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Communication

Covalently Linked Plasticizers: Triazole Analogues of Phthalate Plasticizers Prepared by mild Copper-free "Click" Reactions with Azide-functionalized PVC [1]

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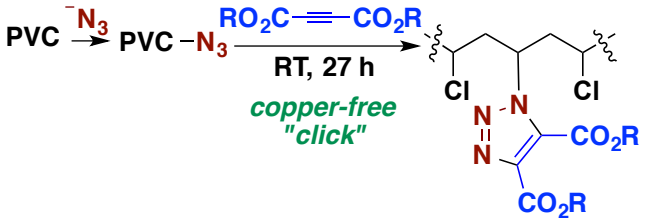


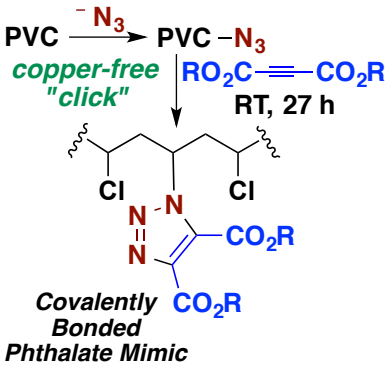
Covalently Bonded Phthalate Mimic

Copper-free azide-alkyne click chemistry is utilized to covalently modify polyvinyl chloride (PVC). Phthalate plasticizer mimics di(2-ethylhexyl)-1H-triazole-4,5 dicarboxylate (DEHT), di(n-butyl)-1H-1,2,3-triazole-4,5-dicarboxylate (DBT), and di(methyl)-1H-triazole-4,5-dicarboxylate (DMT) are covalently attached to PVC. DEHT, DBT, and DMT have similar chemical structures to traditional plasticizers di(2-ethylhexyl) phthalate (DEHP), di(n-butyl) phthalate (DBP), and dimethyl phthalate (DMP), but pose no danger of leaching from the polymer matrix and forming small endocrine disrupting chemicals. The synthesis of these

[1] **Supporting Information** is available online from the Wiley Online Library or from the author.

covalent plasticizers is expected to be scalable, providing a viable alternative to the use of phthalates, thus mitigating dangers to human health and the environment.

FIGURE FOR ToC_ABSTRACT



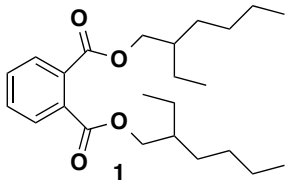
1. Introduction

Polyvinyl chloride (PVC) is one of the most widely utilized plastics. It is found in a wide range of consumer products such as packaging, cling films, bottles, credit cards, CDs and DVDs, and imitation leathers as well as in construction materials such as window frames, cables, pipes, flooring, wallpaper and window blinds. PVC is also used in blood storage bags as well as in many other medical devices. Pure PVC is brittle; in order to obtain the desired durability and flexibility, and to allow for extrusion molding of consumer products, PVC is mixed with large amounts of plasticizers.[1,2] The most common plasticizers are low molecular weight esters of phthalic acid such as di(2-ethylhexyl) phthalate (DEHP) **1** (also known as dioctyl phthalate, DOP), di(*iso*decyl) phthalate (DIDP), di(*iso*nonyl) phthalate (DINP), di(*n*-butyl) phthalate (DBP) **2**, and di(methyl) phthalate (DMP) **3**, as well as esters of adipic acid such as di(2-ethylhexyl) adipate (DEHA).[3] These low molecular weight plasticizers have a tendency to migrate to the surface of the PVC matrix when it comes into contact with air, liquid, and some absorbent solid materials.[3-7] The loss of plasticizer causes changes in the physical properties of PVC, contributing to loss of flexibility with aging and contamination of the environment.[8,9] Leaching of DEHP out of blood bags and food packaging is a major route into the human body. Many of these plasticizers are suspected to be carcinogens. The metabolic products of DEHP and other phthalates are believed to behave as endocrine disruptors,[10] particularly in young males. DEHP is under strong scrutiny because of its reprotoxic properties in rats.[10] It is commonly accepted that exposure to high levels of DEHP should be avoided by newborns, trauma patients, and pregnant women. Recently, mono(2-ethyl-hexyl) phthalate (MEHP), the main active metabolite of DEHP, has been demonstrated to increase the production of reactive oxygen

species (ROS), resulting in oxidative damage, apoptosis, and differential expression of redox-sensitive genes.[11] The lipophilicity of DEHP enables it to enter the body in many different ways, passing through the skin and pulmonary tissues in addition to oral and intravenous routes of exposure.[12,13] However, blood bags made of PVC with DEHP enhance the survival rate of red blood cells used in transfusion.[14,15]

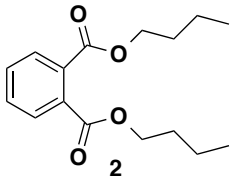
Multiple alternatives to phthalate plasticizers have been investigated, including the use of adipates, succinates, glutarates, terphthalates, trimelliates, sebaccates, and citrates.[16] Plasticizer migration can also be suppressed by blending PVC with polymeric plasticizers such as poly(caprolactone) and poly(butyleneadipate).[17-19] Although many of these plasticizers have less tendency to migrate compared to DEHP, they reduce the chain mobility and flexibility of the PVC. Another approach to minimizing plasticizer migration from PVC is to chemically crosslink PVC with diamines. For example, use of isophoron diamine (IPDA)[20] as a PVC crosslinking agent resulted in reduced DEHP migration, but thermal degradation of the PVC was enhanced. Recently, our group has investigated polymerized 4-vinyl-phthalates as an alternative to traditional phthalate plasticizers. These polymeric phthalates in PVC blends are expected to minimize plasticizer migration and are unlikely to be metabolized into endocrine disrupting chemicals.[21] However a significant drawback to this approach is the multistep synthesis required to prepare the vinyl phthalate monomers. New generation plasticizers di(2-ethylhexyl) terphthalate (DEHTP) **6** and di(isononyl) 1,2-cyclohexanedicarboxylic acid (DINCH) **5** (**Figure 1**) show lower migration rates than DEHP,[14] yet are still able to leach out to contaminate the human population, and the environment.

[Insert Figure 1 near here]



1

DEHP: Di(2-ethylhexyl) phthalate



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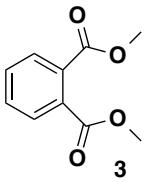
DBP: Di(*n*-butyl) phthalate



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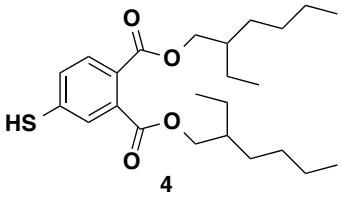
DMP: Dimethyl phthalate



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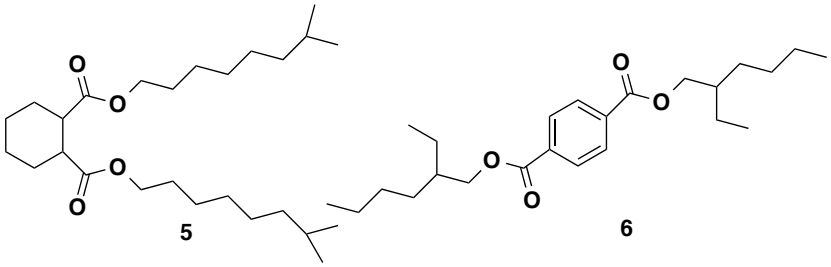
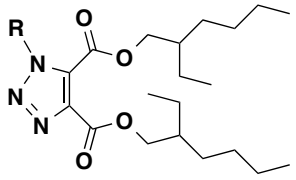
DEHP-SH: Di(2-ethylhexyl)-4-mercaptophthalate



5 6

DINCH: Di(isononyl)-1,2-cyclohexane dicarboxylate

DEHTP: Di(2-ethylhexyl) terphthalate



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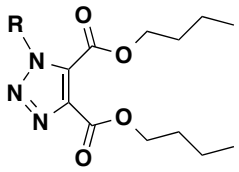
DEHT: Di(2-ethylhexyl)-1H-triazole-4,5-dicarboxylate



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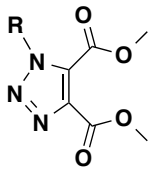
DBT: Di(*n*-butyl)-1H-triazole-4,5-dicarboxylate



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DMT: Dimethyl-1H-triazole-4,5-dicarboxylate

R = PVC Chain

The most effective approach to avoid migration of plasticizer from the PVC matrix is to covalently attach the plasticizer to the polymer. The covalent modification of PVC by displacing chlorine with the thiol derivatized plasticizer di(2-ethylhexyl) 4-mercaptophthalate (DOP-SH) **4**, and di(2-ethylhexyl) 5-mercapto isophthalate (*iso*DOP-SH) was recently demonstrated by Reinecke et al.[22] The resulting materials showed good plasticization and zero migration, however the viability of using this elegant approach is restricted by the cost of preparing the thiol phthalate esters. Historically, PVC has been modified by simple nucleophilic substitution of the chlorine atoms; the most common nucleophiles have been azide, thiolates, thiocyanate, hydroxide, iodide, and phthalimides.[23-29] There are a number of reports of PVC being converted into PVC-N_3 in which some of the chlorides have been replaced by azide groups.[26-27,29-31] The degree of substitution depends on the polarity of the solvent, temperature, and the duration of the

reaction. Up to 66% displacement of chlorine atoms by azide groups can be achieved in DMF at 100° C.[29]

The Huigsen 1,3-dipolar cycloaddition, colloquially known as a "click" reaction, has become a powerful tool for the transformation of azide groups into triazoles.[32-34] Triazoles are flat aromatic rings, similar in size and shape to benzene rings. Treatment of alkyl azides with acetylenedicarboxylate esters result in the formation of 1,2,3-triazoles bearing esters at the 4 and 5 positions. Bakker et al. deployed the popular azide/alkyne copper catalyzed "click" reaction to append a ferrocene group pendant to a PVC membrane as an electron transducer to formulate an electrochemical ion sensor.[35] Recently, Bakker's group has also demonstrated functionalization of plasticized PVC membranes bearing partial azide substitution to attach fluorophores to the surface.[35] Kébir et al. have attached cationic copolymers to PVC bearing partially azidized surfaces by copper catalyzed click reaction to impart bactericidal properties.[36] To install a phthalate plasticizer analogue, Huisgen cycloaddition of PVC-N_3 with di(2-ethylhexyl) acetylenedicarboxylate would form compound **7,** in which R is the PVC chain. This triazole is expected to mimic phthalate ester **1**. Alkynes bearing ester groups on both termini are extremely electrophilic, thus enhancing the thermal 1,3-dipolar cycloaddition reaction by lowering the LUMO of the alkyne. Huisgen thermal cycloadditions with very electron-poor alkynes proceed near or at room temperature in the absence of a metal catalyst, providing materials free of metal (particularly copper) contamination. There are a few reports of such copper-free Huisgen cycloadditions with electron poor alkynes under thermal conditions.[37-43] Thus triazoles formed from acetylenedicarboxylate esters should be easily prepared from PVC-N_3; these phthalate mimics will be covalently linked to the PVC chains. Herein is a preliminary investigation into the synthesis of these covalently-bound phthalate mimics.

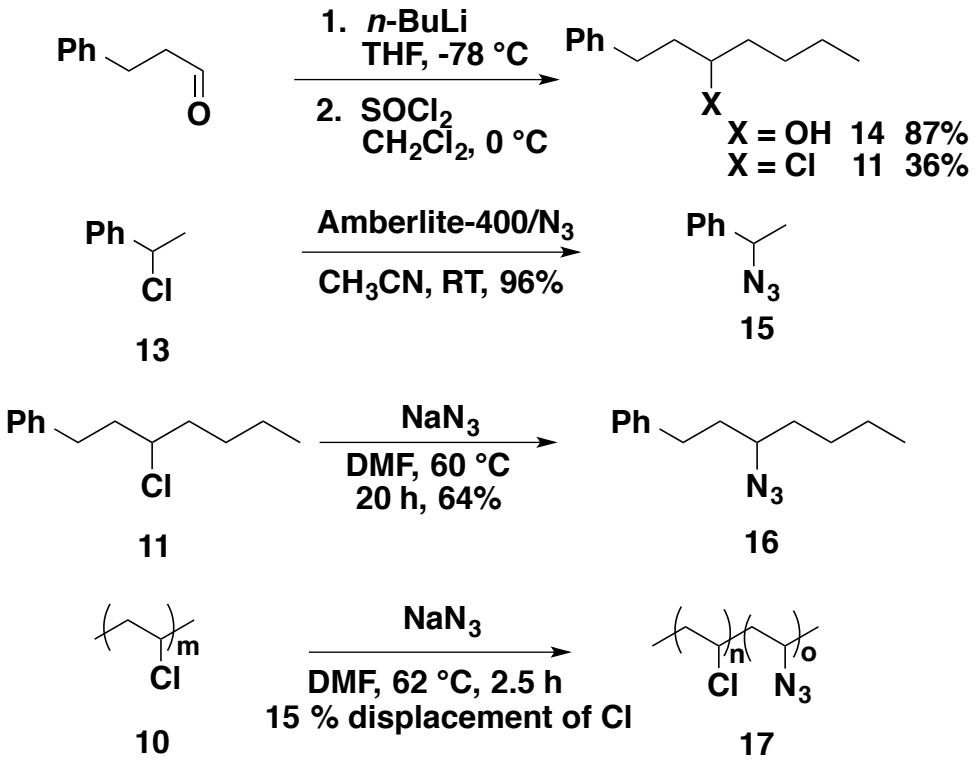
2. Results and Discussion

Synthetic modification of polymers results in polydisperse products, which are not amenable to facile characterization by ^{1}H and ^{13}C NMR or mass spectrometry. Thus two small molecule models were investigated to confirm the viability of the key Huisgen cycloaddition with dialkyl acetylene dicarboxylates using well-defined secondary alkyl azides.

2.1. Small Molecule Models

Azide substitution on PVC can take place either by the S_N2 mechanism at secondary alkyl chlorides or by the S_N2' mechanism at secondary allylic chlorides, generated by thermal, photo, or chemical dehydrochlorination of PVC.[29,44-47] Two low molecular weight compounds: 3(chloroheptyl)benzene **11** and (1-chloroethyl) benzene **13** were selected as small molecule models for secondary alkyl and secondary allylic chlorides of PVC (**Scheme 1**). The benzylic substrate **13** was obtained commercially whereas the secondary alkyl substrate **11** was synthesized by converting hydrocinnamaldehyde into 1-phenylhept-3-ol **14** by addition of *n*-BuLi, and subsequently transforming the alcohol into chloride **11** using thionyl chloride.

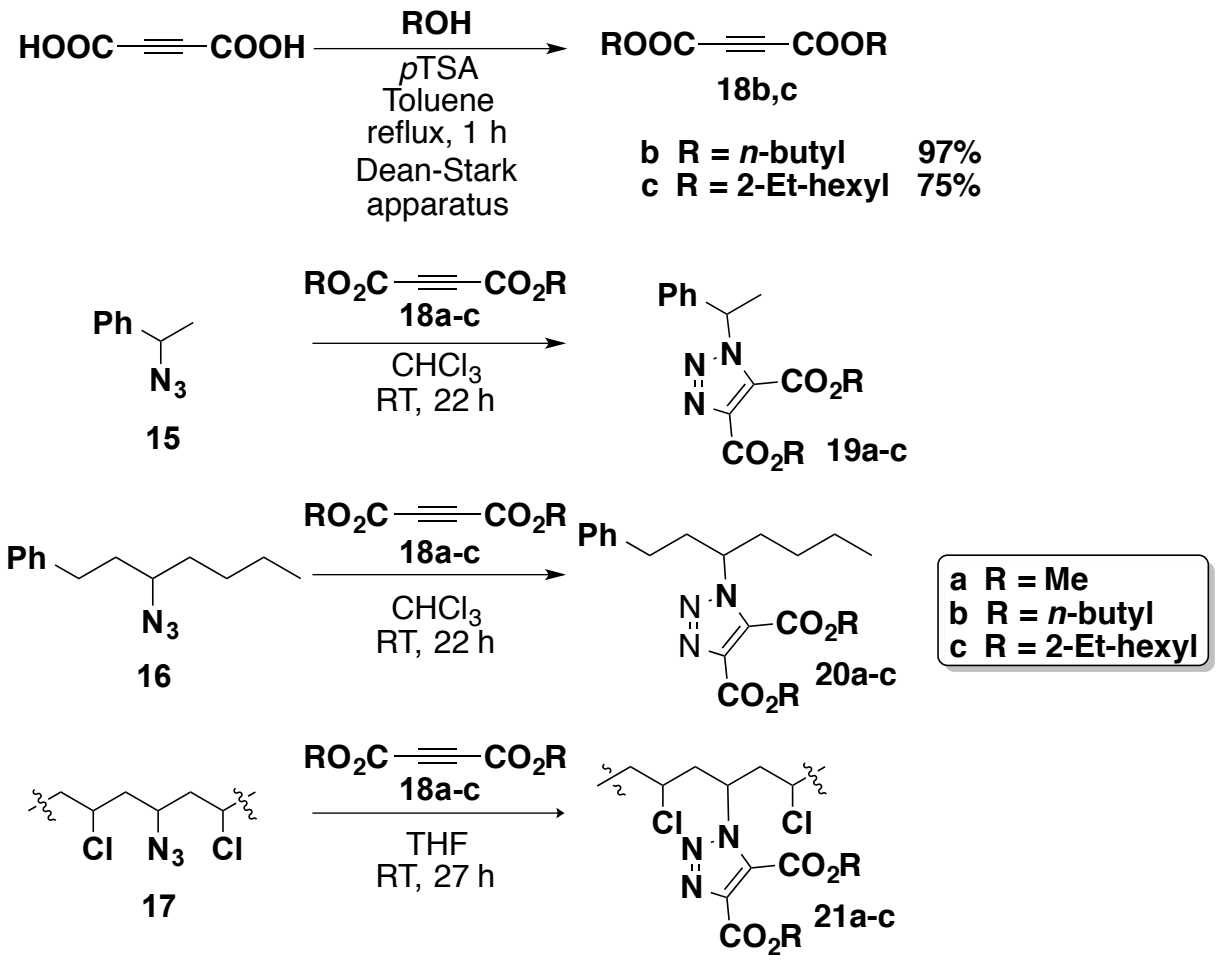
[Insert Scheme 1 here]



The benyzlic chloride **13** underwent straight-forward azidation using Amberlite 400/N_3 resin[47] (**Scheme 1**). The azidation of (3-chloroheptyl) benzene **11** was carried out in dimethylformamide with NaN_3 at 60° C to yield secondary alkyl azide **16**. The distinctive peak at 2100-2000 cm^{-1} in the FTIR spectra of **15** and **16** is characteristic of the azide functional group**.** The initial thermal Huisgen cycloaddition of benzylic azide **15,** following the general procedure of Brimble et al.[32] used 50 equivalents of commercially available dimethyl acetylenedicarboxylate (DMAD) **18a** at 100° C for 40 minutes to form **19a** (**Table 1 in supporting information**). This reaction was repeated with fewer equivalents of DMAD and at lower temperatures. The reaction went to completion in 40 minutes at 50° C using only 1.5 equivalents of DMAD. Under ambient temperature, the reaction was complete within 22 hours with 1.5 equivalents of DMAD, both as a neat reaction, as well as in deuterochloroform solution as an NMR tube experiment. Subsequent cycloaddition reactions on model substrates **15** and **16** were carried out in chloroform at 0.3 M

for 22 hours. Di(*n*-butyl) acetylenedicarboxylate (DBD) **18b** and di(2-ethyl-hexyl) acetylenedicarboxylate (DEHAD) **18c** were prepared by Fischer esterification of the diacid, as shown in **Scheme 2**.

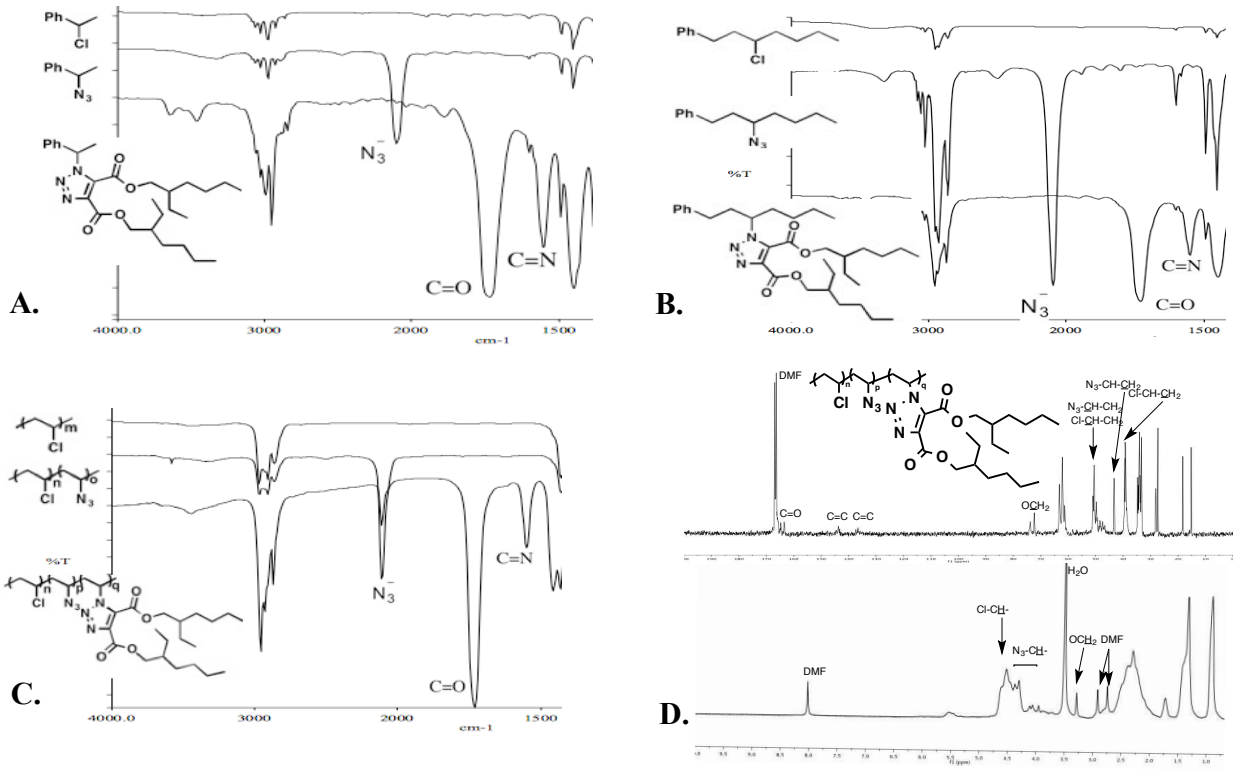
[Insert Scheme 2 here]



Treatment of small model alkyl azides **15** and **16** with 1.5 equivalents of acetylene-dicarboxylates **(18a-c)** at room temperature resulted in 1,3-dipolar cycloaddition to give derivatives **19a-c**, and **20a-c** (**Scheme 2**). Triazoles **19a-c** and **20a-c** were fully characterized by ^{1}H NMR, ^{13}C NMR, IR, and high resolution mass spectrometry (HRMS). The disappearance of

the azide peak at 2100-2000 cm^{-1} accompanied by the appearance of peaks at 1725-1635 cm^{-1} attributed to carbonyl (C=O), and 1550-1500 cm^{-1} attributed to the triazole (C=N) in the FTIR spectra of **19a-c** and **20a-c** provide a convenient method to monitor the formation of the triazoles (**Figure 2**, **spectra A and B**).

[Insert Figure 2 near here]



2.1. Modification of PVC

Following the procedure of Rusen et al,[31] PVC **10** was partially converted into PVC-N_3 **17** with the use of NaN_3 in dimethylformamide at 62° C (**Scheme 1**). The degree of azidation was determined by elemental analysis (38.17% C, 4.70% H, 9.81% N), indicating 14.7% displacement of Cl by N_3. In the ^{1}H NMR spectrum of PVC-N_3, the N_3-C**H**-CH_2 methine is observed as a collection of peaks between δ 3.85-4.22 ppm, the Cl-C**H**-CH_2- methine protons

are observed as a family of peaks between δ 4.31-4.39 ppm, and the N_3-CH-C**H**$_2$- and Cl-CH-C**H**$_2$- methylene protons are found at δ 2.11-2.50 ppm. From the ^{13}C NMR spectrum, N_3-**C**H-CH_2- and Cl-**C**H-CH_2- methine carbons are observed as a family of peaks between δ 53.8-55.9 ppm, N_3-CH-**C**H_2- methylene carbons appear as a family of peaks between δ 42.5–43.2 ppm, and the Cl-CH-**C**H_2- methylene carbons are found between δ 39.1-39.9 ppm. The characteristic peak of azide functional group at 2112 cm^{-1} in the FTIR spectrum confirmed the partial azidation of PVC (**Figure 2C**). PVC-N_3 was then subjected to the key Huisgen thermal cycloaddition at room temperature for 22 h to form triazoles PVC-DMT **21a**, PVC-DBT **21b**, and PVC-DEHT **21c** by copper-free "click" reaction using 1.5 equivalents of DMAD **18a**, DBD **18b**, and DEHAD **18c** (**Scheme 2**). This cycloaddition reaction was carried out in THF rather than $CHCl_3$ due to the lack of solubility of PVC in $CHCl_3$. The conversion of azide to triazole diester groups pendant to the PVC is conveniently monitored by FTIR spectroscopy (**Figure 2C**): specifically the shrinking of the diagnostic azide band at 2100-2000 cm^{-1}, with concomitant appearance of the ester C=O band at 1725-1635 cm^{-1}, and C=N band at 1550-1500 cm^{-1}. It is noteworthy that FTIR indicates that a small amount of azide remains in the PVC substrate, whereas the small alkyl azides were converted entirely to triazole under the same conditions, presumably due to steric inaccessibility of some azide groups in the polymeric substrate. Subjecting the "click" reaction of PVC-N_3 to sonication did not improve the conversion. Elemental analysis for PVC-DEHT **21c** (49.08% C, 6.62% H, 6.54% N) further supports the transformation of the azide groups to triazole phthalate mimics. ^{1}H NMR in DMF-d_7 shows a characteristic peak at δ 3.29 for the methylene –OC**H**$_2$-CH doublets of the esters, and ^{13}C NMR (and DEPT) peaks at δ 156.1 and 157.3 for **C=O**, δ 131.8 and 136.2 for aromatic **C=C**, and δ 64.8 and 66.4 ppm for the –O**C**H_2-CH methylene carbons provide further evidence for the formation of PVC-DEHT (**Figure**

2D). Thus, the attachment to PVC of an aromatic triazole bearing *ortho* ester substituents occurs under extremely mild conditions. Whether these triazoles function effectively as phthalate-like plasticizers is now under investigation.

3. Conclusion and Future Directions

PVC has been modified to carry pendant triazoles bearing *ortho* ester groups, as a covalently bonded mimic of phthalate plasticizers**.** Three different triazoles: PVC-DEHT, PVC-DBT, and PVC-DMT have been prepared using a copper-free "click" reaction, as analogues of traditional phthalate ester plasticizers DEHP, DBP, and DMP. As the triazole diesters are covalently bound to the PVC chain, no migration of these plasticizer mimics is expected. The hydrolysis of these modified PVC materials are expected to be alcohols, avoiding the release of small compounds that can mimic endocrine signaling molecules. These PVC-triazoles mimics are easily synthesized, and the degree of azidation of PVC can be varied to optimize material properties. The photo- and biodegradation products of these triazole diesters are of importance; these experiments are a current focus. The testing of the physical properties of these plasticizer mimics is now underway. It is hoped that this approach may contribute to solving the worldwide problem of phthalate ester contamination in an affordable manner and on a commercially viable scale.

Supporting Information

Table 1, experimental details, ^{1}H NMR, ^{13}C NMR, DEPT and FTIR spectra of small molecules **11, 14-16, 18a,b**, **19a-c,** and **20a-c,** and PVC-derivatives **17** and **21a-c**. Supporting Information is available from the Wiley Online Library or from the author.

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***Scheme 1*:** Synthesis of secondary alkyl chloride **11**; azidation of small molecule models **13** and **11**, and partial azidation of PVC **10**

***Scheme 2*:** Fischer esterification to form dialkyl acetylenedicarboxylates **18b,c;** thermal "click" reactions to prepare triazoles **19a-c** and **20a-c,** and triazoles attached to PVC **21a-c**

***Figure 1*:** Chemical structures of common phthalate plasticizers 1-3, several current substitutes 4-6, and new triazole mimics 7-9

Figure 2: FTIR spectra of A: 1-chloroethyl benzene **13**, 1-azidoethyl benzene **15**, and bis(2-ethylhexyl)-1-(1-phenylethyl)-1H-1,2,3-triazole-4,5-dicarboxylate **19c**; B: (3-chloroheptyl) benzene **11**, (3- azidoheptyl) benzene **16**, and bis(2-ethylhexyl)-1-(1-phenyl-heptan-3-yl)-1*H*-1,2,3-triazole-4,5-dicarboxylate **20c**; C: PVC, PVC-N_3 **17**, and PVC-DEHT **21c;** D**:** ^{1}H NMR and ^{13}C NMR of PVC-DEHT **21c** in DMF-d_7

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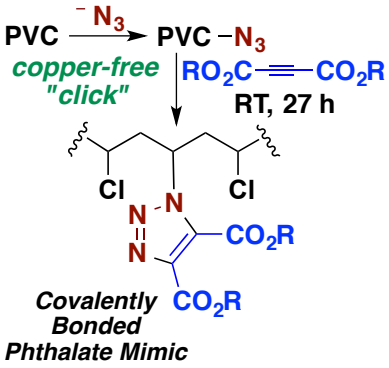
Covalently attached mimics of conventional phthalate plastacizers are synthesized on modified PVC by simple and scalable chemistry. Substitution of some of the chloride by azide, followed by thermal Huisgen cycloaddition with dialkyl acetylenedicarboxylates forms pendant triazoles bearing *ortho* esters resembling phthalate diesters. This copper-free cyclization is demonstrated at room temperature: first on small molecule models, then on PVC.

Aruna Earla and Rebecca Braslau*

Covalently Linked Plasticizers: Triazole Analogues of Phthalate Plasticizers Prepared by mild Copper-free "Click" Reactions with Azide-functionalized PVC



Supporting Information

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