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Synthesis of *N*-substituted-3,4,5,6-tetrachlorophthalimide using trichloroacetimidate C-C bond formation method

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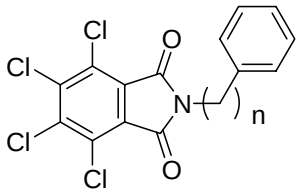
Dedicated to Professor Fakher El-Shahed, Faculty of Science, Suez Canal University.

Abstract:
A series of *N*-substituted-3,4,5,6-tetrachlorophthalimides were prepared by a novel sequential reaction of trichloroacetimidate **3** with C-nucleophiles in the presence of TMSOTf. The nucleophiles include arenes, alkenes and active methylene to give the imidomethylation product of 3,4,5,6-tetrachlorophthalimide **5**, **7**, **9** and **11**, respectively.

Keywords: Tetrachlorophthalimid**e**, novel α-glucosidase inhibitors, trichloroacetimidate, C-C bond formation, C-nucleophiles.

Introduction

α-Glucosidase catalyzes the final step in the digestive process of carbohydrates and the biosynthesis of the *N*-linked oligosaccharides on the envelope glycoprotein.[1,2]
Considerable attention was directed to the design and synthesis of α-glucosidase inhibitors. These compounds retard the uptake of dietary carbohydrates.[3] and were used as potent antiviral agents.[4]
N-Phenyl-3,4,5,6-tetrachlorophthalimide (**I**) and *N*-(4-phenylbutyl)-3,4,5,6-tetrachlorophthalimide (**II**) showed very potent α-Glucosidase inhibitory activity, being more potent than 1-deoxynojirimycin.[5-7]



I, n= 0

II, n= 4

potent α-glucosidase inhibitors

Tetrachlorophthalimid**e** system is a valuable amine-protecting group that can be cleaved under neutral or mild conditions.[8]

The use of trichloroacetimidates method is well recognized.[9-10] Trichloroacetimidates method have been widely used to activate the anomeric oxygen exchange reactions with the consequent glycosidec bond formation; useful in the glycoside synthesis area.[11,12] Ibrahim A. I. Ali*, et al,*[13] reported the reaction of *O*-phthalimidomethyl trichloroacetimidate with *C*-nucleophiles to afford *N*-substituted phthalimides. We have extended the scope of this process enabling the efficient and selective carbon-carbon bond formation *via N*-substituted alcohol conversion into *N*-substituted alkanes.

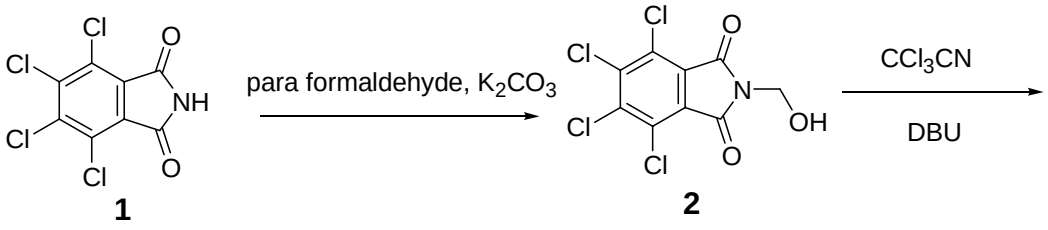
This research offers the development of a series of *N*-substituted-3,4,5,6-tetrachloro-phthalimide *via* C-C bond formation using trichloroacetimidate method as potent α-glucosidase inhibitors and anti-viral agents

Results and Discussion:

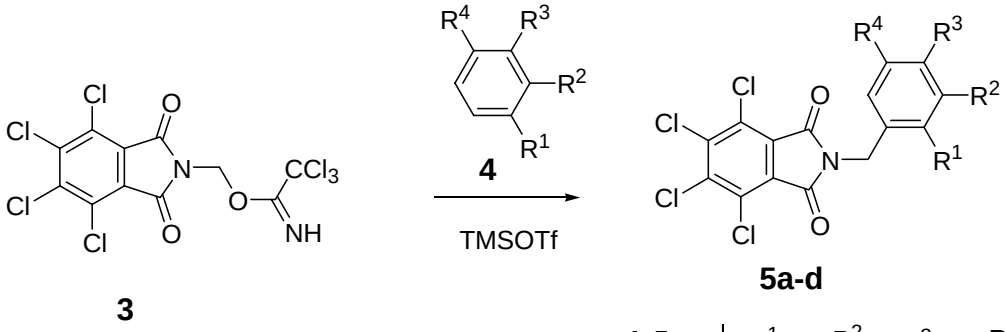
The base catalyzed addition reaction of trichloroacetonitrile to *N*-hydroxymethyl-3,4,5,6-tetrachlorophthalimide hydroxyl group afforded the trichloroacetimidate **3** in 91 % yield. The reaction of **3** with C-nucleophiles in the presence of catalytic amount of TMSOTf at room temperature gave readily the imidomethylation product in high yield. Thus, trichloroacetimidate **3** was reacted with a series of substituted benzenes derivatives **4a-d** in the presence of TMSOTf to give 2-substituted benzyl-3,4,5,6-tetrachloro-phthalimides **5a-d,** respectively in good to moderate yield, scheme1.

Trichloroacetimidate proved to be a versatile intermediate for the efficient and selective synthesis of valuable compounds; 2-substituted benzyl-3,4,5,6-tetrachloro-phthalimides **5a-d** as α-glucosidase inhibitors relative to template **I** and **II** whose chemical modification include aryl substitutions.[5-7]

The structure assignment of the 2-substituted benzyl-3,4,5,6-tetrachlorophthalimides **5a-d** is based on ^{1}H and ^{13}C NMR spectral and physicochemical analysis. The ^{1}H NMR spectra clearly confirm the selective aromatic electrophilic substitution site. Thus, the ^{1}H NMR spectrum of **5b** gave a doublet and a multiplet signals at δ 7.19 and 6.41–6.37 ppm associated with the three aromatic protons. ^{1}H NMR spectrum also reveals a singlet signal at δ 4.80 ppm typicallty associated with NCH_2, which confirms the generated C–C linkage. The ^{13}C NMR spectrum of **5b** displays signals at δ 55.8, 55.75 and 37.8 ppm associated with $2OCH_3$ and NCH_2, respectively.

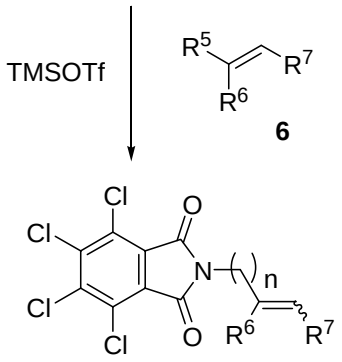


1 **2**



3 **4** **5a-d**

4, 5a-e	R^1	R^2	R^3	R^4
a	H	H	H	H
b	OMe	H	OMe	H
c	OMe	OMe	OMe	H
d	OMe	OMe	OMe	Me



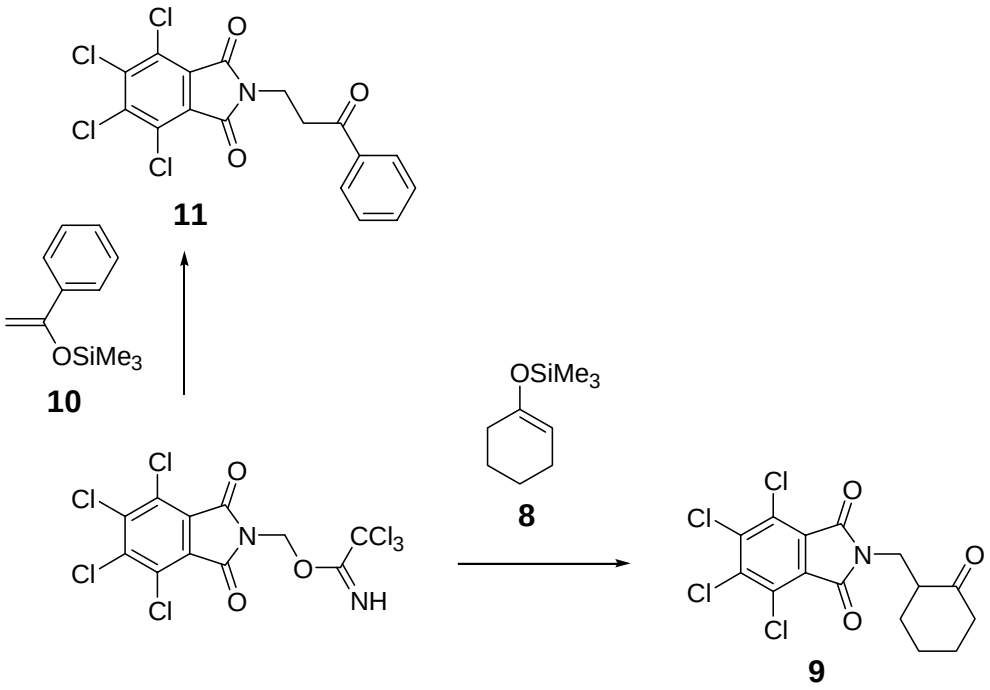
6 **7a-c**

6, 7a-c	n	R^5	R^6	R^7
a	1	H	H	C_6H_5
b	2	Me_3SiCH_2	H	H

Scheme 1

Similarly trichloroacetimidate **3** reacted with alkenes; styrene **6a** and allyl-trimethyl-silane **6b** to afford *N*-substituted phenyl allyl and *N*-substituted butene derivatives, **7a** and **7b**, respectively, Scheme 1. The ^{1}H NMR spectrum of the 2-(3-phenyl-allyl)-3,4,5,6-tetrachlorophthalimide (**7a**) exhibits a doublet, multiplet and doublet signals at δ 6.67, 6.27–6.14 and 4.43 ppm corresponding to 2CH and NCH_2 groups, respectively. The ^{13}C NMR showed signals at δ 163.1, 135.0, 128.5, and 40.4 corresponding to (C=O), 2(CH) and (NCH_2), respectively.

N-Substituted ketones **9** and **11** could be readily achieved by the reaction of C-nucleophiles; 1-trimethylsiloxy-cyclohexene **8** or 1-phenyl-1-trimethylsiloxy-ethylene **10**, with trichloroacetimidate **3** in the presence of TMSOTf, respectively, Scheme 2**.**



Scheme 2

The structures of ketone **11** was established through ^{1}H NMR spectrum which reveal the presence of NCH_2 generated from the C–C linkage as a triplet at 4.11 ppm. On the other hand, the ^{1}H NMR of cyclohexanone **9** gave two doublet of doublets signals at δ 4.11 and 3.74 attributed to NCH_2.

Conclusion:

A general method has been developed for formation of *N*-substituted-3,4,5,6-tetrachlorophthalimides by a novel sequential reaction of trichloroacetimidate **3** with C-nucleophiles. The prepared compounds might act as novel α-glucosidase inhibitors.

Experimental Section

General procedures.
Solvent were purified and dried in the usual way. The boiling range of the petroleum ether used was 40-60 ^{o}C. Analysis of the reaction mixtures and purity control of the products were carried out by TLC on Silufole UV-254. Elemental analyses were performed on a *Flash EA-1112* instrument at the Microanalytical laboratory, Faculty of

Science, Suez Canal University, Ismailia, Egypt. Melting points were determined on a Buchi 510 melting-point apparatus. ^{1}H NMR spectra were recorded at 250 MHz (Bruker AC 250) in $CDCl_3$ solution with tetramethylsilane as an internal standard. The starting compounds **1** and **2** was prepared according to described methods.[14-15]

General procedure for the preparation of 3,4,5,6-tetrachloro-*O*-phthalimido-methyl trichloroacetimidate (3).

A stirred solution of *N*-hydroxymethyl-3,4,5,6-tetrachlorophthalimide (**2)** (1.58 g, 5 mmol) in dry dichloromethane (30 mL) and trichloroacetonitrile (1.5 mL, 10 mmol) was treated with DBU (71 μL) at room temperature and then left for 2 h. The solvent was evaporated under reduced pressure and the product was purified by column chromatography 5 % triethylamine in toluene/ethylacetate, 25:1 to give 3 as white

General procedure for the reaction of 3,4,5,6-tetrachloro-*O*-phthalimidomethyl trichloroacetimidate with C-nucleophiles

A stirred solution of **3** (0.64 g, 1.4 mmol) and *C*-nucleophiles as acceptor (1.4 mmol) in dry dichloromethane (40 mL) under nitrogen was treated with TMSOTf (0.06 mmol) at room temperature. After completion of the reaction (TLC monitored), the mixture was neutralized with solid sodium bicarbonate, filtered and concentrated in vacuo. The residue was purified by flash chromatography.

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