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High-Load, Soluble Oligomeric Carbodiimide: Synthesis and Application in Coupling Reactions

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A facile preparation of a high-load, soluble oligomeric alkyl cyclohexylcarbodiimide (OACC) reagent via ROM polymerization from commercially available starting materials is described. This reagent is exploited as a coupling reagent for esterification, amidation, and dehydration of carboxylic acids (aliphatic and aromatic) with an assortment of alcohols (aliphatic primary, secondary, and benzylic), thiols, phenols, and amines (aliphatic primary, secondary, benzylic, and aromatic/anilines), respectively. Following the coupling event, precipitation with an appropriate solvent (Et_2O, MeOH, or EtOAc), followed by filtration through a SPE provides the products in good to excellent yield and purity.

Introduction

Over the past decade, the growth in combinatorial chemistry has facilitated the rapid production of compounds for high-throughput screening and led to intense efforts aimed at the development of improved synthetic protocols, whereby the science of synthesis and purification are integrated. In this context, an array of polymer-bound scavengers and reagents have appeared, effectively eliminating or circumventing the need for chromatographic purifications.[1,2] Despite huge advances in this area, the need for improvements in resin-load capacity, reaction rates, means of dispensing reagents, and means of producing designer resins continues to warrant the development of new and improved immobilized reagents.

One means of achieving solution-phase reaction rates, while retaining the advantages of the solid phase, is through the use of soluble polymers[3] with differential solubility profiles. In this context, ring-opening metathesis polymerization (ROMP)[4] has surfaced as a means of generating designer polymers with tunable properties and increased load levels. Our interest in the development of facilitated synthetic protocols now leads us to report the synthesis and utility of a high-load, soluble oligomeric alkyl cyclohexylcarbodiimide (OACC) reagent prepared using ROM polymerization.

Carbodiimides rank as one of the most important classes of reagents in organic synthesis due to their accessibility, versatile chemical properties, and utility in coupling reactions.[5] The most widely used carbodiimide is dicyclohexylcarbodiimide (DCC), which serves as a versatile coupling agent in the preparation of amides,[6] esters,[7] and anhydrides.[8] Although very powerful, complete removal of the dicyclohexylurea (DCU) byproduct usually necessitates additional cumbersome purifications. This limitation has prompted the development of an

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10.1021/jo048870c CCC: $27.50

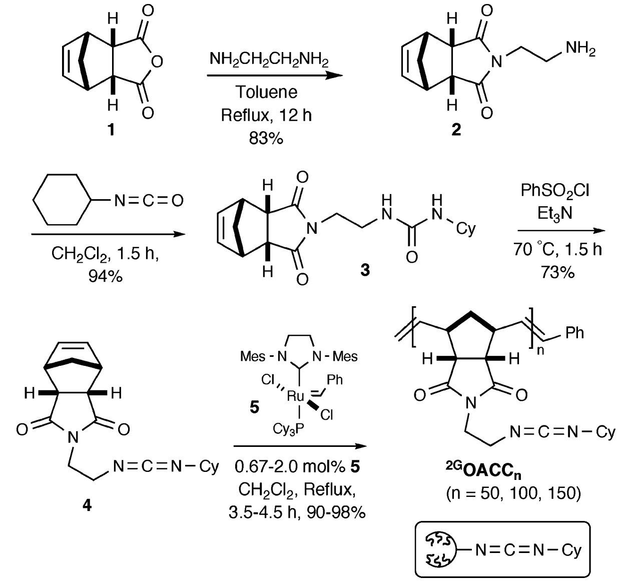
array of surrogate DCC coupling reagents including water-soluble carbodiimide derivatives such as 1-cyclohexyl-3-(2-morpholinoethyl)carbodiimide metho-*p*-toluenesulfonate[9] and 1-ethyl-3-(3′-dimethylaminopropyl)carbodiimide hydrochloride (EDCI).[10] In addition, polymer-bound carbodiimides such as polystyrene isopropylcarbodiimide,[11] polystyrene-*N*-benzyl-*N*′-cyclohexylcarbodiimide,[12] polystyrene-carbodiimide resin,[13] and polymer-tethered 1-ethyl-3-(3- dimethylaminopropyl)carbodiimide (PS-EDC)[14] have been developed as viable replacements for DCC. Typically, these systems have load values of 1.0−1.5 mmol/g. Recently, Barrett and co-workers have reported a ROMP sphere-supported formamidinium reagent and a ROMPgel-supported pyridinium reagent as replacements for DCC in amide or peptide bond-forming reactions.[4a]

Previously, we have developed two high-load, soluble scavenging agents, oligomeric sulfonyl chloride (OSC)[15] and oligomeric bis-acid chloride (OBAC),[16] and high-load soluble oligomeric sulfonate ester reagents which effectively serve as benzylating agents.[17] We now report a high-load, soluble oligomeric reagent (^{2G}OACC$_n$)[18] that serves as a viable alternative to DCC. This reagent offers flexible oligomer design and has favorable reaction kinetics. Furthermore, the soluble aspects of this reagent enable convenient dispensing that ultimately provides an enormous advantage in parallel array synthetic protocols where automated liquid handling systems can be employed.

Results and Discussion

As shown in Scheme 1, the requisite monomer, *N*-cyclohexyl-*N*′-(2-succinimidoethyl)carbodiimide (**4**), is produced in a three-step sequence starting with *cis*-5-norbornene-*endo*-2,3-dicarboxylic anhydride (**1**). Anhydride **1** is commercially available and can also be easily prepared by a Diels−Alder reaction on large scale.[19] Refluxing **1** with 4 equiv of 1,2-diaminoethane in toluene overnight gave mono-*endo*-amine **2** in high yield (83%),[20] which was treated with cyclohexyl isocyanate to produce norbornenyl-tagged urea **3** in high yield. Dehydration[21] of urea **3** with phenylsulfonyl chloride using 5 equiv of Et_3N at 70 °C afforded monomer **4** in moderate to good yield (65−73%). Subsequent ROM polymerization with $(IMesH_2)(PCy_3)(Cl)_2Ru{=}CHPh$ (Grubbs' second-generation catalyst **5**)[22] yielded ^{2G}OACC$_n$ of differing lengths (n) depending upon the mol % of the catalyst used.[23] Quenching of ROM polymerization with ethyl vinyl ether, followed by precipitation with ether, provided reagent OACC in excellent yield as free-flowing solids.

SCHEME 1



The OACC agent has been characterized by EA, IR, ^{1}H and ^{13}C NMR spectra, and wet chemical methods. The ^{2G}OACC$_{50}$ shows a theoretical load of 3.2 mmol/g. We next sought to verify this load level and therefore conducted saturation experiments with a simple wet chemical method. Initially, we established that hydrolysis of the carbodiimide group had not taken place as evident by the IR spectrum of the OACC reagent, which showed a strong absorption at 2122 cm^{-1} with the absence of a urea carbonyl (∼1645 cm^{-1}). Reaction of 3 equiv of 2,6-dichlorophenyl acetic acid with 1 equiv of ^{2G}OACC$_{50}$ provided the corresponding homocoupled anhydride along with unreacted acid in a molar ratio of 0.53:1.00 as calculated from analysis of the ^{1}H NMR spectrum[24] correlating to an actual loading of 2.5 mmol/g (77% of its theoretical loading).[25]

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[18] ^{2G}OACC$_n$ stands for n-mer OACC (n = 50, 100, 150, oligomeric alkyl cyclohexyl carbodiimide) prepared by ROM polymerization of monomer carbodiimide **4** using the secondary generation Grubbs' catalyst **5**.

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[23] We have previously found that there is good correlation between the mol % of Grubbs' catalyst added and the Gaussian distribution of oligomers formed, which we believe is the case with the OACC shown in Scheme 1. We have made this reagent several times (i.e., the preparation and reactivity are repeatable and consistently reliable). We normally obtain MALDI-TOF and/or GPC data on all oligomers formed; however, both methods have failed to give good results for this reactive oligomer.

[24] Integration of the CH_2 resonance in both the anhydride and acid revealed a proton ratio of 1.07:1.00 corresponding to 77% of theoretical load.

[25] An improved procedure for the final dehydration step en route to the ^{2G}OACC$_{100}$ reagent found that treating urea **3** with bromotriphenylphosphonium bromide (Ph_3PBr_2) and Et_3N in CH_2Cl_2 generated monomer **4** in 66% yield. Subsequent ROM polymerization gave 98% of ^{2G}OACC$_{100}$ which had an increased load of 3.13 mmol/g (98% of the theoretical load) using the aforementioned wet chemical method.

SCHEME 2. General Protocol Using $^{2G}OACC_n$

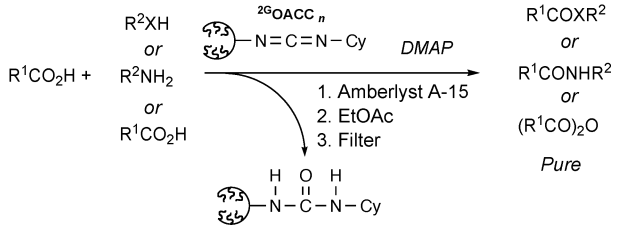

TABLE 1. Application of $^{2G}OACC_{50}$ in Direct Esterification

entry	R^1	R^2XH (ROH/RSH)	pdt	yield[a] (%)	purity[b] (%)
1	Ph	BnOH	**6a**	95	97
2	Ph	$CH_2{=}CH(CH_2)_2OH$	**6b**	91	98
3	$Br(CH_2)_5$	BnOH	**6c**	95	95
4	$Br(CH_2)_5$	$MeS(CH_2)_3OH$	**6d**	94	98
5	$Br(CH_2)_5$	BnCH(OH)Me	**6e**	99	95
6	Ph	*n*-BuSH	**6f**	98	97
7	Ph	$CH_3(CH_2)_{10}SH$	**6g**	95	98
8	$Br(CH_2)_5$	*n*-BuSH	**6h**	81	97
9	$Br(CH_2)_5$	$CH_3(CH_2)_{10}SH$	**6i**	85	96
10	$Br(CH_2)_5$	PhOH	**6j**	97	97
11	$Br(CH_2)_5$	C_6F_5OH	**6k**	98	98

[a] Yield of isolated crude product after silica gel plug. [b] Determined by GC and confirmed by ^1H NMR spectra (no polymer present, see the Supporting Information).

To assess the synthetic utility of $^{2G}OACC_{100}$ versus commercially available resins, a comparative experiment was performed between $^{2G}OACC_{100}$ and commercially available PS-DCC[13] possessing a load of 1.2 mmol/g. We found that under repeat conditions, 0.100 mmol of substrate (2-bromo-5-furoic acid) could be coupled with benzylamine using a slight excess of OACC (50 mg, 0.125 mmol at 2.5 mmol/g) while the PS-DCC required a 2-fold excess (175 mg, 0.21 mmol at 1.2 mmol/g).[26]

Another key feature of the titled reagent is its wide solubility profile. The oligomeric reagents, $^{2G}OACC_n$ (n = 50, 100, 150), are soluble in a panel of solvents including CH_2Cl_2, THF, DMF, and DMSO and insoluble in Et_2O, EtOAc, and MeOH. This wide solubility profile allows reactions to be conducted in CH_2Cl_2 followed by precipitation of the spent oligomer and any excess OACC with Et_2O, MeOH or EtOAc. Thus, the sole purification protocol is limited to a simple precipitation/filtration method providing the products in good to excellent yields and purities.

This reagent has been effectively used for the facile generation of amides, esters, and anhydrides in good to excellent yield as outlined in Scheme 2. Certain coupling reactions required the use of DMAP, which could be easily removed by an aqueous workup or by the use of a scavenger resin (Amberlyst A-15 resin), thus avoiding the use of chromatography, yet retaining the virtues of both solution- and solid-phase chemistry.

Initial investigations focused on the esterification of carboxylic acids (aromatic and aliphatic) with a variety of alcohols, thiols, and phenols (entries 1−11, Table 1) using $^{2G}OACC_{50}$ as a coupling reagent. Facile esterification was accomplished in 2 h using 1.0 equiv of acid and 1.0 equiv of alcohol, thiol, or phenol in the presence of 1.5 equiv of $^{2G}OACC_{50}$ (based on 3.2 mmol/g theoretical load) and 10 mol % of DMAP at room temperature. The resulting mixture was precipitated with ether, and the ether filtrate was washed with water to eliminate DMAP (alternatively Amberlyst A-15 resin can be used, vide infra). Concentration of the ether solution under reduced pressure gave a residue, which upon filtration thru a silica plug, using EtOAc as the eluent, yielded the esters or thioesters **6a**−**k** as slightly colored oils in excellent yields and purities. No polymeric residue was observed by ^1H NMR spectra analysis of the crude, isolated esters. In addition, an ICP-MS (inductively coupled plasma/mass spectrometer) measurement on ester **6a** following the protocol reported by Georg and co-workers[27] was used to determine the ruthenium level that was found to be 1.7 μg (±10%) per 5 mg of sample. This level [0.34 μg (±10%) per mg or 0.0085 mol % ruthenium in benzyl benzoate (**6a**)] is within the acceptable ranges that have been reported for ruthenium removal in RCM processes.[27,28]

Following this success, amidation reactions using $^{2G}OACC_{50}$ as the coupling agent were investigated. In a typical procedure (method A), a solution of $^{2G}OACC_{50}$ in CH_2Cl_2 was added to a concentrated solution of carboxylic acid (1.0 equiv) and amine (1.0 equiv) in CH_2Cl_2 at 0 °C. The reaction is generally complete within 7 h at room temperature, affording the desired amides in excellent yields and purities (Table 2). Again, ICP-MS measurement on amide **7a** determined a ruthenium level that was found to be 1.9 μg (±10%) per 5 mg of sample [0.38 μg (±10%) per mg or 0.0095 mol % ruthenium in benzyl benzoamide (**7a**)].[27,28]

The formation of carboxylic anhydrides using $^{2G}OACC_{50}$ to dehydrate carboxylic acids was next studied. Again, it was observed that the $^{2G}OACC_{50}$ reagent could readily dehydrate acids at 0 °C to generate anhydrides in excellent yields and purities. The results are summarized in Table 3.

To further expand its utility, the $^{2G}OACC_{50}$ reagent was examined in the amidation of 5-bromofuroic acid using an array of amines (method B). Coupling reactions proceeded smoothly with a variety of amines (primary, secondary, benzylic, and anilines) to furnish the corresponding amides as slightly colored solids in excellent yields and purities. To trace the origin of color in the resulting products, couplings were attempted using a longer oligomeric reagent, $^{2G}OACC_n$ (n = 100 and 150), which were generated using a smaller amount of ruthenium catalyst **5** (0.66 mol %, 1 mol % vs 2 mol %). As depicted in Table 4, use of $^{2G}OACC_{100}$ also proceeded smoothly with a variety of amines (primary, secondary, benzylic, and anilines) to furnish the corresponding amides as off-white solids in good to excellent yields and purities. Although, the use of $^{2G}OACC_{50}$ gave products in high purity and within the acceptable ruthenium

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[26] These experimental results are in close agreement with the published experimental protocols in the Argonaut sales catalogue, see ref 13.

[27] For a detailed ICP-MS protocol, see ref 6 in: Ahn, Y. M.; Yang, K.; Georg, G. I. *Org. Lett.* **2001**, *3*, 1411−1413.

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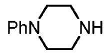
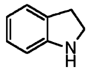
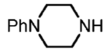
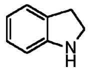
TABLE 2. Amidation Using ^{2G}OACC$_{50}$ as the Coupling Reagent

$$R^1COOH + R^2R^3NH \xrightarrow[\text{CH}_2\text{Cl}_2 \\ 0\text{-}25\ ^\circ\text{C, 2-7 h}]{^{2G}\text{OACC}_{50}} \underset{\mathbf{7}}{R^1CONR^2R^3}$$

entry	R^1	amines (R^2R^3NH)	pdt	yield (%)[a]	purity (%)[b]
1	Ph	$BnNH_2$	**7a**	90	98
2	Ph		**7b**	98	99
3	Ph	$(CH_2{=}CHCH_2)_2NH$	**7c**	90	95
4	Ph	n-$BuNH_2$	**7d**	85	91
5	Ph	 9	**7e**	94	91
6	$Br(CH_2)_5$	n-BuSH	**7f**	92	95
7	$Br(CH_2)_5$		**7g**	94	98
8	$Br(CH_2)_5$	n-$BuNH_2$	**7h**	88	96
9	$Br(CH_2)_5$	$(CH_2{=}CHCH_2)_2NH$	**7i**	91	96
10	$Br(CH_2)_5$		**7j**	95	93

[a] Yield of isolated crude product after silica gel plug. [b] Determined by GC and confirmed by ^{1}H NMR spectra (no polymer present, see the Supporting Information).

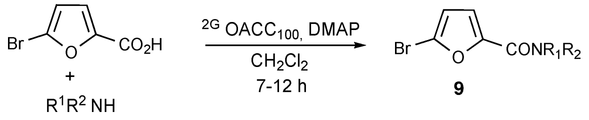
TABLE 3. Formation of Anhydrides 8 Using Coupling Reagent ^{2G}OACC$_{50}$

$$2\ RCOOH \xrightarrow[\text{CH}_2\text{Cl}_2 \\ 0\ ^\circ\text{C, 1.5-2 h}]{^{2G}\text{OACC}_{50}} \underset{\mathbf{8}}{(RCO)_2O}$$

entry	R	pdt	yield[a] (%)	purity[b] (%)
1	Ph	**8a**	97	97
2	$Br(CH_2)_5$	**8b**	92	96

[a] Yield of isolated crude product after silica gel plug. [b] Determined by GC and confirmed by ^{1}H NMR spectra (no polymer present, see the Supporting Information). Products were also identified by lack of the OH absorption in IR.

TABLE 4. Amidation of 5-Bromofuroic Acid Using ^{2G}OACC$_{100}$ as the Coupling Reagent



entry	amines (R^1R^2NH)	pdt	yield[a] (%)	purity[b] (%)
1	benzylamine	**9a**	90	90
2	4-Me-benzylamine	**9b**	65	93
3	4-MeO-benzylamine	**9c**	96	98
4	4-Cl-benzylamine	**9d**	87	95
5	aniline	**9e**	86	98
6	*p*-anisidine	**9f**	77	97
7	3-fluoroaniline	**9g**	75	95
8	hexylamine	**9h**	78	97
9	phenylethylamine	**9i**	82	91
10	dibenzylamine	**9j**	92	88

[a] Yield of isolated crude product after silica gel plug. [b] Determined by GC and confirmed by ^{1}H NMR spectra (no polymer present, see the Supporting Information).

levels, vide supra, we deem the purity of products produced from the ^{2G}OACC$_{100}$ to be higher.

Likewise, the use of the ^{2G}OACC$_{150}$ was examined and found to be acceptable. However, during the course of the reaction, the resulting urea oligomer precipitated from solution resulting in a lower isolated yield. This lower yield was presumably due to the products being trapped by the insoluble oligomer byproduct. Taken collectively, we view the ^{2G}OACC$_{100}$ reagent as superior and are now implementing it in standard practice.

In conclusion, a high-load, soluble oligomeric variant of DCC has been developed that serves as a facile coupling reagent of carboxylic acids with a variety of alcohols, thiols, phenols, and amines. Excess ^{2G}OACC$_{50}$ and the oligomeric urea byproduct can be easily removed by simple precipitation and filtration illustrating the wide solubility profile of the titled oligomeric reagent. Although this reagent gave acceptable results, we now deem the ^{2G}OACC$_{100}$ reagent to be superior and are now using it in standard practice. Implementation of this reagent in the area of combinatorial library development is underway and will be reported shortly.

Experimental Section

Synthesis of Mono-*endo*-amine 2.[20] *cis*-5-Norbornene-*endo*-2,3-dicarboxylic anhydride (10 g, 60.9 mmol) was refluxed with 1,2-diaminoethane (16.3 mL, 243.7 mmol) in toluene (80 mL) overnight to give 10.5 g (83%) of product as a pale yellow solid. ^{1}H NMR and ^{13}C NMR spectra are consistent with literature examples.

Preparation of Urea 3. Cyclohexyl isocyanate (0.95 g, 7.6 mmol) was added dropwise to a solution of mono-*endo*-amine **2** (1.42 g, 6.9 mmol) at 0 °C in CH_2Cl_2 (30 mL). After completion of the addition, the ice bath was removed, and the reaction solution was stirred at rt for 1.5 h. CH_2Cl_2 was evaporated under reduced pressure, and the residue was recrystallized using ethanol to give 2.14 g of urea **3** as a slightly yellow solid (94%): ^{1}H NMR δ 6.08 (s, 2H), 4.87 (br s, 1H),), 4.63 (br s, 1H), 3.49−3.23 (m, 9H), 1.88 (d, $J = 9.9$, 2H), 1.73−1.66 (m, 3H), 1.60−1.50 (m, 2H), 1.37−1.27 (m, 2H), 1.15−1.04 (m, 3H); ^{13}C NMR δ 178.0, 157.3, 134.3, 52.1, 49.0, 45.8, 44.8, 39.0, 38.1, 33.8, 25.5, 24.9; HRMS (FAB) calcd for M + H ($C_{18}H_{26}N_3O_3$) required 332.1974, found 332.1948.

Dehydration of Urea 3 To Form Monomer Carbodiimide 4. Using the same procedure as shown in ref 21, to a suspension of urea **3** (1.15 g, 3.47 mmol) in triethylamine (2.4 mL, 17.3 mmol) was added phenylsulfonyl chloride (1.02 mL, 6.9 mmol) at rt. After the addition was completed, the resulting suspension was stirred and heated to 70 °C for 1.5 h. The reaction was quenched with ice−water and partitioned between water and ether. The organic portion was separated, washed with water and brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by column chromatograph (40% EtOAc in hexanes) to obtain 793 mg of required carbodiimide **4** (73%): ^{1}H NMR δ 6.05 (t, $J = 1.7$, 2H), 3.41 (t, $J = 6.6$, 2H), 3.34−3.28 (m, 2H), 3.24−3.19 (m, 5H), 1.83−1.77 (m, 2H), 1.67−1.60 (m, 3H), 1.47 (d, $J = 8.7$, 2H), 1.29−1.10 (m, 5H); ^{13}C NMR δ 177.2, 139.1, 134.2, 55.3, 51.9, 45.5, 44.7, 43.5, 38.8, 34.5, 25.1, 24.2; HRMS (FAB) calcd for M + H ($C_{18}H_{24}N_3O_2$) required 314.1869, found 314.1868.

ROM Polymerization Procedure for the Generation of the Oligomeric Alkyl Cyclohexylcarbodiimide (^{2G}OACC$_{50}$). In a 100 mL round-bottom flask, *N*-cyclohexyl-*N*′-(2-succinimidoethyl)carbodiimide (**4**) (0.80 g, 2.55 mmol) was dissolved in degassed (argon) CH_2Cl_2 (30 mL). To this solution was added the second-generation Grubbs' metathesis catalyst **5** (43 mg, 0.051 mmol) in one portion. The reaction was refluxed under argon and monitored by TLC analysis. Once the polymerization was complete (∼3.5 h), the reaction was quenched by ethyl vinyl ether (approximately 1.0 mL) over a 10 min period. The mixture was reduced to 1/3 of the original volume and dripped into 60 mL of dry Et_2O to induce precipitation. Subsequent filtration produced 0.78 g (98%) of ^{2G}OACC$_{50}$ as a light-brown free-flowing solid: ^{1}H NMR δ 7.83−6.99 (m, terminal Ph), 5.72−5.60 (m, 2H, olefin), 3.94−2.92 (m, 9H), 2.12−0.80 (m, 12H); ^{13}C NMR δ 176.5, 139.4, 129.5 55.5, 48.8, 45.2, 43.6, 40.2, 39.4, 34.7, 25.3, 24.4; FTIR (film) 2122 (N═C═N), 1703 cm^{-1}. Anal. Calcd for $CH_2{=}(C_{18}H_{25}N_3O_2)_{50}{=}CHC_6H_5$: C, 69.14; H, 7.40; N, 13.32. Found: C, 69.48; H, 7.28; N, 13.01.

General Procedure for Esterification Using ^{2G}OACC$_{50}$. To a stirring solution of acid (0.1 mmol), alcohol [or phenol or thiol (0.1 mmol)], and DMAP (1.2 mg, 10 mmol %) in CH_2Cl_2 (0.5 mL) at 0 °C was added dropwise a solution of ^{2G}OACC$_{50}$ (47 mg, 0.15 mmol) in CH_2Cl_2 (0.5 mL). After complete addition, the ice bath was removed, and the reaction solution was stirred at rt for 2 h. The reaction mixture was precipitated by addition to Et_2O followed by filtration. The resulting ether solution was washed with water to eliminate DMAP, concentrated under reduced pressure, and filtered through silica gel (EtOAc) to produce the corresponding ester in good to excellent yield and purity.

General Procedure for Amidation Using ^{2G}OACC$_n$. Method A. To a stirring solution of acid (0.1 mmol) and amine (0.1 mmol) in CH_2Cl_2 (0.5 mL) at 0 °C was added dropwise a solution of ^{2G}OACC$_{50}$ (43 mg, 0.13 mmol) in CH_2Cl_2 (0.5 mL). After addition, the ice bath was removed, and the reaction solution was stirred at rt for 2−7 h. The reaction mixture was precipitated by addition to EtOAc (or Et_2O or MeOH) followed by filtration. The resulting filtrate was concentrated under reduced pressure and filtered through a silica gel (EtOAc) to produce the corresponding amide in good to excellent yield and purity.

Method B. To a suspension of 5-bromo-2-furoic acid (0.52 mmol), amine (1.0−1.5 equiv), and DMAP (10 mol %) in CH_2Cl_2 (0.3 mL) at rt was added dropwise a solution of ^{2G}OACC$_{100}$ (1.5−2.0 equiv) in CH_2Cl_2 (2 mL). After addition, the reaction mixture was stirred at rt for 7−12 h. After completion of reaction (TLC), the DMAP and excess amine were scavenged using Amberlyst A-15 ion-exchange resin (purchased from Aldrich, load = 4 mmol/g). The reaction mixture was precipitated by addition to EtOAc (or MeOH), filtered through a short SPE (SiO_2), and concentrated under reduced pressure to produce the corresponding amide in good to excellent yield and purity.

General Procedure for Anhydride Formation Using ^{2G}OACC$_{50}$. To a stirring solution of acid (0.2 mmol) in CH_2Cl_2 (0.5 mL) at 0 °C was added dropwise a solution of ^{2G}OACC$_{50}$ (43 mg, 0.13 mmol) in CH_2Cl_2 (0.5 mL). After addition, the reaction solution was stirred at 0 °C for 1.5−2.0 h. The reaction mixture was precipitated by addition to an Et_2O followed by filtration. The resulting filtrate was concentrated under reduced pressure and filtered through silica gel (EtOAc) to produce the corresponding anhydride in good to excellent yield and purity.

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Supporting Information Available: Tabulated ^{1}H NMR, ^{13}C NMR, and mass data of crude products **6**−**9** obtained by ^{2G}OACC$_n$ coupling reactions; ^{1}H NMR spectra of **3**, **4**, ^{2G}OACC$_{50}$, and **6**−**9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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