α -Heteroarylation of Ketones *via* the Umpolung Reaction of *N*-Alkoxyenamine

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A new method has been developed for the umpolung α -heteroarylation of ketones *via* an *N*-alkoxyenamine. The treatment of ketones with tris(heteroaryl)aluminum reagents in the presence of isoxazolidine gave the corresponding α -heteroarylated ketones in moderate to good yields.

Key words umpolung; heteroarylation; *N*-alkoxyenamine; aluminum

Heteroaromatic units are important substructures that can be found in a wide range of both naturally occurring and synthetic organic compounds with important pharmacological activities.^{1–3)} Because of the interesting and important properties of heterocyclic compounds, a number of methodologies for the introduction of heterocycles into α -position of ketones have been reported. The addition-elimination reaction of enolates to electron-deficient hetero-arenes is one of the classical methods.^{4,5)} Several other methods have also been developed for this reaction, including the nucleophilic substitution of α -haloketones and α -pseudo haloketones with electron-rich arenes,^{6–9)} the direct coupling of enolates and electron-rich arenes using a single-electron-transfer (SET) process,^{10–12)} and the transition-metal catalyzed coupling of enolates with aryl halides.^{13–16)} The scope and overall utility of these reactions, however, have been limited by their requirement for strong bases and high temperatures.

We interested in developing alternative methods for the efficient construction of α -heteroarylated ketones that would provide facile access to these compounds and allow them to be used in further synthetic applications. We recently reported the development of a procedure for the umpolung α -arylation of ketones, which was triggered by the reaction of *N*-alkoxyenamines with triarylaluminum reagents.^{17,18)} It was envisaged that the use of heteroarylaluminum reagents **3** under these conditions would allow for the α -heteroarylation of ketones with electron-rich heteroaryl groups to give **2** (Chart 1). The application of this method to *N*-alkoxyenamines, which can be generated under mild conditions, would provide an attractive synthetic approach to α -heteroarylated ketones. Herein, we described the umpolung α -heteroarylation reaction of ketones with a range of heterocycles, including thiophene, furan, benzothiofene, benzofuran, and indole.

Results and Discussion

We initially examined the reaction of 5-nonanone (**1a**) with tris(2-thienyl)aluminum, which was generated by the transmetalation reaction of commercially available 2-thienyllithium with aluminum chloride (Chart 2). The resulting aluminum reagent was then applied to our previously described method for the umpolung α -arylation reaction of ketones *via* *N*-alkenylisoxazolidine.¹⁸⁾ The tris(2-thienyl)aluminum reagent reacted with **1a** as anticipated to give the desired α -heteroarylated

product **4a** in 70% yield.

Encouraged by this result, we proceeded to evaluate the scope of this reaction by investigating the introduction of various thiophenes and furans to 5-nonanone (**1a**) (Table 1). Several heteroarenes were lithiated under standard conditions and transmetalated with aluminum chloride before being added to a solution of **1a** and isoxazolidine in dichloromethane. In the cases of the tris(5-substituted 2-thienyl)aluminums, which were derived from thiophenes containing methyl and methoxy groups, the reactions proceeded at the 2-position of thiophene to afford the desired products **4b** and **4c** in 80 and 65% yields, respectively. The conditions were also applied to tris(5-chloro-2-thienyl)aluminum to allow for the introduction of a 5-chlorothiophenyl group to **1a**. This reaction proceeded smoothly to give the α -heteroarylated product **4d** in 73% yield. The reactions of **1a** with tris(2-furyl)aluminum and tris(5-methyl-2-furyl)aluminum also proceeded smoothly to give the corresponding α -furylated products **4e** and **4f** in 64 and 77% yields, respectively.

To further explore the scope of this transformation, we investigated the reactions of various ketones with tris(5-methyl-2-thienyl)aluminum and tris(5-methyl-2-furyl)aluminum (Table 2). When the reaction was applied to unsymmetrical acyclic ketone **1b** bearing a methyl group as R¹, the α -heteroarylation proceeded in a regioselective manner on the opposite side to that of the methyl group to afford **4g** (Table 2, entry 1). Ketones bearing an olefin **1c** or a nitrile **1d** were also successfully heteroarylated with tris(5-methyl-2-thiophenyl)aluminum under the standard conditions to give **4h** and **4i** in 71 and 86% yields, respectively (Table 2, entries 2 and 3). The reaction conditions were also applicable to cyclic ketones, including cyclohexanone (**1e**) and cycloheptanone (**1f**), which gave the α -heteroarylated ketones **4j** and **4k** in moderate yields (Table 2, entries 4 and 5). Tris(5-methyl-2-furyl)aluminum also reacted with various *N*-alkoxyenamines generated from **1b–d** under these conditions to afford the corresponding α -furylketones **4l–n** in moderate yields (Table 2, entries 6–8).

We next investigated the introduction of heteroaryl groups fused to a benzene ring, such as benzothiophene, benzofuran and 1-methylindole. The heteroarylaluminum reagents were prepared according to the same procedure described above for the thienylation reactions. Pleasingly, 5-nonanone (**1a**) reacted successfully with the aluminum reagents prepared from 2-lithium benzothiophene, 2-lithium benzofuran, and 2-lith-

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Chart 1. Umpolung α -Heteroarylation of Ketones **1** Chart 2. Umpolung α -Thienylation of 5-Nonanone (**1a**)Table 1. Umpolung α -Heteroarylation of 5-Nonanone (**1a**) with Various Tris(heteroaryl)aluminums Table 2. Umpolung α -Heteroarylation of Ketones **1b–f** with Tris(5-methyl-2-thienyl)aluminum and Tris(5-methyl-2-furyl)aluminum

Entry	Substrate	R ¹	R ²	X	Product	Yield (%)
1	1b	Me	<i>n</i> Pr	S	4g	83
2	1c	Me	Allyl	S	4h	71
3	1d	Me	(CH ₂) ₂ CN	S	4i	86
4	1e		–(CH ₂) ₄ –	S	4j	63
5	1f		–(CH ₂) ₅ –	S	4k	60
6	1b	Me	<i>n</i> Pr	O	4l	62
7	1c	Me	Allyl	O	4m	58
8	1d	Me	(CH ₂) ₂ CN	O	4n	58

Table 3. Umpolung α -Heteroarylation of Ketones **1a–e** with Benzene-Fused Heteroarylaluminum Reagents

Entry	Substrate	R ¹	R ²	X	Products	Yield (%) (5 : 6)
1	1a	<i>n</i> Bu	<i>n</i> Pr	S	5a , 6a	68 (1:1)
2	1a	<i>n</i> Bu	<i>n</i> Pr	O	5b , 6b	70 (3:1)
3	1a	<i>n</i> Bu	<i>n</i> Pr	NMe	5c , 6c	60 (1:3)
4	1b	Me	<i>n</i> Pr	NMe	5d , 6d	62 (1:3)
5	1c	Me	Allyl	NMe	5e , 6e	60 (1:3)
6	1d	Me	(CH ₂) ₂ CN	NMe	5f , 6f	73 (1:3)
7	1e		–(CH ₂) ₄ –	NMe	5g , 6g	63 (1:3)

Chart 3. Proposal Reaction Pathways for the Formation of 3-Substituted Indole **6** and 2-Substituted Indole **5**

ium 1-methylindole to give the heteroarylated products as a mixture of the two regioisomers **5** and **6** (Table 3, entries 1–3). Surprisingly, the umpolung reaction had proceeded not only at the 2-position, but also at the 3-position of these heteroarene systems, despite the lithiation reaction taking place exclusively at their 2-position.¹⁹ Furthermore, in the case of the tris(1-methyl-2-indolyl)aluminum reagent, the reaction occurred preferentially at the 3-position. Various ketones **1b–e** were also subjected to the reaction with tris(1-methyl-2-indolyl)aluminum (Table 3, entries 4–7). The use of unsymmetrical linear ketones **1b–d** also gave the heteroarylated products **5d–f** and **6d–f** as 1:3 mixtures of the regioisomers in moderate yields (Table 3, entries 4–6). Cyclohexanone (**1e**) also reacted in a similar manner with tris(1-methyl-2-indolyl)aluminum to afford the corresponding α -heteroarylated cyclohexanones **5g** and **6g** as a 1:3 mixture of regioisomers in 63% yield (Table 3, entry 7).

Based on these results, we have proposed a plausible mechanism for the formation of **5** and **6** (Chart 3). Several reports have been published in the literature concerning the reaction of aryl borates with electrophiles, where the reaction does not proceed in a regioselective manner at the *ipso*-position.^{20–26} Mayr and colleagues²⁷ reported that the presence of a trifluoroborate group at the 2-position of the indole effectively enhanced the nucleophilicity of the carbon at the 3-position, and demonstrated that the vicinal-activation of the indole with a trifluoroborate group was much more effective than *ipso*-activation. In the case of the indolylaluminum reagent, the presence of aluminum at the 2-position of *N*-methylindole may have enhanced the nucleophilicity of its 3-position, causing the reaction to occur preferentially at the 3-position of the indole. The aluminum ate complex **8** would be generated

from the lithium chloride formed *in situ* by the reaction of the corresponding indolyl lithium with aluminum chloride. The aluminum ate complex **8** would react at the 3-position with *N*-alkoxyenamine **7** to form the Wheland intermediate **A**, and the hydride shift of intermediate **A** would give intermediate **B**, which would subsequently release aluminum to generate the 3-substituted indole **6**²⁸ (Chart 3, Eq. 1). The 2-substituted indole **5**, however, would be obtained as a result of reaction at the *ipso*-position of the 2-indolylaluminum reagent^{17,18} (Chart 3, Eq. 2).

In conclusion, we have developed a new method for the umpolung α -heteroarylation of ketones *via* an *N*-alkoxyenamine. The heteroarylaluminum reagents were prepared by the lithiation of the corresponding heteroarene compounds followed by transmetalation with aluminum chloride, and were suitable for the umpolung reactions of *N*-alkoxyenamines. Furthermore, the carbon–carbon bond-forming reaction proceeded at both the 2- and 3-positions of the benzene-fused heteroarylaluminum reagents.

Experimental

General Remarks Melting points are uncorrected. ¹H- and ¹³C-NMR spectra were recorded at 300 or 500 MHz and at 75 or 125 MHz for solution in deuteriochloroform (with tetramethylsilane in ¹H-NMR and deuteriochloroform in ¹³C-NMR each as an internal reference). IR spectra were recorded using FTIR apparatus for solutions in CHCl₃ except for neat. Mass spectra were obtained by electrospray ionization (ESI) method. Flash column chromatography (FCC) was performed using SiliaFlash[®] F60. Preparative TLC (PTLC) separations were carried out on precoated silica gel plates (E. Merck 60F₂₅₄).

4-(Thiophen-2-yl)nonan-5-one (4a) (Chart 2) To a so-

lution of 2-thienyllithium in tetrahydrofuran (THF) (1.0M, 3.0mL, 3.0mmol) was added AlCl_3 (133.0mg, 1.0mmol) at 0°C. The resulting solution was stirred at 0°C for 2h and was then added dropwise to a solution of 5-nonanone (71.0mg, 0.50mmol) and isoxazolidine (73.0mg, 1.0mmol) in dry CH_2Cl_2 (3.0mL) at 0°C. After being stirred at room temperature for 16h, the reaction was quenched by addition of an aqueous Rochelle's salt (1.2M). The resulting mixture was extracted with CHCl_3 . The combined organic layers were dried over MgSO_4 and concentrated under the reduced pressure. The residue was purified by PTLC (*n*-hexane/ AcOEt =20/1) to give **4a** (78.4mg, 70%) as a pale yellow oil. IR ν_{max} (neat) cm^{-1} : 1715 (CO); $^1\text{H-NMR}$ (300MHz, CDCl_3) δ : 7.19 (dm, 1H, $J=5.0\text{Hz}$), 6.95 (dd, 1H, $J=5.0, 3.5\text{Hz}$), 6.87 (dm, 1H, $J=3.5\text{Hz}$), 3.92 (t, 1H, $J=7.5\text{Hz}$), 2.49–2.41 (m, 2H), 2.06–1.94 (m, 1H), 1.80–1.69 (m, 1H), 1.54–1.44 (m, 2H), 1.31–1.19 (m, 4H), 0.91 (t, 3H, $J=7.5\text{Hz}$), 0.84 (t, 3H, $J=7.5\text{Hz}$); $^{13}\text{C-NMR}$ (75MHz, CDCl_3) δ : 209.5, 141.8, 126.9, 125.3, 124.5, 53.4, 40.9, 35.3, 25.8, 22.2, 20.6, 13.84, 13.76; high resolution (HR)-MS (ESI, m/z) Calcd for $\text{C}_{13}\text{H}_{20}\text{NaOS}$ ($\text{M}+\text{Na}^+$) 247.1127, Found 247.1130.

General Procedure for Preparation of Tris(heteroaryl)-aluminum Reagents To a solution of heteroarene (3.0mmol) in THF (3.0mL) was added *n*-BuLi (1.60M in *n*-hexane, 1.8mL, 3.0mmol) dropwise at –40°C. After stirring at 0°C for 30min, AlCl_3 was then added to the reaction mixture. The resulting solution was stirred at 0°C for 2h and was used for the following reaction.

General Procedure for One-Pot α -Heteroarylation of Ketones To a solution of ketones (0.50mmol) and isoxazolidine (73.0mg, 1.0mmol) in dry CH_2Cl_2 (5.0mL) was added tris(heteroaryl)aluminum (1.0mmol) dropwise at 0°C. After being stirred at room temperature for 8–16h, the reaction was quenched by addition of an aqueous Rochelle's salt (1.2M). The resulting mixture was extracted with CHCl_3 . The combined organic layers were dried over MgSO_4 and concentrated under the reduced pressure. The residue was purified by flash column chromatography or PTLC to give **4b–n**, **5a–g**, and **6a–g**.

4-(5-Methylthiophen-2-yl)nonan-5-one (4b) 95mg, 80%; Orange oil; IR ν_{max} (neat) cm^{-1} : 1715 (CO); $^1\text{H-NMR}$ (300MHz, CDCl_3) δ : 6.64 (d, 1H, $J=3.5\text{Hz}$), 6.59–6.57 (m, 1H), 3.81 (t, 1H, $J=7.5\text{Hz}$), 2.55–2.35 (m, 2H), 2.43 (d, 3H, $J=1.0\text{Hz}$), 2.01–1.89 (m, 1H), 1.76–1.63 (m, 1H), 1.55–1.44 (m, 2H), 1.30–1.20 (m, 4H), 0.90 (t, 3H, $J=7.5\text{Hz}$), 0.85 (t, 3H, $J=7.5\text{Hz}$); $^{13}\text{C-NMR}$ (75MHz, CDCl_3) δ : 209.8, 139.4, 139.0, 125.2, 124.8, 53.6, 40.8, 35.1, 25.8, 22.2, 20.6, 15.3, 13.9, 13.8; HR-MS (ESI, m/z) Calcd for $\text{C}_{14}\text{H}_{23}\text{OS}$ ($\text{M}+\text{H}^+$) 239.1464, Found 239.1467.

4-(5-Methoxythiophen-2-yl)nonan-5-one (4c) 82mg, 65%; Yellow oil; IR ν_{max} (neat) cm^{-1} : 1714 (CO); $^1\text{H-NMR}$ (300MHz, CDCl_3) δ : 6.47 (d, 1H, $J=3.5\text{Hz}$), 6.02 (d, 1H, $J=3.5\text{Hz}$), 3.85 (s, 3H), 3.69 (t, 1H, $J=7.5\text{Hz}$), 2.56–2.36 (m, 2H), 1.96–1.84 (m, 1H), 1.72–1.60 (m, 1H), 1.56–1.45 (m, 2H), 1.34–1.18 (m, 4H), 0.90 (t, 3H, $J=7.5\text{Hz}$), 0.86 (t, 3H, $J=7.5\text{Hz}$); $^{13}\text{C-NMR}$ (75MHz, CDCl_3) δ : 209.8, 165.5, 127.8, 122.8, 103.2, 60.1, 53.7, 40.8, 34.9, 25.8, 22.2, 20.6, 13.84, 13.79; HR-MS (ESI, m/z) Calcd for $\text{C}_{14}\text{H}_{22}\text{NaO}_2\text{S}$ ($\text{M}+\text{Na}^+$) 277.1233, Found 277.1239.

4-(5-Chlorothiophen-2-yl)nonan-5-one (4d) 104mg, 73%; Pale yellow oil; IR ν_{max} (neat) cm^{-1} : 1716 (CO);

$^1\text{H-NMR}$ (300MHz, CDCl_3) δ : 6.75 (d, 1H, $J=3.5\text{Hz}$), 6.64 (d, 1H, $J=3.5\text{Hz}$), 3.81 (t, 1H, $J=7.5\text{Hz}$), 2.46 (q, 2H, $J=7.0\text{Hz}$), 1.99–1.87 (m, 1H), 1.74–1.61 (m, 1H), 1.56–1.46 (m, 2H), 1.31–1.21 (m, 4H), 0.90 (t, 3H, $J=7.5\text{Hz}$), 0.86 (t, 3H, $J=7.5\text{Hz}$); $^{13}\text{C-NMR}$ (75MHz, CDCl_3) δ : 209.0, 140.5, 128.8, 125.7, 124.7, 53.8, 41.1, 35.4, 25.7, 22.2, 20.5, 13.8; HR-MS (ESI, m/z) Calcd for $\text{C}_{13}\text{H}_{19}\text{ClNaOS}$ ($\text{M}+\text{Na}^+$) 281.0737, Found 281.0740.

4-(Furan-2-yl)nonan-5-one (4e) 66mg, 64%; Colorless oil; IR ν_{max} (neat) cm^{-1} : 1718 (CO); $^1\text{H-NMR}$ (300MHz, CDCl_3) δ : 7.35–7.34 (m, 1H), 6.33 (dd, 1H, $J=3.5, 2.0\text{Hz}$), 6.15 (dm, 1H, $J=3.5\text{Hz}$), 3.72 (t, 1H, $J=7.5\text{Hz}$), 2.49–2.29 (m, 2H), 1.99–1.72 (m, 2H), 1.51–1.44 (m, 2H), 1.30–1.19 (m, 4H), 0.91 (t, 3H, $J=7.0\text{Hz}$), 0.85 (t, 3H, $J=7.0\text{Hz}$); $^{13}\text{C-NMR}$ (75MHz, CDCl_3) δ : 208.8, 152.7, 141.8, 110.5, 106.9, 52.2, 40.6, 31.7, 25.7, 22.1, 20.5, 13.8, 13.8; HR-MS (ESI, m/z) Calcd for $\text{C}_{13}\text{H}_{20}\text{NaO}_2$ ($\text{M}+\text{Na}^+$) 231.1356, Found 231.1354.

4-(5-Methylfuran-2-yl)nonan-5-one (4f) 85mg, 77%; Yellow oil; IR ν_{max} (neat) cm^{-1} : 1715 (CO); $^1\text{H-NMR}$ (300MHz, CDCl_3) δ : 6.01 (d, 1H, $J=3.0\text{Hz}$), 5.90 (brdd, 1H, $J=3.0, 1.0\text{Hz}$), 3.64 (t, 1H, $J=7.5\text{Hz}$), 2.50–2.30 (m, 2H), 2.25 (d, 3H, $J=1.0\text{Hz}$), 1.93–1.69 (m, 2H), 1.58–1.44 (m, 2H), 1.34–1.20 (m, 4H), 0.91 (t, 3H, $J=7.5\text{Hz}$), 0.85 (t, 3H, $J=7.5\text{Hz}$); $^{13}\text{C-NMR}$ (75MHz, CDCl_3) δ : 209.2, 151.5, 150.8, 107.6, 106.3, 52.3, 40.4, 31.6, 25.7, 22.2, 20.6, 13.9, 13.8, 13.5; HR-MS (ESI, m/z) Calcd for $\text{C}_{14}\text{H}_{23}\text{O}_2$ ($\text{M}+\text{H}^+$) 223.1693, Found 223.1696.

3-(5-Methylthiophen-2-yl)hexan-2-one (4g) 81mg, 83%; Yellow oil; IR ν_{max} (neat) cm^{-1} : 1715 (CO); $^1\text{H-NMR}$ (300MHz, CDCl_3) δ : 6.66 (d, 1H, $J=3.5\text{Hz}$), 6.60 (dm, 1H, $J=3.5\text{Hz}$), 3.79 (t, 1H, $J=7.5\text{Hz}$), 2.44 (s, 3H), 2.13 (s, 3H), 2.02–1.90 (m, 1H), 1.78–1.65 (m, 1H), 1.35–1.22 (m, 2H), 0.91 (t, 3H, $J=7.0\text{Hz}$); $^{13}\text{C-NMR}$ (75MHz, CDCl_3) δ : 207.5, 139.1, 125.3, 124.9, 54.3, 34.7, 28.0, 20.5, 15.3, 13.8; HR-MS (ESI, m/z) Calcd for $\text{C}_{11}\text{H}_{16}\text{NaOS}$ ($\text{M}+\text{Na}^+$) 219.0814, Found 219.0817.

3-(5-Methylthiophen-2-yl)hex-5-en-2-one (4h) 69mg, 71%; Yellow oil; IR ν_{max} (neat) cm^{-1} : 1717 (CO); $^1\text{H-NMR}$ (300MHz, CDCl_3) δ : 6.67 (d, 1H, $J=3.5\text{Hz}$), 6.60 (dm, 1H, $J=3.5\text{Hz}$), 5.71 (ddt, 1H, $J=17.0, 10.0, 7.0\text{Hz}$), 5.10–4.98 (m, 2H), 3.88 (t, 1H, $J=7.5\text{Hz}$), 2.80–2.70 (m, 1H), 2.53–2.45 (m, 1H), 2.44 (d, 3H, $J=1.0\text{Hz}$), 2.14 (s, 3H); $^{13}\text{C-NMR}$ (75MHz, CDCl_3) δ : 206.7, 139.5, 138.2, 135.2, 125.6, 125.1, 117.1, 54.3, 36.8, 28.3, 15.3; HR-MS (ESI, m/z) Calcd for $\text{C}_{11}\text{H}_{14}\text{NaOS}$ ($\text{M}+\text{Na}^+$) 217.0658, Found 217.0661.

4-(5-Methylthiophen-2-yl)-5-oxohexanenitrile (4i) 89mg, 86%; Pale yellow oil; IR ν_{max} (neat) cm^{-1} : 2246 (CN), 1716 (CO); $^1\text{H-NMR}$ (300MHz, CDCl_3) δ : 6.74 (d, 1H, $J=3.5\text{Hz}$), 6.64 (dm, 1H, $J=3.5\text{Hz}$), 3.99 (dd, 1H, $J=8.5, 5.5\text{Hz}$), 2.45 (d, 3H, $J=1.0\text{Hz}$), 2.44–2.34 (m, 1H), 2.31–2.20 (m, 2H), 2.17 (s, 3H), 2.07–1.98 (m, 1H); $^{13}\text{C-NMR}$ (75MHz, CDCl_3) δ : 205.4, 140.5, 136.1, 126.9, 125.5, 119.0, 52.4, 28.5, 27.7, 15.3, 14.9; HR-MS (ESI, m/z) Calcd for $\text{C}_{11}\text{H}_{13}\text{NNaOS}$ ($\text{M}+\text{Na}^+$) 230.0610, Found 230.0617.

2-(5-Methylthiophen-2-yl)cyclohexan-1-one (4j) 61mg, 63%; Pale yellow oil; IR ν_{max} (neat) cm^{-1} : 1716 (CO); $^1\text{H-NMR}$ (300MHz, CDCl_3) δ : 6.60 (brs, 2H), 3.82 (dd, 1H, $J=10.0, 5.0\text{Hz}$), 2.60–2.52 (m, 1H), 2.44 (s, 3H), 2.43–2.34 (m, 2H), 2.11–1.93 (m, 3H), 1.88–1.76 (m, 2H); $^{13}\text{C-NMR}$ (75MHz, CDCl_3) δ : 209.2, 138.8, 138.7, 124.9, 124.6, 52.2, 41.6, 35.9, 27.6, 24.9, 15.2; HR-MS (ESI, m/z) Calcd for $\text{C}_{11}\text{H}_{14}\text{NaOS}$ ($\text{M}+$

Na⁺) 217.0658, Found 217.0659.

2-(5-Methylthiophen-2-yl)cycloheptan-1-one (4k)²⁹ 62 mg, 60%; Colorless oil; IR $\nu_{\max}$ (neat) cm⁻¹: 1706 (CO); ¹H-NMR (300 MHz, CDCl₃) δ : 6.66 (d, 1H, *J*=3.5 Hz), 6.59 (dm, 1H, *J*=3.5 Hz), 3.86 (dd, 1H, *J*=11.0, 5.0 Hz), 2.71 (dt, 1H, *J*=15.0, 3.0 Hz), 2.50–2.42 (m, 1H), 2.43 (d, 3H, *J*=1.0 Hz), 2.33–2.20 (m, 1H), 2.04–1.81 (m, 4H), 1.63–1.32 (m, 3H); ¹³C-NMR (75 MHz, CDCl₃) δ : 212.0, 140.0, 138.8, 124.7, 124.3, 54.3, 41.3, 32.7, 29.9, 27.9, 25.6, 15.2; HR-MS (ESI, *m/z*) Calcd for C₁₂H₁₆NaOS (M+Na⁺) 231.0814, Found 231.0823.

3-(5-Methylfuran-2-yl)hexan-2-one (4l) 56 mg, 62%; Pale yellow oil; IR $\nu_{\max}$ (neat) cm⁻¹: 1713 (CO); ¹H-NMR (300 MHz, CDCl₃) δ : 6.03 (d, 1H, *J*=3.0 Hz), 5.90 (dm, 1H, *J*=3.0 Hz), 3.62 (t, 1H, *J*=7.5 Hz), 2.26 (s, 3H), 2.09 (s, 3H), 1.93–1.70 (m, 2H), 1.33–1.24 (m, 2H), 0.91 (t, 3H, *J*=7.0 Hz); ¹³C-NMR (75 MHz, CDCl₃) δ : 207.1, 151.7, 150.6, 107.8, 106.3, 53.1, 31.4, 28.0, 20.5, 13.9, 13.5; HR-MS (ESI, *m/z*) Calcd for C₁₁H₁₆NaO₂ (M+Na⁺) 203.1043, Found 203.1048.

3-(5-Methylfuran-2-yl)hex-5-en-2-one (4m) 52 mg, 58%; Colorless oil; IR $\nu_{\max}$ (neat) cm⁻¹: 1720 (CO); ¹H-NMR (300 MHz, CDCl₃) δ : 6.05 (d, 1H, *J*=3.0 Hz), 5.91 (dm, 1H, *J*=3.0 Hz), 5.72 (ddt, 1H, *J*=17.0, 10.0, 7.0 Hz), 5.10–4.99 (m, 2H), 3.71 (t, 1H, *J*=7.5 Hz), 2.74–2.65 (m, 1H), 2.58–2.48 (m, 1H), 2.26 (s, 3H), 2.11 (d, 3H, *J*=1.0 Hz); ¹³C-NMR (75 MHz, CDCl₃) δ : 206.1, 151.9, 150.0, 135.2, 116.9, 108.1, 106.4, 52.9, 33.6, 28.3, 13.5; HR-MS (ESI, *m/z*) Calcd for C₁₁H₁₄NaO₂ (M+Na⁺) 201.0886, Found 230.0889.

4-(5-Methylfuran-2-yl)-5-oxohexanenitrile (4n) 55 mg, 58%; Yellow oil; IR $\nu_{\max}$ (neat) cm⁻¹: 2247 (CN), 1719 (CO); ¹H-NMR (300 MHz, CDCl₃) δ : 6.14 (d, 1H, *J*=3.0 Hz), 5.94 (dm, 1H, *J*=3.0 Hz), 3.80 (dd, 1H, *J*=8.5, 5.5 Hz), 2.46–2.18 (m, 3H), 2.26 (d, 3H, *J*=1.0 Hz), 2.12 (s, 3H), 2.11–2.04 (m, 1H); ¹³C-NMR (75 MHz, CDCl₃) δ : 204.6, 152.8, 147.8, 119.0, 109.7, 106.7, 51.1, 28.5, 24.8, 15.0, 13.5; HR-MS (ESI, *m/z*) Calcd for C₁₁H₁₃NNaO₂ (M+Na⁺) 214.0838, Found 218.0844.

4-(Benzo[b]thiophen-3-yl)nonan-5-one (5a) and 4-(Benzo[b]thiophen-3-yl)nonan-5-one (6a) α -Benzothio-phenylated ketones **5a** and **6a** (1:1) were inseparable. 93 mg, 68%; Pale yellow oil; IR $\nu_{\max}$ (neat) cm⁻¹: 1714 (CO); ¹H-NMR (300 MHz, CDCl₃) δ : 7.87 (dm, 1/2H, *J*=8.0 Hz), 7.81–7.76 (m, 2/2H), 7.70 (dm, 1/2H, *J*=8.0 Hz), 7.42–7.26 (m, 4/2H), 7.23 (s, 1/2H), 7.12 (s, 1/2H), 4.07 (t, 1/2H, *J*=7.0 Hz), 3.97 (t, 1/2H, *J*=7.0 Hz), 2.57–2.41 (m, 2/2H), 2.35 (m, 2/2H), 2.18–1.99 (m, 2/2H), 1.89–1.76 (m, 2/2H), 1.55–1.43 (m, 4/2H), 1.34–1.12 (m, 8/2H), 0.92 (t, 3/2H, *J*=7.0 Hz), 0.91 (t, 3/2H, *J*=7.0 Hz), 0.84 (t, 3/2H, *J*=7.0 Hz), 0.78 (t, 3/2H, *J*=7.0 Hz); ¹³C-NMR (75 MHz, CDCl₃) δ : 210.2, 209.1, 142.8, 140.5, 139.7, 139.5, 138.2, 133.8, 124.5, 124.3, 124.2, 124.0, 123.2, 123.1, 122.2, 122.1, 121.7, 54.1, 52.3, 41.2, 40.8, 34.9, 33.5, 25.8, 25.7, 22.2, 22.1, 20.9, 20.6, 14.0, 13.9, 13.8, 13.7; HR-MS (ESI, *m/z*) Calcd for C₁₇H₂₂NaOS (M+Na⁺) 297.1284, Found 297.1285.

4-(Benzofuran-2-yl)nonan-5-one (5b) and 4-(Benzofuran-3-yl)nonan-5-one (6b) α -Benzofuranylated ketones **5b** and **6b** (3:1) were inseparable. 90 mg, 70%; Colorless oil; IR $\nu_{\max}$ (neat) cm⁻¹: 1719 (CO); ¹H-NMR (300 MHz, CDCl₃) δ : 7.58–7.42 (m, 9/4H), 7.31–7.17 (m, 8/4H), 6.55 (s, 3/4H), 3.84 (t, 3/4H, *J*=7.5 Hz), 3.82 (t, 1/4H, *J*=7.5 Hz), 2.57–2.37 (m, 8/4H), 2.12–1.75 (m, 8/4H), 1.55–1.47 (m, 8/4H), 1.35–1.15 (m, 16/4H), 0.93 (t, 9/4H, *J*=7.5 Hz), 0.91 (t, 3/4H, *J*=7.5 Hz), 0.84 (t, 9/4H, *J*=7.5 Hz), 0.81 (t, 3/4H, *J*=7.5 Hz); ¹³C-NMR (75 MHz, CDCl₃) δ : 210.3, 208.1, 155.7, 154.7, 142.3, 128.4, 126.9, 124.5,

123.8, 122.7, 122.6, 120.6, 120.1, 118.3, 111.6, 111.1, 104.0, 52.6, 48.5, 40.9, 40.8, 32.8, 31.6, 25.8, 25.6, 22.1, 20.8, 20.6, 13.91, 13.85, 13.79; HR-MS (ESI, *m/z*) Calcd for C₁₇H₂₂NaO₂ (M+Na⁺) 281.1512, Found 281.1511.

4-(1-Methyl-1*H*-indol-2-yl)nonan-5-one (5c) 20 mg, 15%; Yellow oil; IR $\nu_{\max}$ (neat) cm⁻¹: 1714 (CO); ¹H-NMR (300 MHz, CDCl₃) δ : 7.57 (dm, 1H, *J*=8.0 Hz), 7.29 (dm, 1H, *J*=8.0 Hz), 7.20 (tm, 1H, *J*=8.0 Hz), 7.10 (tm, 1H, *J*=8.0 Hz), 6.38 (s, 1H), 3.82 (t, 1H, *J*=7.0 Hz), 3.67 (s, 3H), 2.45–2.24 (m, 2H), 2.15–2.02 (m, 1H), 1.93–1.81 (m, 1H), 1.50–1.29 (m, 4H), 1.24–1.16 (m, 2H), 0.95 (t, 3H, *J*=7.0 Hz), 0.80 (t, 3H, *J*=7.0 Hz); ¹³C-NMR (75 MHz, CDCl₃) δ : 209.7, 137.9, 137.7, 127.7, 121.3, 120.3, 119.6, 109.1, 100.4, 51.8, 39.2, 32.9, 29.8, 25.8, 22.2, 20.9, 14.0, 13.8; HR-MS (ESI, *m/z*) Calcd for C₁₈H₂₅NNaO (M+Na⁺) 294.1828, Found 294.1830.

4-(1-Methyl-1*H*-indol-3-yl)nonan-5-one (6c) 61 mg, 45%; Colorless oil; IR $\nu_{\max}$ (neat) cm⁻¹: 1709 (CO); ¹H-NMR (300 MHz, CDCl₃) δ : 7.60 (dm, 1H, *J*=8.0 Hz), 7.29 (dm, 1H, *J*=8.0 Hz), 7.23 (tm, 1H, *J*=8.0 Hz), 7.12 (tm, 1H, *J*=8.0 Hz), 6.90 (s, 1H), 3.90 (t, 1H, *J*=7.0 Hz), 3.76 (s, 3H), 2.49–2.32 (m, 2H), 2.11–1.99 (m, 1H), 1.83–1.71 (m, 1H), 1.53–1.40 (m, 2H), 1.32–1.24 (m, 2H), 1.22–1.12 (m, 2H), 0.90 (t, 3H, *J*=7.0 Hz), 0.80 (t, 3H, *J*=7.0 Hz); ¹³C-NMR (75 MHz, CDCl₃) δ : 211.6, 137.0, 127.3, 126.9, 121.7, 119.1, 119.0, 112.6, 109.3, 49.4, 41.0, 34.0, 32.8, 26.0, 22.2, 21.0, 14.1, 13.8; HR-MS (ESI, *m/z*) Calcd for C₁₈H₂₅NNaO (M+Na⁺) 294.1828, Found 294.1830.

3-(1-Methyl-1*H*-indol-2-yl)hexan-2-one (5d) 18 mg, 16%; Orange oil; IR $\nu_{\max}$ (neat) cm⁻¹: 1715 (CO); ¹H-NMR (300 MHz, CDCl₃) δ : 7.58 (dm 1H, *J*=8.0 Hz), 7.29 (dm, 1H, *J*=8.0 Hz), 7.21 (tm, 1H, *J*=8.0 Hz), 7.10 (tm, 1H, *J*=8.0 Hz), 6.41 (s, 1H), 3.80 (t, 1H, *J*=7.0 Hz), 3.67 (s, 3H), 2.15–2.04 (m, 1H), 2.04 (s, 3H), 2.00–1.82 (m, 1H), 1.44–1.34 (m, 2H), 0.96 (t, 3H, *J*=7.0 Hz); ¹³C-NMR (75 MHz, CDCl₃) δ : 207.6, 137.7, 127.7, 121.5, 120.3, 119.7, 109.1, 100.3, 52.5, 32.6, 30.0, 26.7, 20.8, 13.9; HR-MS (ESI, *m/z*) Calcd for C₁₅H₂₀NO (M+H⁺) 230.1539, Found 230.1541.

3-(1-Methyl-1*H*-indol-3-yl)hexan-2-one (6d) 52 mg, 46%; Orange oil; IR $\nu_{\max}$ (neat) cm⁻¹: 1710 (CO); ¹H-NMR (300 MHz, CDCl₃) δ : 7.59 (dm, 1H, *J*=8.0 Hz), 7.30 (dm, 1H, *J*=8.0 Hz), 7.24 (tm, 1H, *J*=8.0 Hz), 7.12 (tm, 1H, *J*=8.0 Hz), 6.92 (s, 1H), 3.88 (t, 1H, *J*=7.5 Hz), 3.77 (s, 3H), 2.12–2.00 (m, 1H), 2.07 (s, 3H), 1.86–1.74 (m, 1H), 1.30 (m, 2H), 0.91 (t, 3H, *J*=7.5 Hz); ¹³C-NMR (75 MHz, CDCl₃) δ : 209.5, 137.1, 127.3, 126.8, 121.8, 119.2, 119.1, 112.4, 109.3, 50.4, 33.5, 32.8, 28.3, 20.9, 14.0; HR-MS (ESI, *m/z*) Calcd for C₁₅H₁₉NNaO (M+Na⁺) 252.1359, Found 252.1362.

3-(1-Methyl-1*H*-indol-2-yl)hex-5-en-2-one (5e) 17 mg, 15%; Orange oil; IR $\nu_{\max}$ (neat) cm⁻¹: 1714 (CO); ¹H-NMR (300 MHz, CDCl₃) δ : 7.58 (dm, 1H, *J*=8.0 Hz), 7.30 (dm, 1H, *J*=8.0 Hz), 7.22 (tm, 1H, *J*=8.0 Hz), 7.10 (tm, 1H, *J*=8.0 Hz), 6.41 (s, 1H), 5.77 (ddt, 1H, *J*=17.0, 10.0, 7.0 Hz), 5.13 (dm, 1H, *J*=17.0 Hz), 5.04 (dm, 1H, *J*=10.0 Hz), 3.90 (t, 1H, *J*=7.0 Hz), 3.69 (brs, 3H), 2.91–2.80 (m, 1H), 2.71–2.62 (m, 1H), 2.06 (brs, 3H); ¹³C-NMR (75 MHz, CDCl₃) δ : 206.4, 136.9, 134.9, 127.6, 121.6, 120.4, 119.7, 117.3, 109.2, 100.6, 52.2, 34.9, 29.8, 27.1; HR-MS (ESI, *m/z*) Calcd for C₁₅H₁₈NO (M+H⁺) 228.1383, Found 228.1384.

3-(1-Methyl-1*H*-indol-3-yl)hex-5-en-2-one (6e) 51 mg, 45%; Orange oil; IR $\nu_{\max}$ (neat) cm⁻¹: 1710 (CO); ¹H-NMR (300 MHz, CDCl₃) δ : 7.60 (dm, 1H, *J*=8.0 Hz), 7.31 (dm, 1H, *J*=8.0 Hz), 7.24 (tm, 1H, *J*=8.0 Hz), 7.13 (tm, 1H, *J*=8.0 Hz),

6.93 (s, 1H), 5.77 (ddt, 1H, $J=17.0, 10.0, 7.0$ Hz), 5.05 (dm, 1H, $J=17.0$ Hz), 4.96 (dm, 1H, $J=10.0$ Hz), 3.97 (t, 1H, $J=7.5$ Hz), 3.77 (s, 3H), 2.90–2.80 (m, 1H), 2.61–2.52 (m, 1H), 2.09 (s, 3H); ^{13}C -NMR (75 MHz, CDCl_3) δ : 208.4, 137.1, 136.4, 127.1, 127.0, 121.9, 119.3, 119.0, 116.3, 111.6, 109.4, 50.4, 35.7, 32.8, 28.6; HR-MS (ESI, m/z) Calcd for $\text{C}_{15}\text{H}_{18}\text{NO}$ ($\text{M}+\text{H}^+$) 228.1383, Found 228.1385.

4-(1-Methyl-1H-indol-2-yl)-5-oxohexanenitrile (5f)

21 mg, 18%; Red oil; IR ν_{max} (neat) cm^{-1} : 2245 (CN), 1715 (CO); ^1H -NMR (300 MHz, CDCl_3) δ : 7.58 (dm, 1H, $J=8.0$ Hz), 7.35 (dm, 1H, $J=8.0$ Hz), 7.26 (tm, 1H, $J=8.0$ Hz), 7.14 (tm, 1H, $J=8.0$ Hz), 6.35 (s, 1H), 4.06 (brdd, 1H, $J=8.5, 6.0$ Hz), 3.78 (s, 3H), 2.52–2.28 (m, 3H), 2.20–2.10 (m, 1H) 2.13 (s, 3H); ^{13}C -NMR (75 MHz, CDCl_3) δ : 204.7, 137.9, 135.0, 127.5, 122.1, 120.5, 120.2, 119.1, 109.4, 101.4, 49.7, 30.0, 28.4, 26.3, 15.2; HR-MS (ESI, m/z) Calcd for $\text{C}_{15}\text{H}_{17}\text{N}_2\text{O}$ ($\text{M}+\text{H}^+$) 241.1335, Found 241.1337.

4-(1-Methyl-1H-indol-3-yl)-5-oxohexanenitrile (6f)

66 mg, 55%; Red oil; IR ν_{max} (neat) cm^{-1} : 2245 (CN), 1710 (CO); ^1H -NMR (300 MHz, CDCl_3) δ : 7.54 (dm, 1H, $J=8.0$ Hz), 7.35 (dm, 1H, $J=8.0$ Hz), 7.27 (tm, 1H, $J=8.0$ Hz), 7.14 (tm, 1H, $J=8.0$ Hz), 7.01 (s, 1H), 4.05 (brdd, 1H, $J=8.5, 6.0$ Hz), 3.80 (s, 3H), 2.41–2.32 (m, 2H), 2.24–2.10 (m, 2H), 2.11 (s, 3H); ^{13}C -NMR (75 MHz, CDCl_3) δ : 207.5, 137.3, 127.8, 126.4, 122.3, 119.8, 119.6, 118.9, 109.7, 109.4, 48.8, 32.9, 28.7, 26.3, 15.2; HR-MS (ESI, m/z) Calcd for $\text{C}_{15}\text{H}_{16}\text{N}_2\text{NaO}$ ($\text{M}+\text{Na}^+$) 263.1155, Found 263.1156.

2-(1-Methyl-1H-indol-2-yl)cyclohexan-1-one (5g)³⁰⁾

18 mg, 16%; Yellow solid; IR ν_{max} (neat) cm^{-1} : 1706 (CO); ^1H -NMR (300 MHz, CDCl_3) δ : 7.56 (dm, 1H, $J=8.0$ Hz), 7.29 (dm, 1H, $J=8.0$ Hz), 7.18 (tm, 1H, $J=8.0$ Hz), 7.07 (tm, 1H, $J=8.0$ Hz), 6.36 (s, 1H), 3.80 (dd, 1H, $J=12.0, 5.5$ Hz), 3.57 (s, 3H), 2.60–2.45 (m, 3H), 2.28–2.11 (m, 3H), 1.91–1.83 (m, 2H); ^{13}C -NMR (75 MHz, CDCl_3) δ : 209.0, 137.9, 137.6, 127.5, 121.1, 120.2, 119.3, 109.0, 99.5, 49.5, 41.9, 32.6, 29.9, 27.7, 25.1; HR-MS (ESI, m/z) Calcd for $\text{C}_{15}\text{H}_{17}\text{NNaO}$ ($\text{M}+\text{Na}^+$) 250.1202, Found 250.1199.

2-(1-Methyl-1H-indol-3-yl)cyclohexan-1-one (6g) 53 mg, 47%; Dark brown oil; IR ν_{max} (neat) cm^{-1} : 1709 (CO); ^1H -NMR (300 MHz, CDCl_3) δ : 7.43 (dm, 1H, $J=8.0$ Hz), 7.27 (dm, 1H, $J=8.0$ Hz), 7.20 (tm, 1H, $J=8.0$ Hz), 7.07 (tm, 1H, $J=8.0$ Hz), 6.99 (s, 1H), 3.90 (dd, 1H, $J=12.0, 5.5$ Hz), 3.72 (brs, 3H), 2.59–2.34 (m, 3H), 2.16–1.94 (m, 3H), 1.91–1.77 (m, 2H); ^{13}C -NMR (75 MHz, CDCl_3) δ : 210.7, 136.7, 127.3, 126.5, 121.5, 119.1, 118.8, 112.1, 109.2, 48.6, 41.9, 35.1, 32.6, 28.0, 25.2; HR-MS (ESI, m/z) Calcd for $\text{C}_{15}\text{H}_{17}\text{NNaO}$ ($\text{M}+\text{Na}^+$) 250.1202, Found 250.1199.

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