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The Pd(II)-catalyzed acetoxylation of the *ortho* C−H bond of benzyl amines, γ and remote δ C(3)−H bond of 2-/3-(aminoalkyl)-thiophenes

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Abstract: The Substituted thiophenes are important synthetic building blocks in the research areas of materials and organic chemistry, medicinal chemistry and drug development. Various thiophene based molecules were found to be biologically active compounds. We present, reagents and chemical methodologies for the synthesis of Regioselective C(3)-H acetoxylation of 2-(aminoethyl)-thiophene systems by using various bidentate directing groups. several thiophene-based biaryl derivatives were reported to show a range of biological activities and considered as medicinally important compounds. Further, thiophene-based biaryl derivatives are used as building blocks in organic materials and organic synthesis

Keywords: Pd $(OAc)_2$, Regioselective Acetoxylation, Picolinamide,$PhI(OAc)_2$.

INTRODUCTION:

Substituted thiophenes are important synthetic building blocks in the research areas of materials and organic chemistry, medicinal chemistry and drug development. Various thiophene based molecules were found to be biologically active compounds. Though the Pd-catalyzed direct introduction of aryl groups or alkyl groups at the C-H bonds of furan- and thiophene-based systems was explored well, the direct C-H oxygenation of the C-H bonds furan-and thiophene-based systems is not explored well. For example, the direct C-H acetoxylation of thiophene system will afford the corresponding C-H acetoxylated thiophene systems (Figure 1).

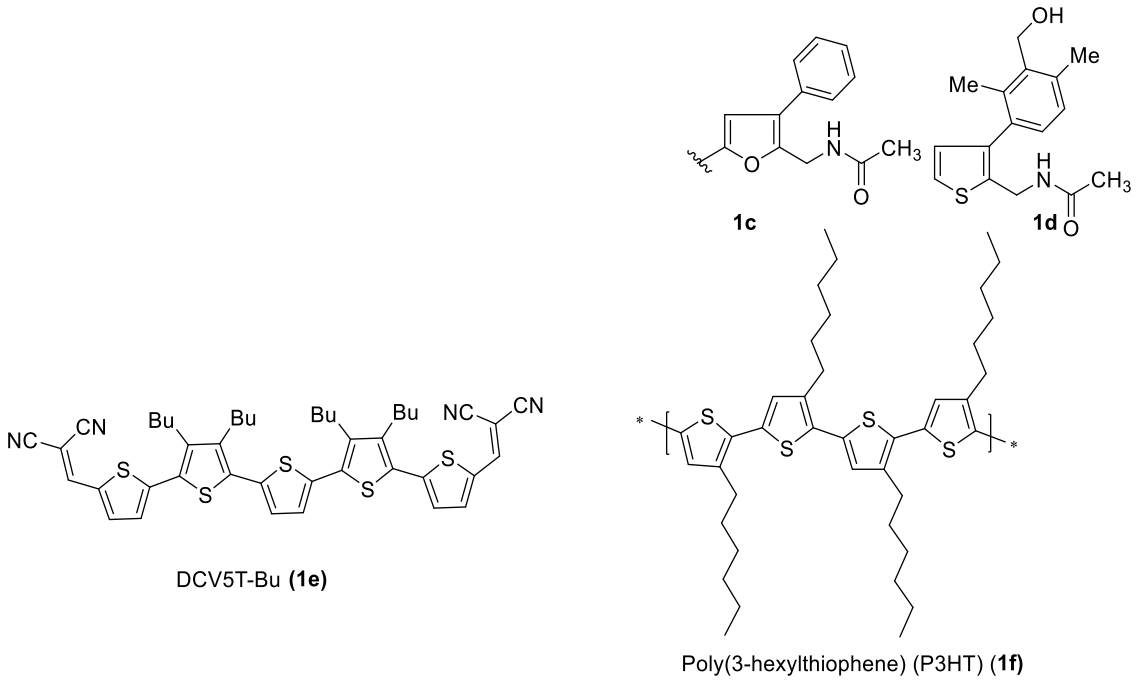


Figure 1. Biologically active and organic material molecules-based on thiophene

The direct C-H activation/arylation of the C2 or C5 positions of thiophenes and related heteroaromatic substrates have received much attention. Various research groups including our group reported the regioselective C3 arylation/functionalization of thiophenes/furans involving the bidentate ligand-directed regioselective C−H activation/functionalization route.

Given the noteworthy progress that has been made with regard to the oxygenation C–H bonds of aryl systems (e.g., aromatic carboxamides, aryl amines and benzylamines) by using various directing groups; however, the direct C-H oxygenation of the C-H bonds of thiophene compounds has been not explored well.

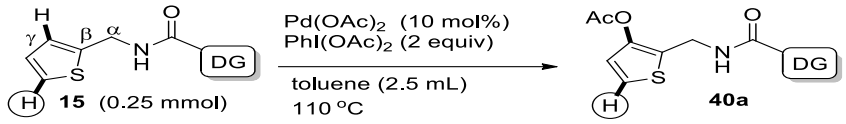
Given the importance of the functionalized thiophenes in various research areas, studying the regioselective acetoxylations of C(sp^2)–H of thiophene systems using directing groups will be very useful. Accordingly, with a desire to foster the regioselective C3 functionalization of thiophenes and in continuation the C-H activation reactions and finding new directing groups, it envisages to examine the Pd-catalyzed highly regioselective C-H acetoxylation of the C3-position of the 2- 3-(aminoalkyl)-thiophene and furfurylamine and derived amides by using the unexplored/less explored directing groups, such as, pyrazine- or quinoline-2-carboxamides. Further, these directing groups were also examined to perform the acetoxylation of the *ortho* C−H bond of benzyl amines under simple reaction conditions and short reaction period (toluene at 110 ^{o}C for 3+-9 h).

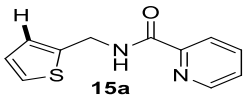
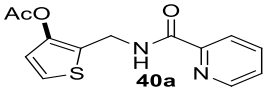
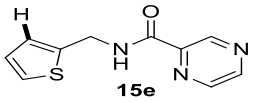
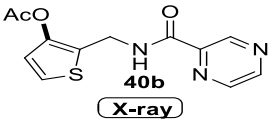
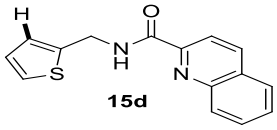
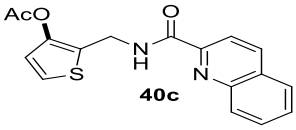
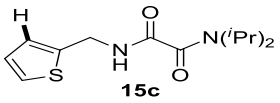
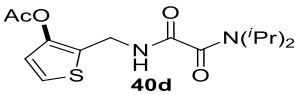
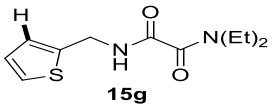
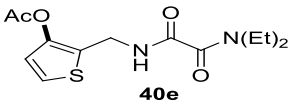
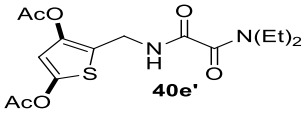
RESULTS AND DISCUSSION:

In continuation of our work, we have investigated generally, the C(3)-H and C(4)-H bonds of thiophene system are relatively less reactive when compared to C(2)-H and C(5)-H bonds and the direct arylation/functionalization of the C(2)-H and C(5)-H bonds of thiophenes is well documented. In the

present case, the C-H acetoxylations of thiophene compounds **15** (Table 1) selectively occurred at the C(3)-H bond with the help of the corresponding bidentate directing groups.

Table1. Bidentate directing group-enabled regioselective C(3)–H acetoxylation of 2-(aminomethyl)-thiophenes.



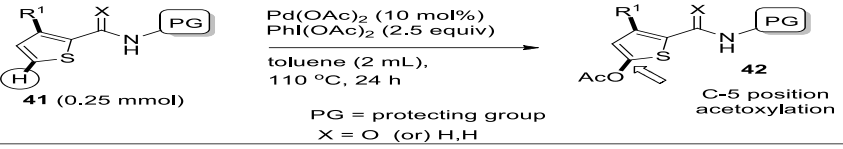
entry	substrate	acetoxylation Product	time (h)	yield (%)
1	 **15a**	 **40a**	12	56[a]
2	 **15e**	 **40b** **X-ray**	6	61[a]
3	 **15d**	 **40c**	3	78
4	 **15c**	 **40d**	2	48
5	 **15g**	 **40e** +  **40e'**	2	**40e**; 57 & **40e'**; 17 **40e** + **40e'** = 74

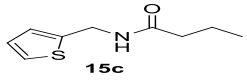
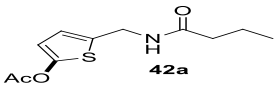
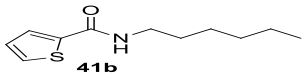
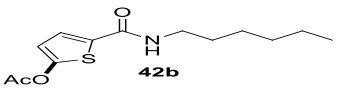
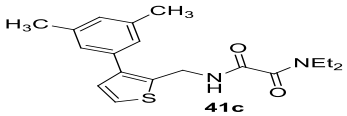
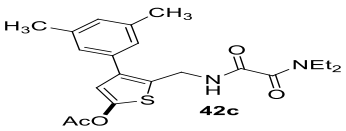
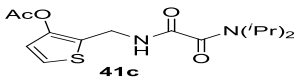
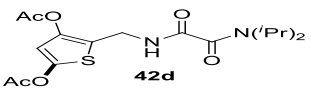
[a]The reaction was carried out by using 1:1 Gla.AcOH and Ac_2O.

Having observed the formation of the C3 and C5-acetoxylated product **40e′** (Table 1) that might have formed after the C3-acetoxylation of the 2-(aminomethyl)-thiophene system **40e**, then, it was envisaged to investigate the selective C5-acetoxylation of 2-(aminomethyl)-thiophene system. In this regard, the 2-(aminomethyl)-thiophene systems that are not having any directing groups **15c**, **41b** or thiophene systems **41c,d** having a substitution at the C3-positionwere assembled(Table 2). The C-H acetoxylation of the 2-(aminomethyl)-thiophene system**15c** in the presence of $PhI(OAc)_2$ and $Pd(OAc)_2$ catalyst in toluene at 110 °C gave the C5-acetoxylated thiophene system **42a** in 40% yield (Table 2). On the other hand, the C-H acetoxylation reaction of thiophene-2-carboxamide **41b** in the presence of $PhI(OAc)_2$ and $Pd(OAc)_2$ catalyst failed to give the corresponding C5-acetoxylated thiophene compound **42b**. Though

the substrates **15c** and **41b** are structurally similar, however, at this stage, an explanation for the failure of the acetoxylation of the substrate **42b** is not known. Along the same line, the acetoxylation reaction of thiophene systems **41c** and **41d** having a substitution at the C3-position in the presence of $PhI(OAc)_2$ and $Pd(OAc)_2$ catalyst in toluene at 110 ^oC gave the corresponding C5-acetoxylated thiophene systems **42c** and **42d** in 40 and 35% yields (Table 2).

Table 2. Directing group free regioselective C(5)–H acetoxylation of various thiophene systems.



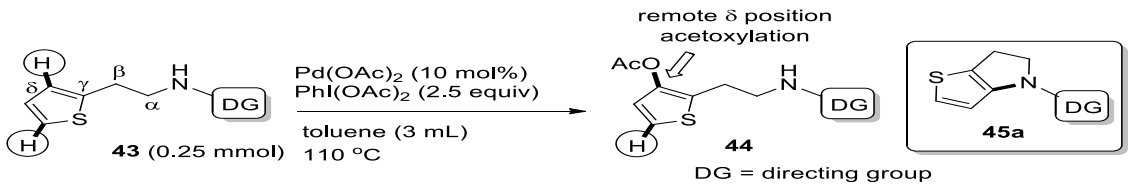
entry	substrate	acetoxylation product	yeld (%)
1	 **15c**	 **42a**	40
2	 **41b**	 **42b**	0
3	 **41c**	 **42c**	40
4	 **41c**	 **42d**	35

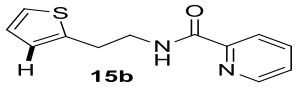
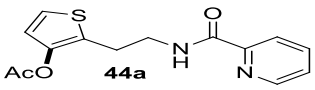
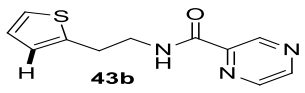
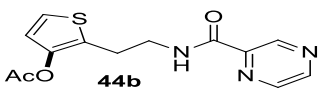
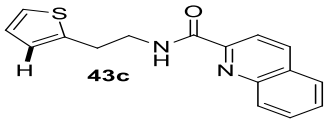
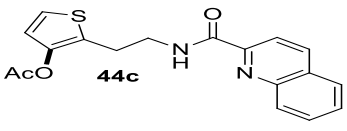
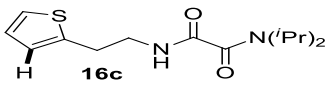
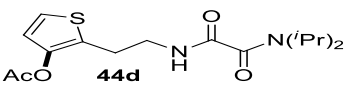
Subsequently, it was envisaged to further expand the substrate scope and the significance of this method comprising Pd-catalyzed C-H acetoxylation of thiophene systems. In this regard, the 2-(aminoethyl)-thiophene systems **11a-d** were prepared by linking 2-(aminoethyl)-thiophene with the corresponding directing groups, such as, picolinamide, pyrazine-2-carboxamide, quinoline-2-carboxamide and oxalylamide (Table 3). It is to be noted that in the thiophene-based amides **7a-e** shown in Table 1, with respect to the amide nitrogen the C(3)-H bond of the thiophene ring is located at the γ position. However, in the thiophene-based amides **11a-d** (Table 3), with respect to the amide nitrogen the C(3)-H bond of the thiophene ring is located at the δ position.It is worth to mention here that a literature survey revealed that the C-H acetoxylation of the sp^2 C-H bond at the γ-position of a designed carboxamide is explored well. On the other hand, the sp^2 C-H acetoxylation of the sp^2 C-H bond at the δ-position of a designed carboxamide is rarely examined. Accordingly, it was envisaged to study the C-H acetoxylation of the thiophene systems **16b,c, 43b,c** (Table 3) which contain the sp^2 C-H bond at the δ-position.

The sp^2 C-H acetoxylation of the sp^2 C-H bond at the δ-position of the 2-(aminoethyl)-thiophene system**16b** containing picolinamide ligand in the presence of $PhI(OAc)_2$ and $Pd(OAc)_2$ catalyst in toluene at 110 ^oC gave the C3-acetoxylated thiophene system **44a** in 27% yield along with the cyclized product **45a** in 20% yield. Similarly, the Pd(II)-catalyzedacetoxylation of the 2-(aminoethyl)-thiophene systems **43b** and **43c** containing the bidentate ligands, such as, pyrazine-2-carboxamide and quinoline-2-carboxamide furnished the corresponding C3-acetoxylated thiophenes **44b** and **44c** in 52 and 43%

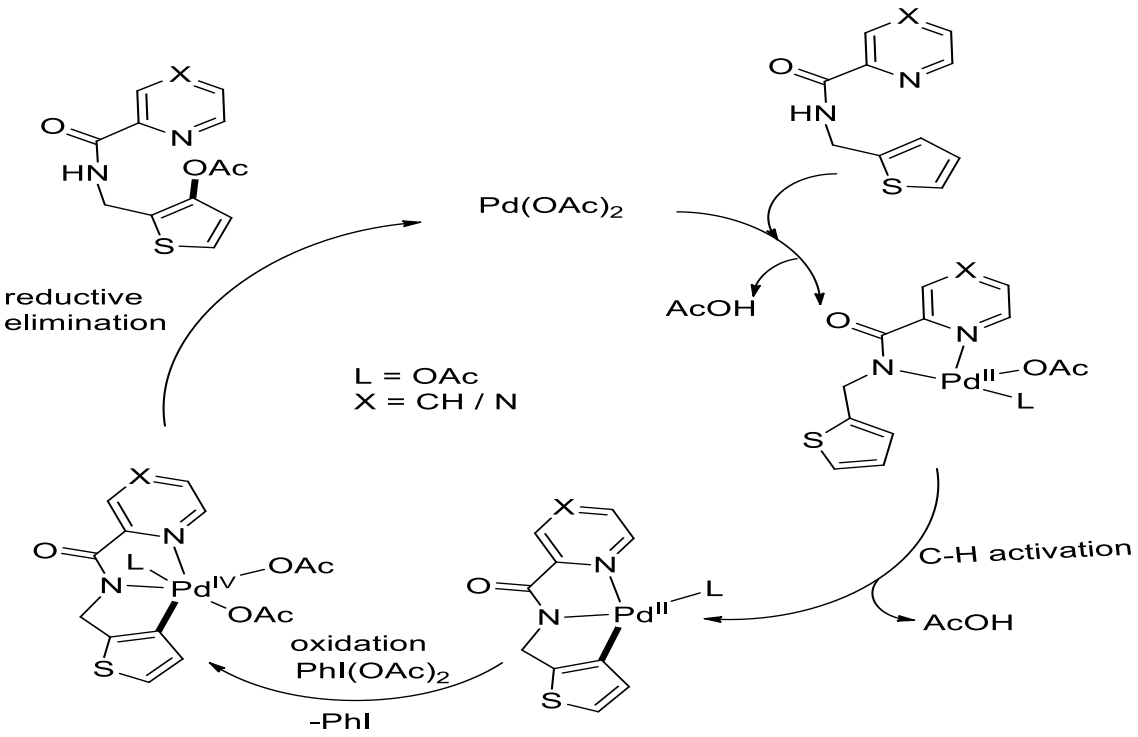
yields. Then the Pd(II)-catalyzed C-H acetoxylation of the 2-(aminoethyl)-thiophene system **16c** containing the oxalylamide directing group failed to give the corresponding C3-acetoxylated products **44d** (Table 3). An exact reason is not clear for the failure of the C-H acetoxylation of **16c**; nevertheless, when compared to the other directing groups used for the C-H acetoxylation of thiophene system shown in Table 3, the oxalylamide directing group may be a weak directing group to assist the acetoxylation of the remote δ C-H bond of the thiophene system **16c**. Except in one case, where the cyclized products **45a** was obtained under the present experimental condition, in other reactions the corresponding cyclized products were not observed under the experimental condition. The observed regioselectivities in the Pd(II)-catalyzed, bidentate ligand-directed, selective C(3)-H acetoxylation of 2- or 3-(aminoalkyl)-thiophenes **15** and **43** and the structure of the regioisomers**40** and **44** were assigned based on the coupling constant (*J*) of values of the doublet peaks of the C4 and C5 protons of the thiophene ring, which were found to be around 5 Hz. Furthermore, the observed regioselectivity in the directing-group aided Pd(II)-catalyzed direct C(3)-H acetoxylation of 2- or 3-(aminoalkyl)-thiophenes and the structures of the representative regioisomer**40b** was unequivocally determined from the single-crystal X-ray structure. The observed *ortho* selective C(3)-H-acetoxylation of 2- or 3-(aminoalkyl)-thiophene derived amides linked with the respective bidentate ligands (e.g., picolinamide) can be exemplified *via* the generally proposed chelation-assisted mechanism comprising the Pd(II/IV) catalytic cycle.

Table 3: Regioselective C(3)–H acetoxylation of 2-(aminoethyl)-thiophene systems by using various bidentate directing groups.



entry	substrate	acetoxylation product	time (h)	yield (%)
1[a]	 **15b**	 **44a**	8	47 **44a**; 27 **45a**; 20
2	 **43b**	 **44b**	72	52
3	 **43c**	 **44c**	48	43
4[b]	 **16c**	 **44d**	3	0

[a] 1.5 Equiv of $PhI(OAc)_2$ was used. [b] This reaction was performed with 2 equiv of $PhI(OAc)_2$ and the reaction afforded a complex inseparable mixture of compounds.



Proposed mechanism (in concurrence generally proposed mechanism) for the regioselective C3-acetoxylation of thiophene system.

CONCLUSION

In summary, we have prepared revealed, (a) the sp^2 C-H acetoxylation of the *ortho* C−H bond of benzyl amines under improved reaction conditions and short reaction period (toluene at 110 ^oC for 3-9 h) with the help of the directing groups, such as, pyrazine- or quinoline-2-carboxamides, (b) then, by using these reaction conditions found for the sp^2 C-H acetoxylation of the *ortho* C−H bond of benzyl amines, the regioselective sp^2C-H acetoxylation of the C3-position of the 2- or 3-(aminoalkyl)-thiophene derived amides was accomplished by using the directing groups, such as, picolinamide, pyrazine- and quinoline-2-carboxamides.

Given the importance of the functionalized thiophenes, this work dealing on the regioselective C-H acetoxylation of 2- or 3-(aminoalkyl)-thiophene systems will be a very useful method to obtain C3-acetoxylated thiophene systems.

All the C-H acetoxylation reactions were regioselective and all the compounds s are characterized by various characterization techniques including ^1H and ^{13}C NMR, IR, X-ray diffraction and HRMS. The structure and observed regioselectivity of representative products were established from the single crystal X-ray structure analyses. The relevant characterization data of all the compounds and complete experimental details are given in the experimental section.

EXPERIMENTAL SECTION

General procedure for the synthesis:

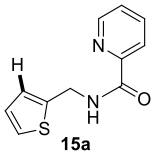
The corresponding carboxylic acid (6 mmol) was dissolved in dry DCM (25 mL) by adding 2 to 3 drops of dry DMF. To this reaction mixture oxalyl chloride (1.5 equiv.) was added at 0 ^oC slowly and the resultant reaction mixture was stirred at rt for 6-8 h under a nitrogen atm. After this period, the reaction

mixture was concentrated in vacuum to remove excess oxalyl chloride and solvent. The resultant acid chloride was dissolved in DCM (25 mL) and this reaction mixture was added to a separate flask which contained the corresponding amine (5 mmol), Et_3N (1.5 equiv, 9 mmol) in DCM (5 mL) at 0 ^oC and the resultant reaction mixture was stirred at rt for 6-8 h under a nitrogen atm. After this period, the reaction mixture was diluted with DCM and then washed with water followed by saturated aqueous $NaHCO_3$ solution. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuum. Purification of the resulting reaction mixture by column chromatography furnished the corresponding carboxamides **15a-e**, **15i**, **16b**, **17** and **18**.

General procedure for the synthesis of carboxamides (34, 37 and 43): The corresponding carboxylic acid (4 mmol) was dissolved in dry DCM (15 mL) by adding 2 to 3 drops of dry DMF. To this reaction mixture oxalyl chloride (1.5 equiv) was added at 0 ^oC slowly and the reaction mixture was stirred for 6-8 h under a nitrogen atmosphere. After this period, the reaction mixture was concentrated in vacuo to remove the excess oxalyl chloride and solvent. The acid chloride was dissolved in DCM (15 mL), this reaction mixture was added to a separate flask which contained the corresponding amine (3 mmol), Et_3N (1.5 equiv) in DCM (5 mL) at 0 ^oC and the reaction mixture was stirred for 6-8 h. After this period of time, the reaction mixture was diluted with dichloromethane and then, washed with water followed by a saturated aqueous $NaHCO_3$ solution. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. Purification of the resulting reaction mixture by silica column chromatography furnished the corresponding carboxamides.

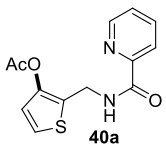
General procedure for the regioselective acetoxylation of compounds: A mixture of the corresponding heterocyclic carboxamides (0.25 mmol), $Pd(OAc)_2$ (10 mol%) and $PhI(OAc)_2$ (2-3 equiv) in anhydrous toluene was heated at 110-130 °C for 2–72 h under a nitrogen atmosphere. After the reaction period, the reaction mixture was concentrated in vacuum and purification of the reaction mixture by silica gel column chromatography gave the corresponding acetoxylated products.

N-(Thiophen-2-ylmethyl)picolinamide **(15a):** Following the general procedure described above **15a** was obtained after purification by column chromatography (EtOAc:Hexane = 30:70); as a brown colored solid (654 mg, 60%); mp: 103-105 ^oC; FT-IR (KBr): 3320, 3058, 1652, 1524, 1292, 703 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.56-8.54 (m, 1H), 8.41 (br s, 1H), 8.25 (dt, 1H, J_1 =7.8, J_2 = 1.0 Hz), 7.88 (td, 1H, J_1 = 7.7, J_2 = 1.7 Hz), 7.46-7.42 (m, 1H), 7.25 (dd, 1H, J_1 = 5.1, J_2 = 1.2 Hz), 7.08-7.06 (m, 1H), 6.98 (dd, 1H, J_1 = 5.1, J_2 = 3.5 Hz), 4.86 (dd, 2H, J_1 = 6.0, J_2 = 0.7 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.0, 149.6, 148.1, 140.8, 137.4, 126.9, 126.3, 126.2, 125.2, 122.4, 38.2; HRMS (ESI) calcd for $C_{11}H_{11}N_2OS$ $[M+H]^+$ 219.0592 found 219.0582.



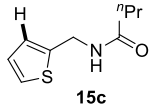
15a

2-(Picolinamidomethyl)thiophen-3-yl acetate **(40a):** Following the general procedure described above **40a**was obtained after purification by column chromatography (EtOAc:Hexane = 45:55); as a dark brown colored semi-solid (39 mg, 56%); FT-IR (DCM): 3380, 3058, 1766, 1673, 1520, 1204, 751 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.55-8.53 (m, 1H), 8.40 (br. s, 1H), 8.22 (dt, 1H, J_1 = 7.8, J_2 = 1.0 Hz), 7.85 (td, 1H, J_1 = 7.7, J_2 = 1.7 Hz), 7.44-7.41 (m, 1H), 7.19 (d, 1H, J = 5.5 Hz), 6.87 (d, 1H, J = 5.5 Hz), 4.70 (d, 2H, J = 6.0 Hz), 2.32 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.0, 164.1, 149.5, 148.2, 144.4, 137.4, 126.3, 125.5, 123.2, 122.4, 121.9, 34.4, 20.8; HRMS (ESI) calcd for $C_{13}H_{12}N_2NaO_3S$ $[M+Na]^+$ 299.0466 found 299.0465.



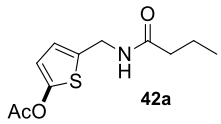
40a

***N-(Thiophen-2-ylmethyl)butyramide*(15c):** Following the general procedure described above **15c** was obtained after purification by column chromatography (EtOAc:Hexane = 30:70); as a colorless solid (750 mg, 82%); mp: 55-57 ^{o}C; FT-IR (KBr): 3399, 2961, 1635, 1548, 1222, 831 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.24 (d, 1H, J = 4.8 Hz), 6.97-6.95 (m, 2H), 5.93 (br s, 1H), 4.62 (d, 2H, J = 5.6 Hz), 2.19 (t, 2H, J = 7.4 Hz), 1.74-1.65 (m, 2H), 0.96 (t, 3H, J = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.7, 141.2, 126.9, 125.9, 125.2, 38.6, 38.2, 19.1, 13.8; HRMS (ESI) calcd for $C_9H_{14}NOS$ $[M+H]^+$ 184.0796 found 184.0790.



15c

***5-(Butyramidomethyl)thiophen-2-yl acetate* (42a):** Following the general procedure described above **42a**was obtained after purification by column chromatography (EtOAc:Hexane = 25:75); as a colorless liquid (24 mg, 40%); FT-IR (DCM): 3301, 2923, 1656, 1539 and 749 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.70 (d, 1H, J = 3.8 Hz), 6.52 (d, 1H, J = 3.8 Hz), 5.85 (br. s, 1H), 4.52 (d, 2H, J = 5.6 Hz), 2.30 (s, 3H), 2.18 (t, 2H, J = 7.3 Hz),1.69 (q, 2H, J = 7.4 Hz), 0.96 (t, 3H, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.7, 167.6, 151.0, 133.4, 122.3, 113.2, 38.7, 38.5, 20.8, 19.1, 13.8; HRMS (ESI) calcd for $C_{11}H_{15}NNaO_3S$ $[M+Na]^+$ 264.0670 found 264.0664.



42a

REFERENCES:

1. Ros, A.; Fernandez, R.; Lassaletta, J. M. *Chem. Soc. Rev.***2014**, *43*, 3229-3243.
2. Li, H.; Li, B.-J.; Shi, Z.-J. *Catal. Sci. Technol.***2011**, *1*, 191-206.
3. Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Rev.***2011**, *111*, 1293-1314.
4.A. R. Dick, K. L. Hull, M. S. Sanford, *J. Am. Chem. Soc.***2004**, *126*, 2300.
5. Kirchberg, S.; Tani, S.; Ueda, K.; Yamaguchi, J.; Studer, A.; Itami, K. *Angew. Chem. Int. Ed.***2011**, *50*, 2387-2391.
6.D.-Tang, D.-T.; Collins, K. D.; Glorius, F. *J. Am. Chem. Soc.* **2013**, *135*, 7450-7453
7. Okazawa, T.; Satoh, T.; Miura, M.; Nomura, M. *J. Am. Chem. Soc.* **2002**, *124*, 5286-5287.
8. Larbi, K. S.; Fu, H. Y.; Laidaoui, N.; Beydoun, K.; Miloudi, A.; Abed, D. E.; Djabbar, S.; Doucet, H. *ChemCatChem***2012**, *4*, 815-823.
9. Shang, R.; Ilies, L.; Asako, S.; Nakamura, E. *J. Am. Chem. Soc.* **2014**, *136*, 14349-14352.
10. Padmavathi, R.; Sankar, R.; Gopalakrishnan, B.; Parella, R.; Babu, S. A. *Eur. J. Org. Chem.* **2015**, 3727-3742.