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Direct Regioselective Alkylation of Non-Basic Heterocycles with Alcohols and Cyclic Ethers through a Dehydrogenative Cross-coupling Reaction under Metal-Free Conditions

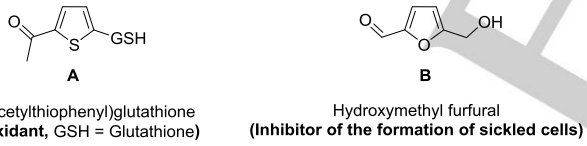
Ebrahim Kianmehr,* Maryam Fardpour and Khalid Mohammed Khan[b]

Dedication ((optional))

Abstract: A metal-free, simple and highly efficient method for the direct alkylation of non-basic heterocycles as well as basic ones with various alcohols and cyclic ethers has been developed based on an oxidative C-H activation process. The corresponding products were generated through a dehydrogenative C-C cross-coupling reaction in the presence of di-*tert*-butyl peroxide in good to high yields.

Introduction

Heteroaromatic moieties are doubtlessly of great importance among pharmaceutical compounds as well as agricultural chemicals and therefore are essential to life (Figure 1).[1] Over the last decade, the direct C-H functionalization of heterocycles in medicinal chemistry has received much attention.[2] Moreover, generating a new C-C bond via the C-H activation of alcohols and ethers has attracted much interest according to its simple introduction of an oxygen-containing functional group into the molecule which provides vital materials for the manufacturing of fine chemicals, pharmaceuticals, agrochemicals and fragrances.[3]

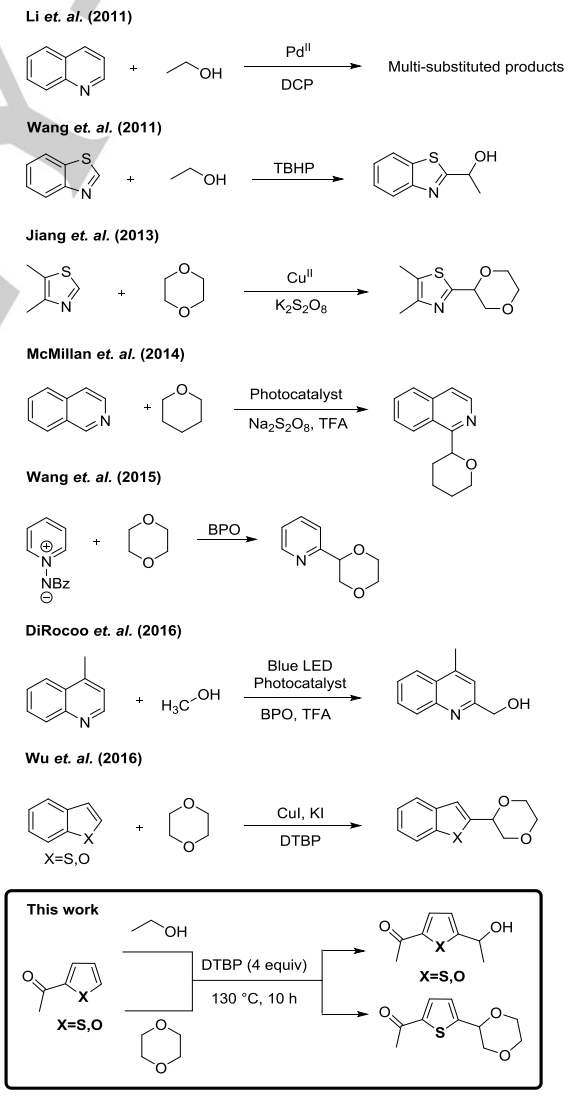


S-(2-acetylthiophenyl)glutathione **(Antioxidant,** GSH = Glutathione)

Hydroxymethyl furfural **(Inhibitor of the formation of sickled cells)**

Figure 1. Examples of Bioactive Compounds with Non-Basic Nitrogen-Free Heterocyclic Cores.

The field of coupling alcohols to heterocyclic bases was first studied by Minisci[4] which describes the hydroxymethylation and hydroxyethylation of 4-methylpyridine and 4-methylquinoline, in the presence of peroxides and stoichiometric amounts of acid, in moderate and low yields, respectively. In 2011, Li *et. al.*[5] published a palladium-catalyzed coupling of quinoline, isoquinoline and *rac*-Binap with simple alcohols and Wang *et. al.*[6] reported a metal-free direct C-2 alkylation of azoles with alcohols and ethers in the presence of *tert*-butyl hydroperoxide (TBHP). In 2013, copper-catalyzed cross-dehydrogenative coupling (CDC) reactions of (benzo)thiazoles with cyclic ethers in the presence of $K_2S_2O_8$ was developed by Jiang and co-workers.[7] In 2014, MacMillan[8] reported direct α-arylation of ethers with electron-deficient nitrogen-containing heteroarenes through the combination of photoredox catalytic approach and the Minisci Reaction. In 2015, Wang *et. al.*[9] explored the ortho-alkylation of N-iminopyridinium ylides with simple alcohols and ethers in the presence of benzoyl peroxide. In the same year, Cai *et. al.*[10] reported a nickel-catalyzed CDC reaction of indoles with 1,4-dioxane with a single example of benzofuran as the substrate.



Scheme 1. Represented Examples of Alkylation in the Literature

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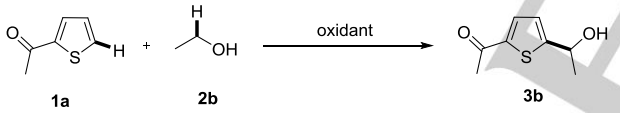
In 2016, DiRocoo *et. al.*[11] developed a photoredox-catalayzed hydroxymethylation of heteroaromatic bases. In the same year, Wu *et. al.*[12] reported a copper-mediated alkylation of furan and thiophene derivatives with cyclic ethers. As mentioned above, although tremendous progress has been made in this area (Scheme 1), some drawbacks such as the requirement of making pyridinium salts at the beginning of the reaction procedure and the use of expensive transition-metal catalysts still remain.

The thiophene and furan cores are present as vital moieties in many different biologically active compounds[13a,b] such as compound **A** (Figure 1, GSH = Glutathione) which is an antioxidant and compound **B**, known as an inhibitor of the formation of sickled cells in blood.[13c,d] Despite the importance of these heterocylic cores, the alkylation with simple alcohols and ethers were rarely explored.[14] Therefore, development of new methods for the direct alkylation of heterocycles with alcohols and cyclic ethers is highly desirable. Herein, we report a simple, efficient and regioselective metal-free CDC reaction of non-basic heterocycles such as thiophenes and furans as well as pyridines with alcohols and cyclic ethers to obtain corresponding products in good to high yields.

Results and Discussion

We chose 2-acetylthiophene (**1a**) and ethanol (**2b**) as the model substrates to investigate the optimization of the reaction conditions (Table 1). Based on the model reaction, several oxidants, solvents and temperatures were investigated to gain the optimized reaction conditions (see the Supporting Information).

Table 1. Optimization of the Reaction Conditions[a]



1a **2b** **3b**

entry	oxidant (equiv)	solvent	Yield[b] (%)
1	TBHP (4)	C_2H_5OH	trace
2	BPO(4)	C_2H_5OH	0
3	DDQ (4)	C_2H_5OH	0
4	BQ (4)	C_2H_5OH	0
5	CHP (4)	C_2H_5OH	trace
6	$K_2S_2O_8$ (4)	C_2H_5OH	0
7	$Na_2S_2O_8$ (4)	C_2H_5OH	0
8	$(NH_4)_2S_2O_8$ (4)	C_2H_5OH	0
9	**DTBP (4)**	**C_2H_5OH**	**81**
10	DTBP (2)	C_2H_5OH	61
11	DTBP (6)	C_2H_5OH	81
12	-	C_2H_5OH	N.D.
13[c]	DTBP (4)	PhCl	70
14[c]	DTBP (4)	DCE	66
15[c]	DTBP (4)	Benzene	61
16[c]	DTBP (4)	Toluene	52
17[c]	DTBP (4)	DMSO	43

[a] Reaction conditions: 2-acetylthiophene (0.3 mmol), ethanol (2.0 mL), oxidant (4.0 equiv), sealed tube, 130 °C, air, 10 h. [b] Isolated yields. [c] ethanol (0.5 mL), solvent (1.5 mL). N.D. = No Desired Product, DCE = 1,2-dichloroethane, DMSO = dimethyl sulfoxide

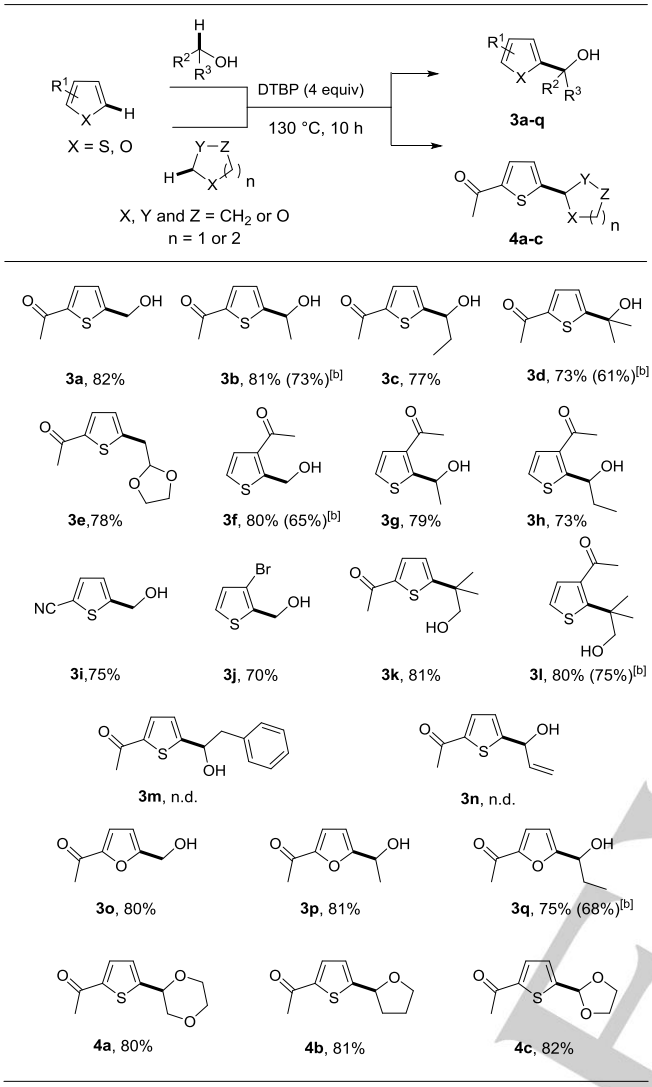
As shown in Table 1, a variety of organic oxidants such as *tert*-butyl hydroperoxide (TBHP), benzoyl peroxide (BPO), 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ), benzoquinone (BQ) and cumene hydroperoxide (CHP) were totally insufficient (Table 1, entries 1-5). Unfortunately, inorganic oxidants, such as $K_2S_2O_8$, $Na_2S_2O_8$ and $(NH_4)_2S_2O_8$ were also ineffective in this reaction and no desired **3b** was isolated (Table 1, entries 6-8). To our delight, an 81% yield of **3b** was obtained with 4 equiv of di-*tert*-butyl peroxide (DTBP) (Table 1, entry 9). The reaction was not completed with less than 4 equiv of DTBP, while increasing the amount of oxidant was not effective in achieving higher yields, either (Table 1, entries 10 and 11). With respect to the amount of oxidant used in the reaction, 4 equiv of DTBP was found to be optimal. The excess amount of DTBP required in the reaction might refer to the fact that at high temperatures, the tert-butoxy radical can further fragment to acetone. The effect of solvent on the model reaction was also examined. Among the tested solvents, ethanol as well as the substrate, was the most effective solvent (Table 1, entry 9). Chlorobenzene (PhCl), 1,2-dichloroethane (DCE), benzene, toluene and dimethyl sulfoxide (DMSO) were subsequently inferior (Table 1, entries 13-17). Therefore, the corresponding alcohol or cyclic ether was chosen as both the reactant and reaction medium considering its environmentally friendliness, cost-effectiveness and high efficiency.

Once the optimized reaction conditions were achieved, the scope of the alcohol in the direct alkylation of thiophenes with a variety of alcohols was investigated. As can be seen in Table 2, the reaction of thiophenes could be performed with a variety of aliphatic alcohols such as methanol, ethanol, n-propanol and 2-propanol to produce the corresponding hydroxyalkylated products **3a-l** in good to high yields.

Amazingly, the reaction of 2-acetylthiophene with ethylene glycol as a diol proceeded through a different path which gave **3e** with 78% yield. Also, when 2-methyl-1-propanol was used as the alcohol substrate, products **3k** and **3l** were obtained with 2-acetylthiophene and 3-acetylthiophene in high yields, respectively. However, when 2-phenyl ethanol and allyl alcohol were used as the reactant, no desired products were obtained (**3m** and **3n**). Reaction of furan as another non-basic heterocycle was also investigated and the corresponding hydroxyalkylated products were obtained in good yields (Table 2, **3o-q**).

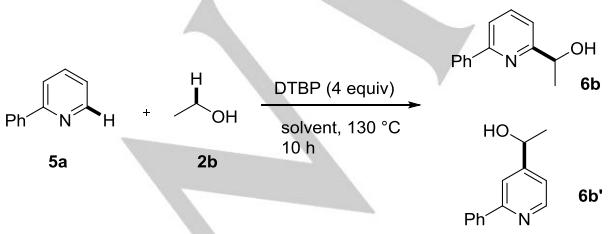
We next decided to try direct alkylation of 2-acetylthiophene with cyclic ethers under the optimized reaction conditions. As can be seen from Table 2, the reaction of 1,4-dioxane, tetrahydrofuran and 1,3-dioxolane with 2-acetylthiophene smoothly generated **4a-c** in high yields.

Table 2. Substrates Scope for Hydroxyalkylation of Non-Basic Nitrogen-Free Heterocycles with Alcohols and Cyclic Ethers via CDC Reaction[a]



[a] Reaction conditions: non-basic heterocycle (0.3 mmol), alcohol/cyclic ether (2.0 mL), DTBP (4.0 equiv), sealed tube, 130 °C, air, 10 h. [b] non-basic heterocycle (2 mmol).

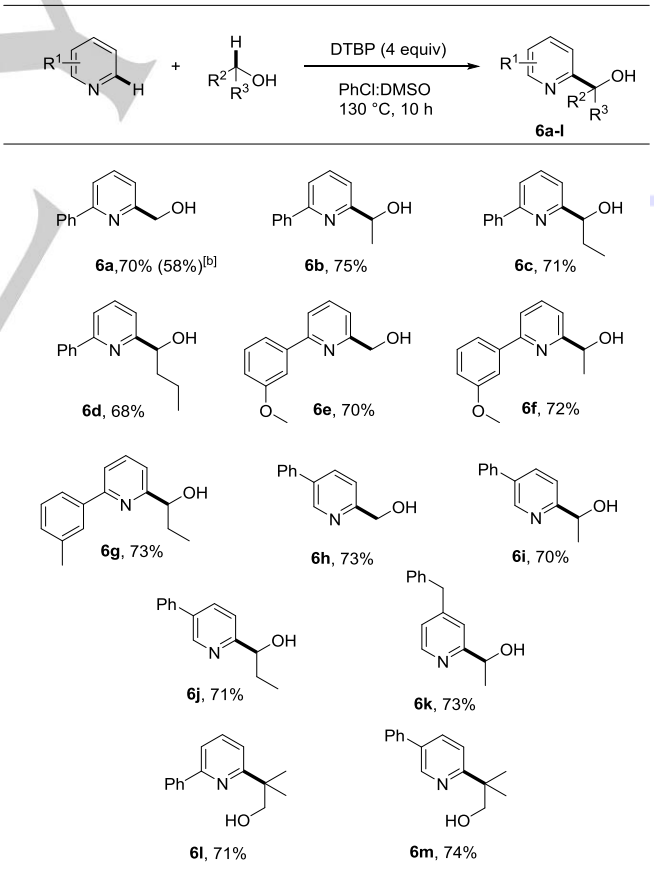
With the satisfying results of the reaction between non-basic heterocycles and alcohols/cyclic ethers in hand, we decided to examine some basic heterocycles, too. We started the investigation with 2-phenylpyridine (**5a**) and ethanol (**2b**) (Scheme 2).



Scheme 2. Hydroxyethylation of 2-phenylpyridine

Under the optimized reaction conditions for the alkylation of non-basic heterocycles, a mixture of **6b**:**6b'** was obtained with 41:38% yield. After solvent screening, it was found that the solvent has a crucial importance on the reaction regioselectivity. When the reaction was carried out in toluene, DMSO and PhCl, both 2- and 4-hydroxylated products were obtained. Gratifyingly, a mixture of PhCl:DMSO with the ratio 2:1 gave the 2-hydroxylated product (**6b**) smoothly in 75% yield and only a trace amount of the 4-hydroxylated product (**6b'**) which was indicated by TLC (see the Supporting Information). In continuation of this investigation, as shown in Table 3, various 2-phenylpyridines, 3-phenylpyridine and 4-benzylpyridine successfully generated the anticipated products **6a-m** in good yields. With 2-methyl-1-propanol as the alcohol substrate, the products **6l** and **6m** were formed with 2-phenylpyridine and 3-phenylpyridine in good yields, respectively. Unfortunately, with unsubstituted pyridine and thiophene, the reaction didn't lead to the formation of desired products. Propitiously, and unlike the previous reports based on radical addition to basic heterocyclic cores,[15] the reaction proceeded smoothly with no need to take extra steps to activate the heterocyclic substrate as pyridinium salts or use any kinds of metal catalysts or even add acid directly into the reaction medium to achieve the corresponding products and therefore, high regioselectivity was obtained only through using a convenient solvent-mixture. To prove the role of DTBP as a free radical generator, a control reaction involving the use of 2,6-di-*tert*-butyl-4-methylphenol (BHT) as a radical scavenger was performed. When **1a** was treated with 1 equiv of butylated hydroxytoluene, no desired product **3b** was observed.[16]

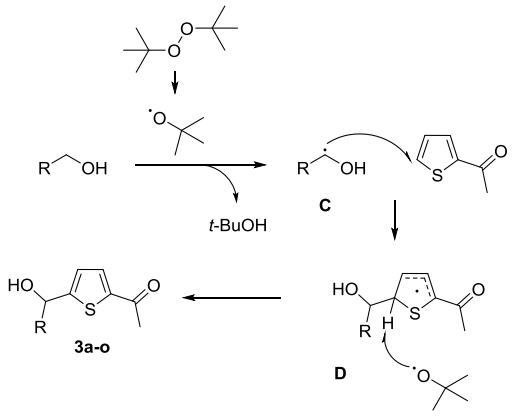
Table 3. Substrates Scope for Hydroxyalkylation of Pyridines with Alcohols via CDC Reaction[a]



[a] Reaction conditions: substituted pyridine (0.3 mmol), alcohol (0.5 ml), PhCl:DMSO (2:1) (1.5 ml), DTBP (0.4 equiv), sealed tube, 130 °C, air, 10 h. [b] substituted pyridine (2 mmol).

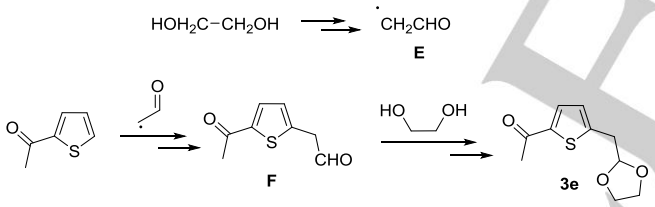
Based on the above results and the previous reports, a plausible mechanism for this reaction is given in Scheme 3.[17] Initially, a

homolytic cleavage of di-*tert*-butyl peroxide affords *tert*-butoxy radical.[18] The obtained free radicals subsequently undergo hydrogen atom abstraction from α-position sp^3 C-H of alcohol. The obtained radical **C** attacks the C-5 position sp^2 C-H of 2-acetylthiophene, producing the corresponding free radical **D**. Finally, a hydrogen atom abstraction from radical **D** affords the desired products **3a-l** and **3o-q**.



Scheme 3. Proposed Reaction Mechanism

When ethylene glycol is used as the alcohol substrate, the reaction proceeds through a different mechanism and leads to the formation of **3e** with (1,3-dioxolan-2-yl)methyl substituent at C-5 position (Scheme 4). First, radical intermediate **E** is formed under the reaction conditions[19] via hydrogen atom abstraction from ethylene glycol by *tert*-butoxy radical. 2-acetylthiophene undergoes the reaction with **E** to give 5-acetylthiophene-2-carbaldehyde **F.** Then, a reaction between **F** and ethylene glycol gives the corresponding product **3e.**



Scheme 4. Proposed Reaction Mechanism for Ethylene Glycol as the Alcohol Substrate

Conclusions

In conclusion, we have developed a novel, simple, regioselective, facile and highly efficient method for the direct C-2 alkylation of non-basic nitrogen-free heterocycles as well as basic nitrogen-containing ones like substituted pyridines with various alcohols and cyclic ethers under metal- and acid-free reaction conditions in the presence of di-*tert*-butyl peroxide to generate the corresponding products in good to high yields.

Experimental Section

General Information. Unless otherwise noted, materials obtained from commercial suppliers (Merck and Sigma-aldrich) were used without further purification. Solvents were freshly distilled prior to use. TLC analyses were performed on commercial plates bearing 0.25-mm layer of Merck Silica gel 60 F254. The products were purified by Silica gel 60 PF_{254} for preparative thin layer chromatography (Merck). ^{1}H and ^{13}C NMR spectra were recorded on Bruker DPX 300, 400 and 500 MHz spectrometers in $CDCl_3$; δ in ppm and J in Hz. Mass spectrometry was performed with an Agilent 5975C VL MSD (ion source: EI+, 70 eV, 230 °C). High resolution mass spectra were obtained with a Kratos Concept IIH mass spectrometer.

General procedure for the CDC reaction of non-basic heterocycles with alcohols/ethers. A 10-mL sealable reaction tube equipped with a magnetic stirrer bar was charged with non-basic heterocycle (1 equiv, 0.3 mmol), DTBP (4 equiv, 1.2 mmol) and alcohol/ether (2.0 mL). The tube was then sealed and placed in an oil bath, which was preheated to 130 °C. After stirring the mixture at this temperature for 10 hours, it was cooled to room temperature and diluted with ethyl acetate, washed with brine and dried over anhydrous $MgSO_4$. The organic layer was then concentrated in vacuo. Finally, the resulting residue was subjected to preparative thin layer chromatography plates [Hex/EtOAc, 3:1] to afford the target CDC reaction products.

General procedure for the CDC reaction of substituted pyridines with alcohols. A 10-mL sealable reaction tube equipped with a magnetic stirrer bar was charged with substituted pyridine (1 equiv, 0.3 mmol), DTBP (4 equiv, 1.2 mmol), alcohol (0.5 mL) and PhCl:DMSO (2:1) (1.5 mL). The tube was then sealed and placed in an oil bath, which was preheated to 130 °C. After stirring the mixture at this temperature for 10 hours, the mixture was diluted with CH_2Cl_2 and washed with brine. The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. Finally, the resulting residue was subjected to preparative thin layer chromatography plates [Hex/EtOAc, 3:1] to afford the target CDC reaction products.

1-(5-(hydroxymethyl)thiophen-2-yl)ethan-1-one (3a). The general procedure was followed using 2-acetylthiophene (0.3 mmol, 38 mg), DTBP (102 mg, 1.2 mmol), methanol (2.0 mL). Purification by preparative thin layer chromatography plates (silica gel, Hex/EtOAc 3:1) gave the final product **3a** as a brown oil (38 mg, 82%); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.57 (d, J = 4 Hz, 1H), 7.01 (d, J = 4 Hz, 1H), 4.85 (s, 2H), 2.53 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 190.9, 153.5, 147.2, 132.5, 125.4, 60.2, 26.6. MS (EI): m/z (%) = 156 (80) $[M]^+$, 141 (100), 127 (40), 113 (46), 97 (21), 85 (78), 69 (19), 57 (22), 43 (89). $C_7H_8O_2S$ (156.2): calcd. C 53.82, H 5.16; found C 53.95, H 5.15.

1-(5-(1-hydroxyethyl)thiophen-2-yl)ethan-1-one (3b). The general procedure was followed using 2-acetylthiophene (0.3 mmol, 38 mg), DTBP (102 mg, 1.2 mmol), ethanol (2.0 mL). Purification by preparative thin layer chromatography plates (silica gel, Hex/EtOAc 3:1) gave the final product **3b** as a brown oil (41 mg, 81%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58 (d, J = 4 Hz, 1H), 7.00 (d, J = 4 Hz, 1H), 5.11 (q, J = 6.6, 1H), 2.54 (s, 3H), 1.60 (d, J = 6.5, 3H). ^{13}C NMR (100 MHz, CDCl3): δ = 190.9 159.4, 142.78, 132.6, 123.9, 66.4, 26.6, 25.4. MS (EI): m/z (%) = 170 (35) $[M]^+$, 155 (70), 127 (100), 111 (27), 85 (15), 65 (14), 43 (71). $C_8H_{10}O_2S$ (170.23): calcd. C 56.45, H, 5.92; found C 56.32, H 5.95.

1-(5-(1-hydroxypropyl)thiophen-2-yl)ethan-1-one (3c). The general procedure was followed using 2-acetylthiophene (0.3 mmol, 38 mg), DTBP (102 mg, 1.2 mmol), n-propanol (2.0 mL). Purification by preparative thin layer chromatography plates (silica gel, Hex/EtOAc 3:1) gave the final product **3c** as a brown oil (42 mg, 77%); IR: ν = 3418, 2966, 2930, 2875, 16474, 1452, 13603, 1276, 1029, 973, 930, 811 (cm^{-1}). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.56 (d, J = 4 Hz, 1H), 6.97 (d, J = 4 Hz, 1H), 4.84 (t, J = 6.5, 1H), 2.52 (s, 3H), 1.83 (m, 2H), 0.96 (t, J = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$); δ = 190.6, 158.1, 142.8, 132.3, 124.3, 71.7, 32.2, 26.5, 9.6. MS (EI): m/z (%) = 184 (11) $[M]^+$, 155 (85), 127 (18), 113 (15), 85 (16), 57 (11), 43 (100). $C_9H_{12}O_2S$ (184.26): calcd. C 58.67, H 6.56; found C 58.59, H, 6.59.

1-(5-(2-hydroxypropan-2-yl)thiophen-2-yl)ethan-1-one (3d). The general procedure was followed using 2-acetylthiophene (0.3 mmol, 38 mg), DTBP (102 mg, 1.2 mmol), 2-propanol (2.0 mL). Purification by

preparative thin layer chromatography plates (silica gel, Hex/EtOAc 3:1) gave the final product **3d** as a viscous brown oil (40 mg, 73%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.52 (d, J = 4 Hz, 1H), 6.97 (d, J = 4 Hz, 1H), 2.50 (s, 3H), 1.65 (s, 6H).^{13}C NMR (100 MHz, $CDCl_3$); δ = 190.6, 141.5, 132.9, 124.2, 114.6, 71.1, 29.6, 25.8. MS (EI): m/z (%) = 184 (12) $[M]^+$, 169 (37), 153 (45), 127 (18), 111 (24), 97 (10), 85 (24), 71 (30), 57 (46), 43 (100). $C_9H_{12}O_2S$ (184.26): calcd. C 58.67, H, 6.56; found C 58.51, H 6.56.

1-(5-(1,2-dihydroxyethyl)thiophen-2-yl)ethan-1-one (3e). The general procedure was followed using 2-acetylthiophene (0.3 mmol, 38 mg), DTBP (102 mg, 1.2 mmol), ethylene glycol (2.0 mL). Purification by preparative thin layer chromatography plates (silica gel, Hex/EtOAc 3:1) gave the final product **3e** as a brown oil (49 mg, 78%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.57 (d, J = 3.6 Hz, 1H), 6.95 (d, J = 3.6 Hz, 1H), 5.14 (t, J = 4, 1H), 3.97 (m, 2H), 3.90 (m, 2H), 3.21 (d, J = 4, 2H), 2.54 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 190.5, 147.2, 143.6, 132.5, 128, 103, 65.2, 35.5, 26.6. MS (EI): m/z (%) = 212 (11) $[M]^+$, 167 (13), 149 (14), 139 (20), 124 (11), 111 (14), 97 (30), 86 (13), 73 (100), 57 (18), 45 (85). $C_{10}H_{12}O_3S$ (212.27): calcd. C 56.58, H 5.70; found C 56.77, H, 5.73.

1-(2-(hydroxymethyl)thiophen-3-yl)ethan-1-one (3f). The general procedure was followed using 3-acetylthiophene (0.3 mmol, 38 mg), DTBP (102 mg, 1.2 mmol), methanol (2.0 mL). Purification by preparative thin layer chromatography plates (silica gel, Hex/EtOAc 3:1) gave the final product **3f** as a brown oil (37 mg, 80%); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.57 (d, J = 3.5 Hz, 1H), 7.01 (d, J = 3.5 Hz, 1H), 4.85 (s, 2H), 2.53 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 191.1, 154.6, 148.7, 133.2, 124.1, 63.2, 25.2. MS (EI): m/z (%) = 156 (80) $[M]^+$, 141 (100), 127 (36), 113 (42), 97 (13), 85 (72), 69 (16), 57 (13), 43 (51). $C_7H_8O_2S$ (156.20): calcd. C 53.82, H 5.16; found C 53.96, H, 5.17.

1-(2-(1-hydroxyethyl)thiophen-3-yl)ethan-1-one (3g). The general procedure was followed using 3-acetylthiophene (0.3 mmol, 38 mg), DTBP (102 mg, 1.2 mmol), ethanol (2.0 mL). Purification by preparative thin layer chromatography plates (silica gel, Hex/EtOAc 3:1) gave the final product **3g** as a brown oil (40 mg, 79%); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.56 (d, J = 4 Hz, 1H), 6.98 (d, J = 4 Hz, 1H), 5.09 (q, J= 6.5 Hz, 1H), 2.52 (s, 3H), 1.58 (d, J = 6.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 190.7, 159.4, 142.7, 132.4, 123.8, 66.3, 26.5, 25.3. MS (EI): m/z (%) = 170 (13) $[M]^+$, 155 (27), 127 (70), 111 (11), 85 (10), 65 (13), 43 (100). $C_8H_{10}O_2S$ (170.23): calcd. C 56.45, H 5.92; found C 56.61, H 5.91.

1-(2-(1-hydroxypropyl)thiophen-3-yl)ethan-1-one (3h). The general procedure was followed using 3-acetylthiophene (0.3 mmol, 38 mg), DTBP (102 mg, 1.2 mmol), n-propanol (2.0 mL). Purification by preparative thin layer chromatography plates (silica gel, Hex/EtOAc 3:1) gave the final product **3h** as a brown oil (40 mg, 73%); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.56 (d, J = 4 Hz, 1H), 6.97 (d, J = 4 Hz, 1H), 4.84 (t, J= 6.5 Hz, 1H), 2.52 (s, 3H), 1.83 (m, 3H), 0.96 (t, J = 6.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 191.7, 157.2, 145.7, 133.1, 124.6, 73.7, 34.1, 26.6, 9.7. MS (EI): m/z (%) = 184 (13) $[M]^+$, 155 (100), 141 (10), 127 (21), 113 (17), 85 (15), 57 (12), 43 (96). $C_9H_{12}O_2S$ (184.26): calcd. C 58.67, H 6.56; found C 58.50, H 6.55.

5-(hydroxymethyl)thiophene-2-carbonitrile (3i). The general procedure was followed using 2-thiophenecarbonitrile (0.3 mmol, 33 mg), DTBP (102 mg, 1.2 mmol), methanol (2.0 mL). Purification by preparative thin layer chromatography plates (silica gel, Hex/EtOAc 3:1) gave the final product **3i** as a yellow oil (31 mg, 75%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.53 (d, J = 3.8 Hz, 1H), 7.00 (d, J = 3.8 Hz, 1H), 4.90 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.9, 137.6, 132.4, 127.8, 124.5, 59.8. MS (EI): m/z (%) = 139 (90) $[M]^+$, 122 (43), 110 (100), 106 (21), 95 (11), 83 (23), 78 (11), 69 (27), 64 (18), 57 (27), 51 (15), 45 (35), 41 (15). C_6H_5NOS (139.18) calcd. C 51.78, H 3.62, N 10.06; found C 51.89, H 3.64, N 10.10.

(3-bromothiophen-2-yl)methanol (3j). The general procedure was followed using 3-bromothiophene (0.3 mmol, 49 mg), DTBP (102 mg, 1.2 mmol), methanol (2.0 mL). Purification by preparative thin layer chromatography plates (silica gel, Hex/EtOAc 3:1) gave the final product **3j** as a brown oil (40 mg, 70%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29 (d, J = 5.0 Hz, 1H), 6.98 (d, J = 5.2 Hz, 1H), 4.83 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 132.4, 130.9, 128.8, 125.4, 68.1. MS (EI): m/z (%) = 193 (15) $[M]^+$, 182 (11), 165 (22), 119 (100), 111 (12), 105 (28), 97 (14), 91 (67), 83 (14), 71 (13), 65 (20), 57 (23), 43 (21). C_5H_5BrOS (193.06) calcd. C 31.11, H 2.61; found C 31.12, H 2.61.

1-(5-(1-hydroxy-2-methylpropan-2-yl)thiophen-2-yl)ethan-1-one (3k). The general procedure was followed using 2-acetylthiophene (0.3 mmol, 38 mg), DTBP (102 mg, 1.2 mmol), 2-methyl-1-propanol (2.0 mL). Purification by preparative thin layer chromatography plates (silica gel, Hex/EtOAc 3:1) gave the final product **3k** as a viscous brown oil (48 mg, 81%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.55 (d, J = 3.6 Hz, 1H), 6.92 (d, J = 3.6 Hz, 1H), 3.58 (s, 2H), 2.48 (s, 3H), 1.37 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$). δ = 190.9, 162.6, 141.9, 132.8, 124.5, 72.8, 40.6, 26.4, 26.1. MS (EI): m/z (%) = 198 (30) $[M]^+$, 181 (10), 167 (100), 153 (19), 139 (34), 125 (30), 111 (20), 97 (27), 85 (14), 69 (10), 55 (14), 43 (74). $C_{10}H_{14}O_2S$ (198.28) calcd. C 60.57, H 7.12; found C 60.73, H 7.15.

1-(2-(1-hydroxy-2-methylpropan-2-yl)thiophen-3-yl)ethan-1-one (3l). The general procedure was followed using 3-acetylthiophene (0.3 mmol, 38 mg), DTBP (102 mg, 1.2 mmol), 2-methyl-1-propanol (2.0 mL). Purification by preparative thin layer chromatography plates (silica gel, Hex/EtOAc 3:1) gave the final product **3l** as a brown oil (48 mg, 80%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.59 (d, J = 3.8 Hz, 1H), 6.96 (d, J = 3.8 Hz, 1H), 3.62 (s, 2H), 2.54 (s, 3H), 1.42 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 191, 162.9, 141.7, 133, 124.5, 72.6, 40.5, 26.4, 26.2. MS (EI): m/z (%) = 198 (15) $[M]^+$, 167 (100), 153 (10), 139 (15), 125 (14), 111 (10), 97 (15), 91 (11), 65 (12), 43 (85). $C_{10}H_{14}O_2S$ (198.28): calcd. C 60.57, H 7.12; found C 60.65, H 7.09.

1-(5-(hydroxymethyl)furan-2-yl)ethan-1-one (3o). The general procedure was followed using 2-acetylfuran (0.3 mmol, 33 mg), DTBP (102 mg, 1.2 mmol), methanol (2.0 mL). Purification by preparative thin layer chromatography plates (silica gel, Hex/EtOAc 3:1) gave the final product **3o** as a brown oil (34 mg, 80%); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.13 (d, J = 3.5 Hz, 1H), 6.43 (d, J = 3.5 Hz, 1H), 4.68 (s, 2H), 2.45 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 186.6, 158.9, 152.2, 118.5, 109.6, 57.5, 25.7; MS (EI): m/z (%) = 140 (60) $[M]^+$, 125 (60), 111 (15), 97 (58), 81 (12), 69 (62), 51 (18), 43 (100). $C_7H_8O_3$ (140.14) calcd. C 60.00, H 5.75; found C 59.84, H 5.77.

1-(5-(1-hydroxyethyl)furan-2-yl)ethan-1-one (3p). The general procedure was followed using 2-acetylfuran (0.3 mmol, 33 mg), DTBP (102 mg, 1.2 mmol), ethanol (2.0 mL). Purification by preparative thin layer chromatography plates (silica gel, Hex/EtOAc 3:1) gave the final product **3p** as a brown oil (37 mg, 81%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.14 (d, J = 3.5 Hz, 1H), 6.41 (d, J = 3.5 Hz, 1H), 4.93 (q, J =6.6 Hz, 1H), 2.47 (s, 3H), 1.58 (d, J = 6.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 186.7, 162.6, 151.7, 118.7, 107.5, 63.7, 25.8, 21.4. MS (EI): m/z (%) = 154 (25) $[M]^+$, 139 (52), 121 (14), 111 (72), 97 (21), 83 (29), 69 (10), 55 (32), 43 (100). $C_8H_{10}O_3$ (154.16): calcd. C 62.33, H 6.54; found C 62.41, H 6.56.

1-(5-(1-hydroxypropyl)furan-2-yl)ethan-1-one (3q). The general procedure was followed using 2-acetylfuran (0.3 mmol, 33 mg), DTBP (102 mg, 1.2 mmol), n-propanol (2.0 mL). Purification by preparative thin layer chromatography plates (silica gel, Hex/EtOAc 3:1) gave the final product **3q** as a brown oil (38 mg, 75%); IR 3449, 2966, 2934, 2877, 1668, 1514, 1359, 1294, 1204, 1098, 1020, 974, 804, 630 (cm-1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.13 (d, J = 3.5 Hz, 1H), 6.39 (d, J = 3.5 Hz, 1H), 4.67 (t, J = 6.5 Hz, 1H), 2.44 (s, 3H), 1.82 (m, 2H), 0.96 (t, J = 7.5, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 186.5, 162, 151.7, 118.5, 108.1, 69.1, 28.7, 25.7, 9.5; MS (EI) m/z (relative intensity %) 168 (16) $[M]^+$, 151 (12), 139 (83), 125 (10), 111 (10), 97 (23), 69 (12), 57 (10), 43 (100). $C_9H_{12}O_3$ (168.19): calcd. C 64.27, H 7.19; found C 64.07, H 7.17.

1-(5-(1,4-dioxan-2-yl)thiophen-2-yl)ethan-1-one (4a). The general procedure was followed using 2-acetylthiophene (0.3 mmol, 38 mg), DTBP (102 mg, 1.2 mmol), 1,4-dioxane (2.0 mL). Purification by preparative thin layer chromatography plates (silica gel, Hex/EtOAc 3:1) gave the final product **4a** as a brown oil (51 mg, 80%); ^{1}H NMR (400 MHz,

$CDCl_3$): δ = 7.57 (d, J = 4 Hz, 1H), 6.98 (d, J = 4 Hz, 1H), 4.83 (dd, J = 9.6 & 2.7 Hz, 1H), 3.94 (d, J = 2.8 Hz, 1H), 3.87 (m, 2H), 3.68 (m, 2H), 3.50 (m, 1H), 2.52 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 190.6, 149.8, 143.6, 132.2, 125, 73.6, 71.9, 66.8, 66.2, 26.7. MS (EI): m/z (%) = 212 (57) $[M]^+$, 183 (12), 169 (17), 154 (29), 139 (100), 111 (218), 97 (14), 86 (26), 73 (15), 65 (11), 57 (10), 43 (60). $C_{10}H_{12}O_3S$ (212.27): calcd. C 56.58, H 5.70; found C 56.42, H 5.71.

1-(5-(tetrahydrofuran-2-yl)thiophen-2-yl)ethan-1-one (4b). The general procedure was followed using 2-acetylthiophene (0.3 mmol, 38 mg), DTBP (102 mg, 1.2 mmol), tetra-hydrofuran (2.0 mL). Purification by preparative thin layer chromatography plates (silica gel, Hex/EtOAc 3:1) gave the final product **4b** as a brown oil (48 mg, 81%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.57 (d, J = 4 Hz, 1H), 6.95 (d, J = 4 Hz, 1H), 5.13 (t, J = 6.4 Hz, 1H), 4.04 (q, J = 6.8, 1H), 3.89 (q, J = 8.1, 1H), 3.07 (t, J = 7 Hz, 1H), 2.60 (s, 3H), 1.98 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 190.8, 157.3, 142.6, 132.6, 124.1, 76.7, 68.7, 34.8, 26.6, 25.8. MS (EI): m/z (%) = 196 (72) $[M]^+$, 179 (29), 153 (100), 111 (10), 71 (12), 43 (18). $C_{10}H_{12}O_2S$ (196.27): calcd. C 61.20, H 6.16; found C 61.33, H 6.19.

1-(5-(1,3-dioxolan-2-yl)thiophen-2-yl)ethan-1-one (4c). The general procedure was followed using 2-acetylthiophene (0.3 mmol, 38 mg), DTBP (102 mg, 1.2 mmol) and 1,3-dioxolane (2.0 mL). Purification by preparative thin layer chromatography plates (silica gel, Hex/EtOAc 3:1) gave the final product **4c** as a brown oil (49 mg, 82%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.17 (d, J = 4.5 Hz, 1H), 7.05 (d, J = 4.5 Hz, 1H), 5.08 (s, 1H), 4.12 (m, 2H), 4.05 (m, 2H), 2.56 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 190.6, 152.2, 143.9, 132.3, 125.4, 95.9, 65.3, 26.6. MS (EI): m/z (%) = 198 (13) $[M]^+$, 184 (15), 167 (43), 149 (100), 127 (15), 113 (18), 97 (16), 83 (22), 71 (42), 57 (74), 43 (57). $C_9H_{10}O_3S$ (198.24): calcd. C 54.53, H 5.08; found C 54.38, H 5.11.

(6-phenylpyridin-2-yl)methanol (6a). The general procedure was followed using 2-phenylpyridine (0.3 mmol, 47 mg), DTBP (102 mg, 1.2 mmol), methanol (0.5 mL) and PhCl:DMSO (2:1) (1.5 mL). Purification by preparative thin layer chromatography plates (silica gel, Hex/EtOAc 3:1) gave the final product **6a** as a dark yellow oil (39 mg, 70%); IR: v = 3433, 2922, 1577, 1448, 1049, 761, 696 (cm^{-1}). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.99 (d, J = 7.2Hz, 2H), 7.72 (t, J = 7.6 Hz, 1H), 7.62 (d, J = 7.6 Hz, 1H), 7.39 (m, 3H), 7.14 (d, J = 7.6, 1H), 4.80 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.4, 156, 139.5, 138.7, 129.3, 128.8, 126.9, 119.1, 118.8, 63.8; HRMS (EI) m/z calculated for $C_{12}H_{11}O_1N_1$ $[M]^+$: 185.0841. found: 185.0831.

1-(6-phenylpyridin-2-yl)ethan-1-ol (6b). The general procedure was followed using 2-phenylpyridine (0.3 mmol, 47 mg), DTBP (102 mg, 1.2 mmol), ethanol (0.5 mL) and PhCl:DMSO (2:1) (1.5 mL). Purification by preparative thin layer chromatography plates (silica gel, Hex/EtOAc 3:1) gave the final product **6b** as a dark orange oil (45 mg, 75%); IR 3396, 2974, 1577, 1448, 1402, 1112, 1074, 817, 761, 696 (cm^{-1}). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.00 (d, J = 7.2 Hz, 2H), 7.74 (t, J = 8 Hz, 1H), 7.62 (d, J = 8 Hz, 1H), 7.39 (m, 3H), 7.18 (d, J = 8 Hz, 1H), 4.92 (q, J = 6.4 Hz, 1H), 1.53 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.5, 155.5, 138.3, 138, 129.3, 128.7, 126.9, 119, 118.3, 68.4, 24.1. HRMS (ESI^+): calculated for $C_{13}H_{13}O_1N_1$ $[M^+]$: 199.0997. found: 199.1007.

1-(6-phenylpyridin-2-yl)propan-1-ol (6c). The general procedure was followed using 2-phenylpyridine (0.3 mmol, 47 mg), DTBP (102 mg, 1.2 mmol), n-propanol (0.5 mL) and PhCl:DMSO (2:1) (1.5 mL). Purification by preparative thin layer chromatography plates (silica gel, Hex/EtOAc 3:1) gave the final product **6c** as a dark orange oil (45 mg, 71 %); IR: v = 3406, 2966, 2927, 2873, 1575, 1452, 1409, 1083, 981, 813, 761, 694, 624 (cm^{-1}). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.99 (d, J = 7.2 Hz, 2H), 7.70 (t, J = 8 Hz, 1H), 7.60 (d, J = 8 Hz, 1H), 7.40 (m, 3H), 7.14 (d, J = 8 Hz, 1H), 4.72 (dd, J=7.2 Hz, 1H), 1.89 (m, 1H), 1.70 (m, 1H), 0.95 (t, J = 7.2, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.5, 155.6, 138.7, 137.4, 129.1, 128.7, 126.9, 118.8, 118.8, 73.4, 31.3, 9.3. MS (EI): m/z (%) = 213 (58) $[M]^+$, 198 (24), 196 (75), 184 (100), 169 (26), 154 (98), 127 (46), 102 (16), 78 (35), 51 (25), 40 (10). $C_{14}H_{15}NO$ (213.28): calcd. C 78.84, H 7.09, N 6.57; found C 78.72, H 7.05, N 6.53.

1-(6-phenylpyridin-2-yl)butan-1-ol (6d). The general procedure was followed using 2-phenylpyridine (0.3 mmol, 47 mg), DTBP (102 mg, 1.2 mmol), n-butanol (0.5 mL) and PhCl:DMSO (2:1) (1.5 mL). Purification by preparative thin layer chromatography plates (silica gel, Hex/EtOAc 3:1) gave the final product **6d** as a brown oil (46 mg, 68%); IR: v = 3408, 3060, 2956, 2869, 1575, 1450, 1407, 1307, 1116, 1072, 1029, 912, 815, 759, 694, 624 (cm^{-1}). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.99 (d, J = 8 Hz, 2H), 7.74 (t, J = 8 Hz, 1H), 7.62 (d, J = 8 Hz, 1H), 7.39 (m, 3H), 7.17 (d, J = 8 Hz, 1H), 4.80 (dd, J = 7.6 Hz,1H), 1.79 (m, 1H), 1.69 (m, 1H), 1.46 (m, 2H), 0.92 (t, J = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.8, 161.8, 155.5, 137.8, 129.3, 128.7, 127, 119.1, 118.8, 72.1, 40.7, 18.5, 14. MS (EI): m/z (%) 227 (10) $[M]^+$, 210 (17), 196 (10), 184 (100), 169 (44), 153 (44), 127 (21), 77 (16). $C_{15}H_{17}NO$ (227.30): calcd. C 79.26, H 7.54, N 6.16; found C 79.41, H 7.49, N 6.13.

(6-(3-methoxyphenyl)pyridin-2-yl)methanol (6e). The general procedure was followed using 2-(3-methoxyphenyl)pyridine (0.3 mmol, 56 mg), DTBP (102 mg, 1.2 mmol), methanol (0.5 mL) and PhCl:DMSO (2:1) (1.5 mL). Purification by preparative thin layer chromatography plates (silica gel, Hex/EtOAc 3:1) gave the final product **6e** as a dark yellow oil (45 mg, 70%); IR: v = 3394, 2927, 1579, 1460, 1313, 1288, 1224, 1164, 1045, 993, 864, 783, 698, 624 (cm^{-1}). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71 (t, J = 7.6 Hz, 1H), 7.53 (m, 3H), 7.34 (t, J = 7.6 Hz, 1H), 7.13 (d, J = 7.6 Hz, 1H), 6.94 (d, J = 7.6 Hz, 1H), 4.78 (s, 2H), 3.86 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160, 158.4, 155.7, 148.6, 137.4, 129.7, 129.6, 120, 119.7, 114.7, 112.4, 63.9, 55.3. HRMS (ESI^+): calculated for $C_{13}H_{13}O_2N_1$ $[M^+]$: 215.0946. found: 215.0957.

1-(6-(3-methoxyphenyl)pyridin-2-yl)ethan-1-ol (6f). The general procedure was followed using 2-(3-methoxyphenyl)pyridine (0.3 mmol, 56 mg), DTBP (102 mg, 1.2 mmol), ethanol (0.5 mL) and PhCl:DMSO (2:1) (1.5 mL). Purification by preparative thin layer chromatography plates (silica gel, Hex/EtOAc 3:1) gave the final product **6f** as a dark yellow oil (49 mg, 72%); IR: v = 3408, 2970, 2929, 2839, 1575, 1461, 1404, 1315, 1286, 1224, 1161, 1114, 1078, 1043, 875, 783, 700, 624 (cm^{-1}). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.72 (t, J = 7.6 Hz. 1H), 7.55 (m, 3H), 7.35 (t, J = 8 Hz, 1H), 7.19 (d, J = 7.6 Hz, 1H), 6.95 (dd, J = 8 & 1.6, 1H), 4.92 (q, J = 6.4 Hz, 1H), 3.87 (s, 3H), 1.53 (d, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.4, 160, 155.3, 140.1, 137.8, 129.7, 119.3, 119.2, 118.5, 114.8, 112.5, 68.4, 55.4, 24.2; HRMS (ESI^+): calculated for $C_{14}H_{15}O_2N_1$ $[M^+]$: 229.1103. found: 229.1120.

1-(6-(m-tolyl)pyridin-2-yl)propan-1-ol (6g). The general procedure was followed using 2-(m-tolyl)pyridine (0.3 mmol, 51 mg), DTBP (102 mg, 1.2 mmol), n-propanol (0.5 mL) and PhCl:DMSO (2:1) (1.5 mL). Purification by preparative thin layer chromatography plates (silica gel, Hex/EtOAc 3:1) gave the final product **6g** as an orange oil (50 mg, 73%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.84 (s, 1H), 7.79 (d, J = 7.5 Hz, 1H), 7.72 (t, J = 8 Hz, 1H), 7.62 (d, J = 8 Hz, 1H), 7.35 (t, J = 7.5 Hz, 1H), 7.23 (d, J = 8 Hz, 1H), 7.15 (d, J = 7.5 Hz, 1H), 4.84 (t, J = 6.5 Hz, 1H), 2.44 (s, 3H), 1.90 (m, 1H), 1.72 (m, 1H), 0.97 (t, J = 6.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.5, 158.8, 142.5, 142.2, 137.3, 129.8, 128.6, 127.6, 124, 118.8, 118.6, 73.4, 31.4, 21.5, 9.3. MS (EI): m/z (%) 227 (15) $[M]^+$, 212 (34), 196 (74), 198 (100), 170 (43), 141 (15), 128 (10), 115 (15), 91 (23), 77 (10), 65 (15), 51 (10), 43 (10). $C_{15}H_{17}NO$ (227.30): calcd. C 79.26, H 7.54, N 6.16; found C 79.38, H 7.52, N, 6.12.

(5-phenylpyridin-2-yl)methanol (6h). The general procedure was followed using 3-phenylpyridine (0.3 mmol, 47 mg), DTBP (102 mg, 1.2 mmol), methanol (0.5 mL) and PhCl:DMSO (2:1) (1.5 mL). Purification by preparative thin layer chromatography plates (silica gel, Hex/EtOAc 3:1) gave the final product **6h** as a brown oil (41 mg, 73%); IR: v = 3192, 2922, 2854, 1595, 1473, 1442, 1375, 1072, 1016, 759, 692 (cm^{-1}). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.84 (s, 1H), 8.15 (d, J = 7.5 Hz, 1H), 7.56 (m, 3H), 7.42 (m, 3H), 4.98 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.4, 142.5, 139.2, 135.3, 129.5, 129.3, 127.1, 122.8, 62.2. HRMS (ESI^+): m/z calculated for $C_{12}H_{11}O_1N_1$ $[M^+]$: 185.0841. found: 185.0850.

1-(5-phenylpyridin-2-yl)ethan-1-ol (6i). The general procedure was followed using 3-phenylpyridine (0.3 mmol, 47 mg), DTBP (102 mg, 1.2 mmol), ethanol (0.5 mL) and PhCl:DMSO (2:1) (1.5 mL). Purification by

preparative thin layer chromatography plates (silica gel, Hex/EtOAc 3:1) gave the final product **6i** as a brown oil (42 mg, 70%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.78 (s, 1H), 7.90 (dd, J = 8 & 1.9 Hz, 1H), 7.60 (dd, J = 5 & 1.9 Hz, 2H), 7.49 (m, 2H), 7.39 (m, 2H), 4.97 (q, J = 6.5 Hz, 1H), 1.57 (d, J = 6.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162, 146.5, 137.5, 135.44, 129.1, 128.1, 127.1, 119.8, 68.9, 24.2. MS (EI): m/z (%) = 199 (15) $[M]^+$, 184 (100), 156 (92), 154 (45), 127 (26), 102 (10), 77 (15), 51 (11), 43 (10). $C_{13}H_{13}NO$ (199.25): calcd. C 78.36, H 6.58, N 7.03; found C 78.59, H 6.62, N 7.08.

1-(5-phenylpyridin-2-yl)propan-1-ol (6j). The general procedure was followed using 3-phenylpyridine (0.3 mmol, 47 mg), DTBP (102 mg, 1.2 mmol), n-propanol (0.5 mL) and PhCl:DMSO (2:1) (1.5 mL). Purification by preparative thin layer chromatography plates (silica gel, Hex/EtOAc 3:1) gave the final product **6j** as a brown oil (45 mg, 71%); IR: v = 3392, 2960, 2923, 2860, 1593, 1471, 1450, 1371, 1332, 1107, 1043, 977, 912, 844, 748, 688 (cm^{-1}). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.77 (s, 1H), 7.95 (dd, J = 8.4 & 1.6 Hz, 1H), 7.55 (d, J = 7.6 Hz, 2H), 7.45 (t, J = 7.6, 2H), 7.39 (m, 2H), 4.80 (dd, J = 6.8 Hz, 1H), 1.90 (m, 1H), 1.76 (m, 1H), 0.95 (t, J = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.4, 145, 136.6, 136, 129.2, 128.4, 127, 121, 73.3, 31.2, 9.5. HRMS (ESI^+): calculated for $C_{14}H_{15}O_1N_1$ $[M]^+$: 213.1154. found: 213.1157.

1-(4-benzylpyridin-2-yl)ethan-1-ol (6k). The general procedure was followed using 4-benzylpyridine (0.3 mmol, 51 mg), DTBP (102 mg, 1.2 mmol), ethanol (0.5 mL) and PhCl:DMSO (2:1) (1.5 mL). Purification by preparative thin layer chromatography plates (silica gel, Hex/EtOAc 3:1) gave the final product **6k** as a brown oil (47 mg, 73%); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.40 (d, J = 5 Hz, 1H), 7.24 (m, 3H), 7.16 (d, J = 7.5 Hz, 2H), 7.09 (s, 1H), 6.99 (d, J = 5 Hz, 1H), 4.81 (q, J = 6.5 Hz, 1H), 3.97 (s, 2H), 1.46 (d, J = 6.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.3, 150.9, 148.1, 138.7, 129, 128.7, 126.7, 122.8, 120.1, 68.8, 41.3, 24.2. MS (EI): m/z (%) = 213 (12) $[M]^+$, 210 (23), 199 (100), 183 (15), 168 (23), 154 (11), 141 (10), 115 (10), 78 (11), 43 (10). $C_{14}H_{15}NO$ (213.28): calcd. C 78.84, H 7.09, N 6.57; found C 78.65, H 7.04, N 6.52.

2-methyl-2-(6-phenylpyridin-2-yl)propan-1-ol (6l). The general procedure was followed using 2-phenylpyridine (0.3 mmol, 47 mg), DTBP (102 mg, 1.2 mmol), 2-methyl-1-propanol (0.5 mL) and PhCl:DMSO (2:1) (1.5 mL). Purification by preparative thin layer chromatography plates (silica gel, Hex/EtOAc 3:1) gave the final product **6l** as a brown oil (48 mg, 71%); IR: v = 3386, 3062, 2962, 2869, 1573, 1448, 1267, 1043, 763, 698, 623 (cm^{-1}). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.91 (d, J = 7.2 Hz, 2H), 7.71 (t, J = 7.6 Hz, 1H), 7.56 (d, J = 8 Hz, 1H), 7.40 (m, 3H), 7.24 (d, J = 8 Hz, 1H), 3.81 (s, 2H), 1.36 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.1, 160, 155.5, 138, 129.1, 128.9, 126.8, 118.8, 118.2, 72, 41.2, 25.7. MS (EI): m/z (%) = 227 (10) $[M]^+$, 222 (10), 210 (100), 208 (30), 197 (37), 196 (56), 182 (20), 169 (15), 154 (15), 127 (13), 91 (16), 76 (17), 57 (10). $C_{15}H_{17}NO$ (227.30): calcd. C 79.26, H 7.54, N 6.16; found C 79.45, H 7.59, N 6.12.

2-methyl-2-(5-phenylpyridin-2-yl)propan-1-ol (6m). The general procedure was followed using 3-phenylpyridine (0.3 mmol, 47 mg), DTBP (102 mg, 1.2 mmol), 2-methyl-1-propanol (0.5 mL) and PhCl:DMSO (2:1) (1.5 mL). Purification by preparative thin layer chromatography plates (silica gel, Hex/EtOAc 3:1) gave the final product **6m** as a brown oil (168 mg, 74%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.71 (d, J = 2.4 Hz, 1H), 7.86 (dd, J = 8.2 & 2.4 Hz, 1H), 7.56 (m, 2H), 7.43 (m, 2H), 7.39 (m, 2H), 3.81 (s, 2H), 1.40 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167, 146.2, 137.5, 135.3, 134.2, 129.1, 128, 127, 120.3, 72.1, 41, 25.6. MS (EI): m/z (%) = 227 (20) $[M]^+$, 210 (58), 196 (100), 182 (28), 154 (19), 127 (22), 102 (10), 77 (16), 51 (15), 41 (15). $C_{15}H_{17}NO$ (227.30): calcd. C 79.26, H 7.54, N 6.16; found C 79.11, H 7.57, N 6.19.

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Keywords: heterocycles • alcohols • alkylation • C-C coupling • C-H activation

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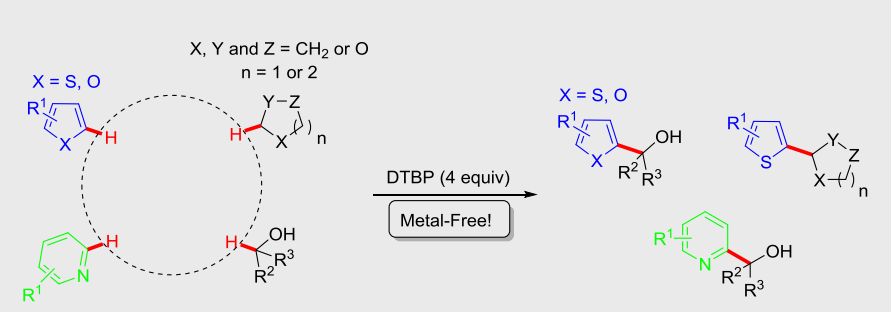
Full Paper

A metal-free direct alkylation of non-basic nitrogen-free heterocycles as well as basic nitrogen-containing ones with alcohols and cyclic ethers in the presence of di-*tert*-butyl peroxide is described.



Cross Dehydrogenative Coupling, Hydroxyalkylation

Ebrahim Kianmehr, Maryam Fardpour and Khalid Mohammed Khan*

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Direct Regioselective Alkylation of Non-Basic and Basic Heterocycles with Alcohols and Cyclic Ethers through a Dehydrogenative Cross-coupling Reaction under Metal-Free Conditions