed by methanol).



Scheme 2. Synthetic route to hydroxamic acids based on aniline derivatives.

Table 1. Compounds synthesized according to Scheme 2.

	Ar	Yield of 1, %		Yield of 2, %
		One-Pot Approach	Two-Step Approach	
a		15	68	73
b		35	54	66
c		52	65	53
d		31	44	64
e		42	64	38
f		33	48	34

The experimental conditions for the last step in Scheme 2 were optimized using **1a**. We found that if the reaction of *N*-phenyl succinimide with hydroxylamine was carried out in absolute methanol, it was difficult to isolate and purify the target compound **2a** from impurities. Using hydroxylamine water solution (see Section 2) proved to be a more suitable approach. Despite poor water solubility of the succinimides **1a–f**, the imide ring opening reaction can be carried out directly in hydroxylamine water solution, and the reaction proceeds with visible change in the appearance of the precipitate (the precipitate structure changing from crystalline to amorphous). Addition of some amount of methanol

into the reaction mixture can increase the reaction rate, which is most likely related to a slight increase in the imide solubility.

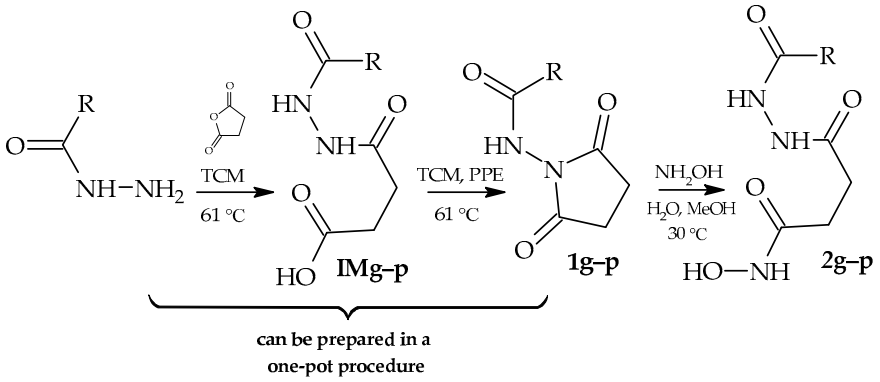
Using a water-based reaction medium simplifies the separation and purification process, and all impurities can be removed easily by washing the filtered precipitate with water and TCM. The yield primarily depends on the solubility of the product in the reaction medium and can be changed by varying the amount of methanol in the reaction mixture.

A necessary condition for imide ring opening in the presence of hydroxylamine is the acidity of initial R-NH_2 (Scheme 2) that must be more than that for hydroxylamine. As it can be seen from Table 2, the p*K*a value for anisidine (used for **2b** synthesis) is close to the p*K*a of hydroxylamine, and the synthesis of **2b** proceeded much slower in comparison to the other compounds, and it had to be carried out at a higher temperature for longer time (see Section 2 for details). The additional confirmation of the found effect of initial amine acidity is the fact that the reaction between hydroxylamine and commercially available pyrrolidine-2,5-dione does not take place (because p*K*a (NH_3) > p*K*a (NH_2OH), see Table 2).

Table 2. A comparison of p*K*a values for Ar-NH_2 and some hydrazides.

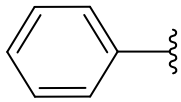
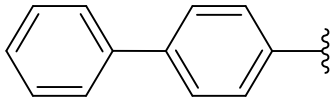
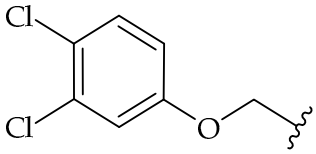
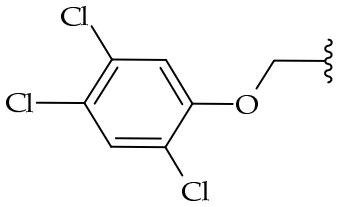
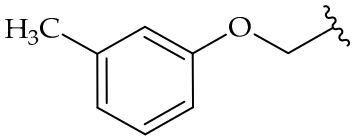
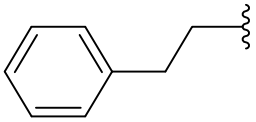
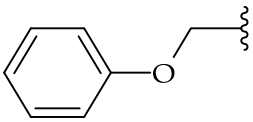
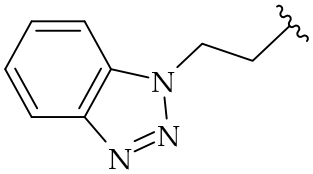
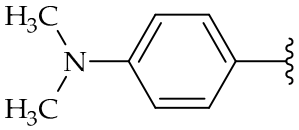
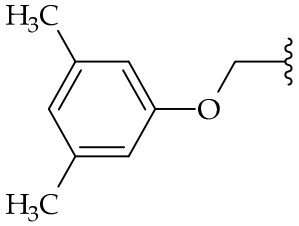
	Amine	**p*K*a** [36]
	Ammonia	9.25
	Hydroxylamine	5.94
a	Aniline	4.87
b	4-Methoxyaniline	5.36
c	4-Bromoaniline	3.89
d	4-Nitroaniline	1.02
e	4-Fluoroaniline	4.65
f	3-(Trifluoromethyl)aniline	3.49
	Hydrazide	**p*K*a** [37]
	Acetohydrazide	3.25
	Benzohydrazide	3.06
	4-Methoxybenzohydrazide	3.26

To expand the potential of the proposed approach, hydrazides of carboxylic acids were used. Their basicity is noticeably lower than that of hydroxylamine (Table 2) and does not depend substantially on the nearest substituents (Table 2 shows that aliphatic and aromatic hydrazides have close values of p*K*a). The reaction conditions used for aniline derivatives described above proved to be suitable for the synthesis based on hydrazides (Scheme 3). Table 3 shows the resulting structures obtained using various carboxylic acid hydrazides. It can be seen (Table 3) that the yield difference between the "one-pot" and "two-step" syntheses of **1g–p** is not so noticeable as for **1a–f**, which is primarily due to the fact that hydrazides are more stable (contain less impurities) than derivatives of aniline.



Scheme 3. Synthetic route to hydroxamic acids based on hydrazides.

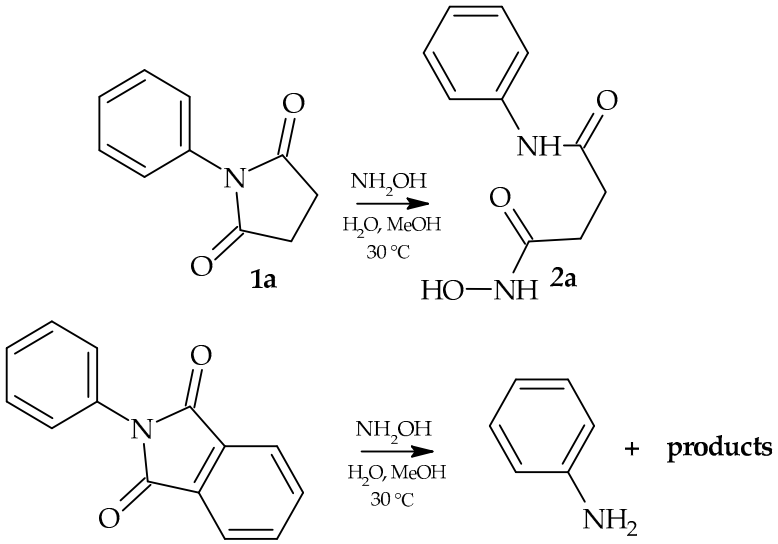
Table 3. Compounds synthesized according to Scheme 3.

	R	Yield of 1, %		Yield of 2, %
		One-Pot Approach	Two-Step Approach	
g		42	45	75
h		39	43	69
i		68	76	72
j		42	44	63
k		71	69	35
l		46	45	43
m		77	80	46
n		53	60	85
o		59	70	86
p		81	88	80

The nature of the imide ring opening reaction described here looks similar to the one of hydrazine hydrate interaction with phthalimides. The fact that hydrazine reacts with phthalimide was first observed at the end of the 19th century [38] and was used as the basis for

the Ing–Manske procedure (the Gabriel synthesis) [39]. Additionally, there are many examples of using the mentioned reaction for *N*-aminophthalimide synthesis [40–42]. It is known that hydrazine hydrate reacts with phthalimide even at –20 °C [42], which is important to exclude the transformation of *N*-amino phthalimide into 2,3-dihydrophthalazine-1,4-dione. This fact is a further confirmation that reactions between five-membered cyclic imides and ammonia derivatives (in particular, the reaction between *N*-substituted succinimides and hydroxylamine) can easily undergo without heating.

Taking into account the similarity mentioned above, it was important to compare the reactions of hydroxylamine with succinimides and phthalimides at the same conditions. For this purpose, *N*-phenyl phthalimide was synthesized and compared with **1a**. In contrast to **1a**, which reacts with NH_2OH with the formation of **2a** only (Scheme 4), *N*-phenyl phthalimide in hydroxylamine water solution decays into a number of products, including aniline (the reaction was monitored by TLC).



Scheme 4. A comparison of the hydroxylamine reactions with *N*-phenyl succinimide and *N*-phenyl phthalimide.

Moreover, the aniline formation was also observed with a hydroxylamine concentration that was less than that expected based on the stoichiometry of the reaction (whereas the reaction of **1a** with a tenfold excess of hydroxylamine did not lead to aniline formation). Although the phthalimide ring opening has to be occurred [43], we could not separate phthalic analogue of **2a** using the approach proposed in the present work. Unlike the reaction of hydroxylamine with **1a**, that of with *N*-phenyl phthalimide leads to homogenization of the reaction mixture, which significantly complicates the separation of the products. Thus, we can conclude that our approach is so far suitable only for *N*-substituted succinimides (if the p*K*a inequality condition described above is satisfied). Some questions still remain to be answered, such as: (i) is it possible to find the experimental conditions optimal for the separation of the phthalimide ring opening product?; (ii) how will the reaction of hydroxylamine with *N*-substituted maleimides proceed?; (iii) will the experimental conditions affect the composition of the isomers formed during the described [13,14] interaction of hydroxylamine with succinimides substituted in positions 1 and 3 simultaneously?; and (iv) is it possible to involve six-membered imide cycles in the reaction with hydroxylamine?

4. Conclusions

A novel approach for hydroxamic acids synthesis has been proposed based on the reaction between *N*-substituted succinimides and hydroxylamine. The reaction occurs through imide ring opening and results in the formation of *N*-hydroxybutaneamide derivatives (the imide ring opening is possible only when p*K*a (RNH_2) < p*K*a (NH_2OH), where RNH_2 is the

initial amine used for imide synthesis). To obtain *N*-substituted succinimides of different structures, a new method based on the reaction of amines or hydrazides with succinic anhydride in the presence of polyphosphate ester has been proposed. The developed approach provides a simple tool to obtain a broad spectrum of new hydroxamic acids that can be used in medicinal chemistry research or for free radical C–O coupling reactions. Compared to the previously described methods (Figure 1), the reactions of N-substituted succinimides with hydroxylamine make it possible to synthesize *N*-hydroxybutanamide derivatives with fewer steps and without expensive additives.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/org4020015/s1. The compounds and spectrum view Figures S1–S104.

Author Contributions: Conceptualization, S.Y.G.; methodology, S.Y.G.; validation S.Y.G. and B.A.T.; formal analysis, B.A.T. and S.Y.G.; investigation, B.A.T. and S.Y.G.; resources, S.Y.G. and A.A.T.; data curation, S.Y.G. and B.A.T.; writing—original draft preparation, S.Y.G.; writing—review and editing, S.Y.G. and A.A.T.; visualization, S.Y.G. and A.A.T.; supervision, A.A.T.; project administration, A.A.T.; funding acquisition, A.A.T. All authors have read and agreed to the published version of the manuscript.

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Data Availability Statement: The authors confirm that the data supporting the findings of this study are available within the article and its Supplementary Materials.

Conflicts of Interest: The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

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