Tetrabutylammonium tribromide mediated condensation of carboxylic acids with alcohols

Sarala Naik, Veerababurao Kavala, Rangam Gopinath, and Bhisma K. Patel*

Department of Chemistry, Indian Institute of Technology, Guwahati-781 039, India
E-mail: patel@iitg.ernet.in

Abstract

The direct condensation of various carboxylic acids and alcohols was achieved efficiently at reflux temperature under a solvent free condition using a catalytic amount of tetrabutylammonium tribromide (TBATB). Chemoselective acylation of primary alcohols in presence of secondary alcohols and phenols has been achieved. Steric factors in carboxylic acids played a crucial role during chemoselective acylation of diols. Reaction under a solvent free condition, absence of any dehydrating agent or use of any special techniques for removal of water and higher yields are the important features of this protocol.

Keywords: Catalysis, alcohol, carboxylic acid, tetrabutylammonium tribromide, acylation, chemoselective

Introduction

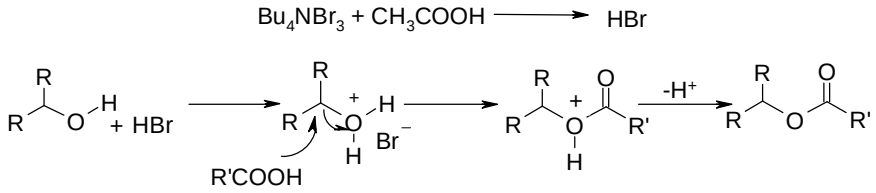
The acylation of alcohol is one of the fundamental and most consistently used transformation in organic synthesis because of the use of esters as fine chemicals, drugs, plasticizers, perfumes, food preservatives, cosmetics, pharmaceuticals, solvents and chiral auxiliaries.[1] In general this can be achieved by treating alcohols with acid anhydrides or acid chlorides in the presence of stoichiometric amounts of amine bases such as tertiary amines,[2] 4-(dimethylamino)pyridine (DMAP) or 4-(1-pyrrolidino) pyridine (PPY) [3] and Bu_3P.[4] Acylation of alcohols can also be achieved under an acid catalyzed condition by treating alcohols with acid anhydrides in presence of protic acids[5] and Lewis acids.[6] Acylations using acid anhydrides work well, but the conversion is inherently wasteful since half of every acid anhydride molecule is lost as carboxylic acid utilizing only one acyl group for acylation. On the other hand acyl chlorides are equally efficient acylating agents but their use is restricted owing to their moisture sensitive, corrosive and lacrymating properties. The use of large amount of acylating reagents and activators should be avoided in order to promote Green chemistry and atom efficiency. To fulfill these requirements direct condensation of alcohols with carboxylic acids is the ultimate choice.

But the direct condensation of carboxylic acids with alcohols is generally avoided because the equilibrium between the substrates and the products require the elimination of water from the reaction mixture using dehydrant or azeotropically to shift the equilibrium in favor of product. This has been achieved conventionally by condensing carboxylic acid and alcohol with one being in large excess to drive the reaction in forward direction. The reagents and procedures for direct condensation include $B(OH)_3$,[1b] R_2SnO[7] diorgano tin chloride.[8] Stoichiometric condensation of alcohols and acids using $TiCl(OTf)_3$[9c] involve silyl dehydrating additives where as for $TiCl_2(ClO_4)_2$[9ab] and $Sc(OTf)_3$[9d] mediated condensation, anhydride is essential for the removal of water. Water formed during the condensation catalyzed by Hf(IV) and Zr(IV) salts has been reported to be removed azeotropically using Soxhlet thimble and calcium hydride or 4Å molecular sieves.[10] Besides these, several other reagents and procedures accounting for this transformation includes $La(OTf)_3$,[11a] $Ce(OTf)_3$,[11b] diphenylammoniumtriflate (DPAT),[11c] triaryl bismuthanes,[12] $K_5CoW_{12}O_{40}.3H_2O$[13] montmorillonites clay,[14] Mn(III) salen complex,[15] pillared clays,[16] CAN,[17] KF[18] and $CoCl_2.6H_2O$.[19] Though some of the reported methods are quite useful for this conversion, some of these methods require expensive dehydrating agents like 4-nitrobenzoic anhydride, silyl additives, CaH_2 and special equipment such as Soxhlet thimble. Some of the reagents are toxic and some of these are expensive. Therefore, there is still a need to search for other suitable alternatives circumventing the above mentioned problems. We have been interested in the development of green chemical processes in aqueous media[20]and exploring the properties of tetrabutylammonium tribromide (TBATB) for various organic transformations.[21] Organic ammonium tribromides has been prepared in an environmentally benign way without the use of any detrimental chemicals.[22] Organicammonium tribromides are stable crystalline compounds, convenient and safe in maintaining the desired stoichiometry in comparison to elemental bromine. TBATB in an organic medium being an *in-situ* source of anhydrous HBr manifests itself as a milder alternative to conventional protic and Lewis acids. In continuation to the applications of TBATB for various organic transformations[21] we wish to report here the acylation of alcohols using various carboxylic acids under a solvent free condition.

Results and Discussion

To investigate this reaction 3-phenyl propanol **3** (5 mmol) was treated with glacial acetic acid (5 mL) in the presence of TBATB (0.5 mmol) at room temperature and progress of the reaction was monitored by thin layer chromatography. Only 40% conversion was achieved even after 24 h. However, shorter reaction time (15 min) and better yield (95%) was achieved by performing the reaction at reflux temperature. Surprisingly, even without the removal of water, esterification was very satisfactory; hence no special precaution was required for the removal of water from the reaction mixture. In a control reaction when decanol **1** (1 mmol) was treated with TBATB (0.1 mmol) no alcohol bromination was observed at all. TBATB is known to release anhydrous

HBr in an alcoholic medium and other organic solvent.[21] The pH of the neat acetic acid recorded was 0.8 which drop to a value of -0.9 on addition of TBATB under the identical reaction condition. The HBr with pKa (-9) is sufficiently acidic as compared to protonated carboxylic acid pKa (-7) and protonated alcohol pKa (-2).[23] Thus, alcohol would preferentially protonated over carboxylic acid. The nucleophilic attack of carboxylate on the oxonium species will yield acylated product as shown in Scheme 1.



Scheme 1. Mechanism of acylation

By employing this reagent a wide variety of aliphatic, aromatic primary, secondary benzylic alcohols containing electron releasing and electron withdrawing groups could be acetylated to produce the corresponding esters in good to excellent yields (Table 1). Under the present optimized reaction condition, aliphatic alcohols (Table 1, entries **1-3**) were transformed to corresponding acetates in excellent yields. Benzylic alcohols with electron donating substituent (Table 1, entry **4**) and electron withdrawing substituent (Table 1, entry **5**) could also be acetylated in shorter time. Acetylation of hindered primary alcohols (Table 1, entries **7-8**) could be achieved in good yields. However, symmetrical diols (Table 1, entries **9-11**) were diacetylated completely under the present reaction condition. Hindered secondary alcohols (Table 1, entries **12-15**) were converted to their acetates in moderate yield. Small percentage of brominated product (< 5%) was observed as side product for substrate containing double bond (Table 1, entries **16-17**). More over, acid sensitive groups such as OMe (Table 1, entry **4**); allyloxy group (Table 1, entry **17**) as well as base sensitive benzoate group (Table 1, entries **18-19**) remained intact under the described reaction condition revealing the functional group compatibility of this method.

Table 1. Acylation[a] of alcohols with acetic acid in the presence of TBATB

Alcohols	Esters[b]	Time/min	Yield[c] %
$CH_3(CH_2)_8CH_2OH$ (**1**)	$CH_3(CH_2)_8CH_2OAc$ (**1a**)	15	92
$CH_3(CH_2)_{10}CH_2OH$ (**2**)	$CH_3(CH_2)_{10}CH_2OAc$ (**2a**)	15	93
$C_6H_5CH_2CH_2CH_2OH$ (**3**)	$C_6H_5CH_2CH_2CH_2OAc$ (**3a**)	15	95
4-$CH_3OC_6H_4CH_2OH$ (**4**)	4-$CH_3OC_6H_4CH_2OAc$ (**4a**)	10	92
3-$O_2NC_6H_4CH_2OH$ (**5**)	3-O_2N $C_6H_4CH_2OAc$ (**5a**)	30	90
4-Cl $C_6H_4CH_2OH$ (**6**)	4-Cl $C_6H_4CH_2OAc$ (**6a**)	10	92
9- Flurenyl-CH_2OH (**7**)	9- Flurenyl-CH_2OAc (**7a**)	40	95
$(PhCH_2)_2N(CH_2)_2OH$ (**8**)	$(PhCH_2)_2N(CH_2)_2OAc$ (**8a**)	10	92
$HO(CH_2)_5OH$ (**9**)	$AcO(CH_2)_5OAc$ (**9a**)	10	89
Diethylene glycol (**10**)	Diacetoxy diethylene glycol (**10a**)	10	90
2,2-Dimethyl-1,3-propane diol (**11**)	1,3-diacetoxy-2,2-dimethyl propane (**11a**)	10	90
Menthol (**12**)	Menthyl acetate (**12a**)	45	87
$C_6H_5CH(CH_3)OH$ (**13**)	$C_6H_5CH(CH_3)OAc$ (**13a**)	40	80
3-O_2N-C_6H_4-$CH(CH_3)OH$ (**14**)	3-O_2N-C_6H_4CH-$(CH_3)OAc$ (**14a**)	55	80
$(C_6H_5)_2CHOH$ (**15**)	$(C_6H_5)_2CHOAc$ (**15a**)	60	78
$PhCH=CH-CH_2OH$ (**16**)	$PhCH=CH-CH_2OAc$ (**16a**)	45	83
4- Allyloxy-$C_6H_4CH_2OH$ (**17**)	4- Allyloxy-$C_6H_4CH_2OAc$ (**17a**)	20	82
2-Benzyloxy ethylene glycol (**18**)	2-Benzyloxy ethylene glycol acetate(**18a**)	30	92
Benzyloxy diethylene glycol (**19**)	Benzyloxy diethylene glycol acetate (**19a**)	40	94

[a]The reactions were monitored by TLC, GC. [b]Confirmed by comparison with IR, ^{1}H NMR of the authentic sample. [c]Isolated yield.

The differential reactivity of substrates containing primary and secondary alcoholic group prompted us to perform chemoselective acylation amongst these group. When 1,3-butane diol (Table 2, entry **20**), was subjected to react under the described condition with acetic acid, the ratio of primary monoacetylated and diacetylated products obtained were 42:45 respectively, showing poor chemoselectivity between primary and secondary alcohol. However, as could be seen from (Table 2, entry **21**) for substrate 4-(2-hydroxy-ethyl)-phenol, the primary aliphatic hydroxy group was exclusively acetylated in the presence of phenolic hydroxy group. Benzylic alcoholic group was chemoselectively acetylated over phenolic group under the present condition (Table 2, entry **22**). The scope of the condensation reaction was extended for propionylation, isobutyralation and pivaloylation. When various alcohols were reacted in presence of TBATB (10 mol%) with propionic, isobutyric and pivalic acid respectively furnished corresponding propionates (Table 3, entries **1b**, **3b**, **13b**, **21b**) isobutyrates (Table 3, entries **1c**,

3c, **13c**, **21c**) and pivalates (Table 3, entries **1d**, **3d**, **13d**, **21d**) in good to high yields. As could be observed from the table for a given alcohol the rate of acylation increases with increase in the bulkiness of the carboxylic acid. Taking cue from the above observation, study on the effect of steric bulkiness of the acids on the selectivity in acylation was thought to be quite useful. When butane-1,3-diol (Table 4, entry **20**) was reacted with various acids, the ratio of mono and di products observed is summarized in Table 4. As could be seen from Table 4, a better chemoselective acylation of primary alcohol was observed for primary alcohol with increase in bulkiness of acid group during a specified reaction time.

Table 2. Acetylation[a] of diols with acetic acid in the presence of TBATB

Alcohols	Esters[b]	Time/min	Yield[c] %
$CH_3CHOHCH_2CH_2OH$ (**20**)	$CH_3CHOHCH_2CH_2OAc$ (**20'a**)	20	42
	$CH_3CHO(Ac)CH_2CH_2OAc$ (**20a**)		45
4-OH-$C_6H_4CH_2CH_2OH$ (**21**)	4-OH-$C_6H_4CH_2CH_2OAc$ (**21'a**)	40	87
	4-OAc-$C_6H_4CH_2CH_2OAc$ (**21a**)		00
4-$OHC_6H_4CH_2OH$(**22**)	4-$OHC_6H_4CH_2OAc$ (**22'a**)	30	83
	4-$OAcC_6H_4CH_2OAc$ (**22a**)		00

[a]The reactions were monitored by TLC, GC. [b]Confirmed by comparison with IR, ^{1}HNMR of the authentic sample. [c]Isolated yield.

Table 3. Acylation[a] of alcohols with various acids in the presence of TBATB

Alcohols	Acid employed	Esters[b]	Time/ min	Yield[c] %
$CH_3(CH_2)_8CH_2OH$ (**1**)	CH_3CH_2COOH	$CH_3(CH_2)_8CH_2OCOEt$ (**1b**)	15	90
$Ph(CH_2)_2CH_2OH$ (**3**)	CH_3CH_2COOH	$Ph(CH_2)_2CH_2OCOEt$ (**3b**)	20	95
$PhCH(CH_3)OH$ (**13**)	CH_3CH_2COOH	$PhCH(CH_3)OCOEt$ (**13b**)	30	80
4-OH-$C_6H_4CH_2CH_2OH$ (**21**)	CH_3CH_2COOH	4-OH-$C_6H_4CH_2CH_2OCOEt$ (**21b**)	25	87
$CH_3(CH_2)_8CH_2OH$ (**1**)	$(CH_3)_2CHCOOH$	$CH_3(CH_2)_8CH_2OCOiPr$ (**1c**)	20	88
$Ph(CH_2)_2CH_2OH$ (**3**)	$(CH_3)_2CHCOOH$	$Ph(CH_2)_2CH_2OCOiPr$ (**3c**)	20	80
$PhCH(CH_3)OH$ (**13**)	$(CH_3)_2CHCOOH$	$PhCH(CH_3)OCOiPr$ (**13c**)	45	79
4-OH-$C_6H_4CH_2CH_2OH$ (**21**)	$(CH_3)_2CHCOOH$	4-OH-$C_6H_4CH_2CH_2OCOiPr$ (**21c**)	35	86
$CH_3(CH_2)_8CH_2OH$ (**1**)	$(CH_3)_3CCOOH$	$CH_3(CH_2)_8CH_2OCOt$-Bu (**1d**)	45	83
$Ph(CH_2)_2CH_2OH$ (**3**)	$(CH_3)_3CCOOH$	$Ph(CH_2)_2CH_2OCOt$-Bu (**3d**)	45	86
$PhCH(CH_3)OH$ (**13**)	$(CH_3)_3CCOOH$	$PhCH(CH_3)OCOt$-Bu (**13d**)	60	76
4-OH-$C_6H_4CH_2CH_2OH$ (**21**)	$(CH_3)_3CCOOH$	4-OH-$C_6H_4CH_2CH_2OCOt$-Bu (**21d**)	55	82

[a]The reactions were monitored by TLC, GC. [b]Confirmed by comparison with IR ^{1}HNMR of the authentic sample.[c]Isolated yield.

Table 4. Acylation[a] of butane-1,3-diol with various acids in the presence of TBATB

Alcohol	Acid employed	Esters[b]	Time /min	Yield[c]%
$CH_3CHOHCH_2CH_2OH$ (**20**)	CH_3CH_2COOH	$CH_3CHOHCH_2CH_2OCOEt$ (**20'b**)	30	30
		$CH_3CH(OCOEt)CH_2CH_2OCOEt$ (**20b**)		60
	$(CH_3)_2CHCOOH$	$CH_3CHOHCH_2CH_2OCOiPr$ (**20'c**)	25	60
		$CH_3CH(OCOiPr)CH_2CH_2OCOiPr$ (**20c**)		30
	$(CH_3)_3CCOOH$	$CH_3CHOHCH_2CH_2OCOt$-Bu (**20'd**)	90	70
		$CH_3CH(OCOt$-Bu$)CH_2CH_2OCOt$-Bu (**20d**)		15

[a]The reactions were monitored by TLC, GC. [b]Confirmed by comparison with IR, ^{1}HNMR of the authentic sample. [c]Isolated yield.

Conclusions

In conclusion, TBATB is found to be an excellent source of anhydrous HBr which catalyzes the direct condensation of acid with alcohol. The reagent TBATB is air stable, low toxic and easy to handle. The operation is quite simple, because chemical dehydrating agents such as anhydrides, silyl additives or special apparatus such as Soxhlet-thimble, Dean-Stark apparatus is not necessary. Reaction under a solvent free condition, shorter reaction time accompanied by good yield and operational simplicity are some of the interesting features of this procedure.

Experimental Section

General Procedure for Acetylation of Alcohols with TBATB in Acetic Acid (Table 1, 2). To a solution of alcohol (5 mmol) in acetic acid (5 mL) was added tetrabutylammonium tribromide TBATB (0.5 mmol). The reaction mixture was refluxed and the progress of the reaction was monitored by TLC and GC. After completion of the reaction, the reaction mixture was poured into saturated $NaHCO_3$ solution (20 mL) and the product was extracted with ethyl acetate (2 × 15 mL). The organic layer was separated, dried over anhydrous sodium sulfate and concentrated. Further purification was achieved by column chromatography and products were identified by comparison of their NMR, IR, GC, and GC co-injection with authentic samples prepared by known methods.

General Procedure for Acylation of Alcohols with TBATB in Propionic acid, Isobutyric acid and Pivalic acid (Table 3, 4): Similar to the acetylation with acetic acid.

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24. **Selected spectroscopic data: 2a.** ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, 3H, J = 6.9 Hz), 1.26 (m, 18H), 1.62 (m, 2H), 2.04 (s, 3H), 4.05 (t, 2H, J = 6.6 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 21.0, 22.7, 25.9, 28.6, 29.2, 29.3, 29.50, 29.54, 29.6, 31.9, 64.7, 171.3 ppm. **7a:** ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.09 (s, 3H), 4.17 (t, 1H, J = 7.2 Hz), 4.32 (d, 2H, J = 7.2 Hz), 7.32 (m, 4H), 7.56 (d, 2H, J = 7.5 Hz), 7.72 (d, 2H, J = 7.5 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.9, 46.6, 66.3, 119.9, 124.9, 127.0, 127.7, 141.2, 143.7, 170.8 ppm. **11a:** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.94 (s, 6H), 2.03 (s, 6H), 3.85 (s, 4H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.8, 21.7, 34.4, 69.1, 171.0 ppm. **14a:** ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.58 (d, 3H, J = 6.9 Hz), 2.12 (s, 3H), 5.94 (q, 1H, J = 6.9 Hz), 7.54 (t, 1H, J = 7.8 Hz), 7.68 (d, 1H, J = 7.8 Hz), 8.14 (d, 1H, J = 8.1 Hz), 8.22 (s, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.1, 22.1, 71.1, 120.9, 122.7, 129.5, 132.2, 143.8, 148.3, 170.0 ppm. **1b:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.80 (t, 3H, J = 6.8 Hz), 1.07 (t, 3H, J = 7.6 Hz), 1.19 (brm, 14H), 1.53 (m, 2H, J = 6.8 Hz), 2.26 (q, 2H, J = 7.6 Hz), 3.99 (t, 2H, J = 6.4 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.1, 14.0, 22.6, 25.8, 27.1, 27.6, 28.6, 29.20, 29.24, 29.5, 31.8, 64.4, 174.6 ppm. **3b:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.14 (t, 3H, J = 7.6 Hz), 1.95 (m, 2H), 2.33 (q, 2H, J = 7.6 Hz), 2.68 (t, 2H, J = 8 Hz), 4.09 (t, 2H, J = 6.4 Hz), 7.18 (m, 3H), 7.27 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.6, 28.0, 30.7, 32.6, 63.9, 126.2, 128.59, 128.62, 141.4, 174.5 ppm. **13b:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.13 (t, 3H, J = 7.6 Hz), 1.52 (d, 3H, J = 6.4 Hz), 2.34 (m, 2H), 5.88 (q, 1H, J = 6.4 Hz), 7.33 (m, 5H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.6, 22.7, 28.3, 72.4, 126.2, 127.9, 128.6, 142.0, 173.8 ppm. **1c:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, 3H, J = 7.2 Hz), 1.16 (d, 6H, J = 6.8 Hz), 1.26 (brm, 14 H), 1.62 (m, 2H), 2.53 (septet, 1H, J = 7.2 Hz), 4.05 (t, 2H, J = 6.4 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.5, 19.4, 23.1, 26.3, 27.5, 29.0, 29.6, 29.7, 29.9, 32.3, 34.4, 64.7, 177.2 ppm. **3c:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.17 (d, 6H, J = 7.2 Hz), 1.96 (m, 2H), 2.54 (septet, 1H, J = 6.4 Hz), 2.68 (t, 2H, J = 8.4 Hz), 4.08 (t, 2H, J = 6.4 Hz), 7.14-7.30 (m, 5H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.5, 30.7, 32.6,34.5, 63.9, 126.2, 128.60, 128.63, 141.4, 177.2 ppm. **13c:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.16 (m, 6H), 1.51 (d, 3H, J = 6.8 Hz), 2.56 (septet, 1H, J = 6.8 Hz), 5.87 (q, 1H, J = 6.8 Hz), 7.32 (m, 5H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.4, 22.7, 34.6, 72.2, 126.1, 127.9, 128.5, 142.2, 176.3 ppm. **21c:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.13 (d, 6H, J = 7.2 Hz), 2.53 (septet, 1H, J = 7.2 Hz), 2.85 (t, 2H, J = 7.2 Hz), 4.24 (t, 2H, J = 7.2 Hz), 6.76 (d, 2H, J = 8.4 Hz), 7.06 (d, 2H, J = 8.4 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.4, 34.6, 65.7, 115.6, 129.5, 130.2, 154.8, 178.1 ppm. **1d:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (t, 3H, J = 7.2 Hz), 1.19 (s, 9H), 1.26 (brm, 14H), 1.60 (m, 2H), 4.04 (t, 2H, J = 6.4 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.5, 23.1, 26.3, 27.6, 29.0, 29.6, 29.7, 29.9, 32.3, 39.1, 64.8, 178.6 ppm. **3d:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (s, 9H), 1.94 (m, 2H), 2.68 (t, 2H, J = 8 Hz), 4.06 (t, 2H, J = 6.4 Hz), 7.14-7.29 (m, 5H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.7, 30.7, 32.6, 39.2, 63.9, 126.2, 128.60, 128.63, 141.4, 178.6 ppm. **21d:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.59 (s, 9H), 2.86 (t, 2H, J = 7.0), 4.22 (t, 2H, J = 7.0 Hz), 6.76 (d, 2H, J = 8.4 Hz), 7.07 (d, 2H, J = 8.8 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.6, 34.6, 39.1, 65.4, 65.5, 115.5, 130.1, 130.2, 154.5 ppm.