

Thermal aromatic Claisen rearrangement and Strecker reaction of alkyl(allyl)-aryl ethers under green reaction conditions: Efficient and clean preparation of *ortho*-allyl phenols (naphthols) and alkyl(allyl)oxyarene-based γ -amino nitriles

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Abstract: Chemical transformations of 13 diverse allyl(alkyl)-aryl ethers, easily prepared using Williamson reaction of different hydroxyarenes and allyl bromide and alkyl (*n*-butyl, *n*-octyl) bromides, were studied. Thermal aromatic Claisen rearrangement of allyl-aryl ethers to obtain *ortho*-allyl phenols (naphthols) employing propylene carbonate as a nontoxic and biodegradable solvent was described for the first time. The use of this green solvent allowed to enhance notably product yields and reduce significantly the reaction time comparing with the use of 1,2-dichlorobenzene, toxic solvent, which is traditionally employed in this type of Claisen rearrangement. Three-component Strecker reaction of selected alkyl(allyl)-aryl ethers with formyl function on aryl fragment, piperidine and potassium cyanide in the presence of sulfuric acid supported on silica gel (SSA, SiO₂·O-SO₃H) under mild reaction conditions was used in the preparation of new γ -amino nitriles, analogues of alkaloid girsengsohnine [2-(4-hydroxyphenyl)-2-(piperidin-1-yl)acetonitrile], a perspective biological model in the search for new insecticidal agrochemicals against *Aedes aegypti*. The use of SSA, an inexpensive and reusable solid catalyst, allowed to obtain new series of 2-[4-alkyl(allyl)oxyphenyl]-2-(piperidin-1-yl)acetonitriles in short time at room temperature with good yields.

Keywords: Substituted aryl ethers, Green chemistry, Claisen rearrangement, *ortho*-Allyl hydroxyarenes, Strecker reaction, α -Amino nitriles

Introduction

Phenolics are the most prevalent class of metabolites in nature, and their distribution is almost ubiquitous, so it is not difficult to understand their biological and synthetic importance¹. Among diverse phenolic compounds, simple *ortho*-allyl phenols and naphthols not only stand out as promising pharmacological agents and versatile synthetic intermediates, but as raw materials for the manufacture of a wide assortment of organic products².

On the other hand, α -amino nitriles, common precursors to natural and unnatural α -amino acids, have a profound impact on bio-chemical sciences, serving as suitable models in pharmacological and biological research, inexpensive starting materials and valuable intermediates in chemical synthesis of vitally important heterocyclic and carbocyclic molecules³⁻⁵. Additionally, the α -amino nitriles containing phenolic moiety has been found to occur in diverse alkaloids, for example, simple alkaloid

girsengsohnine [2-(4-hydroxyphenyl)-2-(piperidin-1-yl)acetonitrile] found in the green petals of the shrub *Girsengsohnia oppositiflora*^{6,7}. and some its synthetic analogs, for example, α -amino nitrile with dimethoxyphenyl moiety **A** (Fig. 1) showed promising biological properties such as *in vivo* larvicidal activity against *Aedes aegypti*, the major vector of dengue fever, an endemic disease in America and Asia⁸.

Traditionally, *ortho*-allyl hydroxyarenes (phenols and naphthols) and α -amino nitriles are prepared by use of the aromatic Claisen rearrangement and the Strecker reaction, respectively. Aromatic Claisen rearrangement, belonging to the [3,3] sigmatropic rearrangements, is a valuable *ortho* specific functionalization of phenols, which are important both as substrates and as reagents⁹. Although there are different protocols on metal-catalyzed Claisen rearrangement^{10,11}, this thermal aromatic Claisen rearrangement continues

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to be very important for the construction of a carbon-carbon bond for allylated natural products^{1,12}. The key precursors of this phenolic

functionalization are allyl oxyarenes that can isomerize into C-allyl hydroxyarenes with potential antioxidant properties¹³.

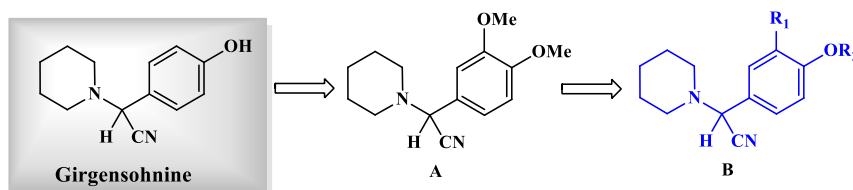


Figure 1. α -Amino nitriles design inspired by natural molecule, girgensohnine alkaloid.

The Claisen rearrangement of allyl-aryl ethers can be realized under Lewis and Brønsted acids catalysis or thermally using different solvents such as toluene, dichlorobenzene, decalin, N,N-diethylaniline. The rearrangement is typical carried out at 150-300 °C and although their products are usually *ortho* isomers, *para* allylated phenols and benzofurans are often formed as side products.

Even though microwave-assisted aromatic Claisen rearrangement protocols have been developed, large-scaled procedures for the preparation of *ortho*-allyl phenols and naphthols are still based on thermal aromatic Claisen rearrangement protocols. While these are very simple, but these conditions have some drawbacks such as prolonged reaction times, use of toxic solvents (and catalysts) and high temperature regimes¹⁴.

The Strecker reaction of amines, aldehydes and cyanide source, which allows for rapidly preparing rapidly α -amino nitriles, occurs generally in the presence of Lewis or Brønsted acids. In addition, cyanating agents employed in three-component Strecker reaction (HCN, KCN, Et₂AlCN, (EtO)₂P(O)CN, Bu₃SnCN, Me₃SiCN, and others) reagents have its serious drawbacks, e.g., some of which involve the intervention of metal catalysts, strong reaction conditions and cautiously handling, others are unstable and corrosive liquids, and some are very expensive products and sensitive to moisture¹⁵. Among this variety of acid catalysts and cyanide sources, several heterogeneous catalysts (polymer-supported Sc(OTf)₃, montmorillonite KSF-clay, silica-H₂SO₄, heteropoly acid, and NH₂SO₃H or sulfated tungstate, among others), which are more advantageous in terms of catalyst/product separation and continuous production, and KCN stand out as simple and inexpensive reagents¹⁶.

Taking into account the above stated and as a part of our medicinal research program directed to the development of small molecule drug discovery, we started preliminary study on these topics paying attention to efficient and green protocols of classical thermal aromatic Claisen rearrangement and Strecker reaction, keeping in mind an irregular

structure of girgensohnine alkaloid and their new analogs methoxy(alkyl- or allyloxy)arene-based α -amino nitriles **B** (Fig. 1). Therefore, now we present our study, based on simple chemical transformations of alkyl(allyl)-aryl ethers that is focused in: *i*) prepare alkyl(allyl)oxybenzaldehydes, *ii*) develop an efficient and simple protocol for the preparation of *ortho*-allyl phenols and naphthols using thermal aromatic Claisen rearrangement of allyloxyarenes, and *iii*) obtain new girgensohnine analogs via acid-catalyzed three-component Strecker reaction. All this, are in order to contribute in generation of diverse methoxy(alkyl- or allyloxy) arene-based α -amino nitriles for forthcoming bio-screenings of insecticidal or/and antioxidant activities.

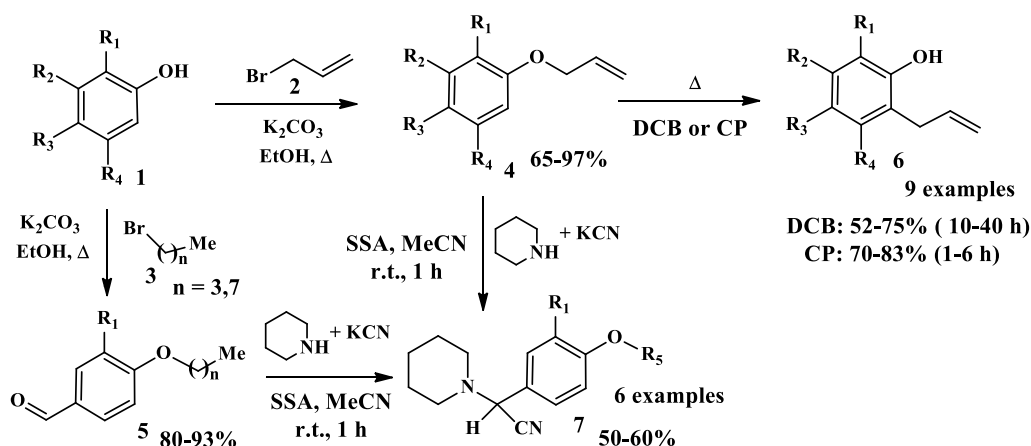
Results and Discussion

The allyl(alkyl)-aryl ethers **4** and **5**, needed in our study, were easily prepared using Williamson reaction of different hydroxyarenes **1** and allyl bromide **2** and alkyl (*n*-butyl, *n*-octyl) bromides **3**, respectively; all these are commercial, low-cost products (Scheme 1).

The Williamson synthesis usually involves the employment of organic solvents or with phase-transfer catalysts in the presence of a base followed by refluxing for several hours^{17,18}. In general, this preparation of allyl(alkyl)-aryl ethers is a S_N2 O-alkylation process, in which polar aprotic solvents (DMF, DMSO, acetone, DMSO, MeCN, etc.), works better¹⁷. However, according to the concepts of green chemistry, these solvents have harmful effects on the environment, and thus would be replaced¹⁹. Noteworthy, reports of the use of polar protic solvents such as methanol and ethanol in this type of transposition are few²⁰. Therefore, we tested reaction of phenols **1** and bromides **2,3** in the presence of K₂CO₃ in boiling ethanol, which is still the most prevalent green solvent derived from natural or renewable resources. Our attempt was successful: 1. All most O-allyloxyarenes **4** were prepared with good to excellent yields (82-97%) for 2-8 h; only one phenolic compound, O-allylated thymol **4d** was obtained in moderate yields (62%) after prolonged boiling (18 h);

2. O-Butyl(octyl)phenols **5** were also produced in good yields (80-93%), but this conversion was

more extended than O-allylated phenols (Table 1).



Scheme 1. Chemical transformations of allyl(alkyl)-aryl ethers **4** and **5** obtained by Williamson reaction.

Table 1. Preparation of allyl(alkyl)-aryl ethers **4** and **5** by Williamson reaction (allyl or alkyl bromides/ K_2CO_3 /EtOH/ Δ).

Entry	R ₁	R ₂	R ₃	R ₄	Products	Yield, % (time)
1	H	H	H	H	4a	82 (6 h)
2	CH=CH-CH=CH	H	H	H	4b	78 (7 h)
3	H	CH=CH-CH=CH	H	H	4c	81 (6 h)
4	CHMe ₂	H	H	Me	4d	63 (18 h)
5	OMe	H	H	H	4e	85 (3 h)
6	CHO	H	H	H	4f	87 (4 h)
7	OMe	H	H	CHO	4g	92 (2 h)
8	H	H	CHO	H	4h	83 (2 h)
9	OMe	H	CHO	H	4i	97 (2 h)
10	H	H	CHO	H	5a (n=3)	90 (11 h)
11	OMe	H	CHO	H	5b (n=3)	84 (10 h)
12	H	H	CHO	H	5c (n=7)	80 (12 h)
13	OMe	H	CHO	H	5d (n=7)	93 (18 h)

All products formed **4** and **5** were purified using column chromatography (SiO₂) eluting with different concentrations of petroleum ether:ethyl acetate to obtain pure substances as clean transparent oils. The structure of these simple products and its purity were confirmed by IR and MS spectra and by comparing their physical and spectral data with those reported in the literature ^{12,21-23}.

After the preparation and spectral characterization (MS and IR spectra) of 13 diverse O-alkylated phenols and naphthols, first we addressed to thermal aromatic Claisen rearrangement of allyl oxyarenes **4a-i** as a simple and inexpensive procedure for the respective *ortho*-allyl phenols and naphthols **6a-i**, needed in our biological investigations. Searching for suitable green solvents ^{24,25}, we decided to use 1,2-dichlorobenzene (DCB), toxic solvent, which is traditionally employed in this type of Claisen rearrangement and propylene carbonate

(CP, 4-methyl-1,3-dioxolan-2-one), nontoxic and bio-degradable solvent ²⁶ in our comparative study. Actually, propylene carbonate is widely used as a polar, aprotic solvent with high molecular dipole moment (4.9 D) in diverse chemical transformations ²⁷, but, to our knowledge, CP as solvent has not been used in Claisen rearrangement (Scheme 1). Results obtained during this study indicated that the use of propylene carbonate permitted to improve particularly product yields and reduce considerably the reaction time comparing with the use of 1,2-dichlorobenzene (Table 2). Although both protocols use high temperature regimes (DCB, 190 °C and CP, 140 °C), new procedure based on CP, green solvent stand out as a perspective method of preparing *ortho*-allyl phenols and naphthols that could be improved by use of microwave irradiation ²⁸. The structure of products **6a-i** obtained and its purity were confirmed by IR and MS spectra. Their ¹H NMR chemical shift values were matched with literature ^{12,21-23}.

Table 2. Comparative study on thermal aromatic Claisen rearrangement of allyloxyarenes **4a-i** in 1,2-dichlorobenzene (DCB) and propylene carbonate (CP) for the preparation of *ortho*-allyl hydroxyarenes **6a-i**.

Entry	R ₁	R ₂	R ₃	R ₄	Product	Yield, %	
						DCB (time)	CP (time)
					6		
1	H	H	H	H	a	55 (40 h)	73 (5 h)
2	CH=CH-CH=CH		H	H	b	52 (30 h)	73 (1h)
3	H	CH=CH-CH=CH		H	c	70 (10 h)	80 (1h)
4	CHMe ₂	H	H	Me	d	nt*	74 (2 h)
5	OMe	H	H	H	e	70 (10 h)	77 (4 h)
6	CHO	H	H	H	f	nt	82 (2 h)
7	H	H	CHO	H	g	75 (40 h)	80 (6 h)
8	OMe	H	CHO	H	h	nt	83 (6 h)
9	OMe	CHO	H	H	i	74 (15 h)	70 (4 h)

* nt – not tested

Next, selected allyl-aryl ethers **4h,i** and alkyl-aryl ethers **5a-d** containing a formyl function on aryl fragment were tested in three component Strecker reaction of piperidine and potassium cyanide in the presence of sulfuric acid supported on silica gel (SSA, SiO₂-O-SO₃H)²⁹ in acetonitrile at room temperature (Scheme 1). Simple stirring of a three-component mixture for 60 min allowed the simple preparation of the needed products as stable white crystal solids purified by flash column chromatography on silica gel, using petroleum ether/ethyl acetate as eluent (Table 3). Structure of the obtained compounds **7a-f** was confirmed strongly by common spectral methods. The IR spectra of α -amino nitriles obtained showed the characteristic C≡N bands appearing in the region of 2215-2298 cm⁻¹. In the ¹H NMR spectra of the amino nitriles **7a,b**, the protons of the O-CH₂CH=CH₂, aromatic and

piperidine rings, and Ar-CH-N_{pipe} fragments gave rise to very characteristic groups of signals. The singlet from a proton at C-4 was observed in the region δ 4.88-5.25 ppm. A signal for two protons corresponding to the O-CH₂ methylene group appeared in the region δ 4.60-4.66 ppm. The two multiples between δ 5.17-5.31 and δ 5.80-5.86 ppm are due to the olefinic hydrogens, -CH= and -CH=, respectively.

Their structures were also confirmed by MS, ¹H-, ¹³C-NMR spectra. Noteworthy, SSA is an inexpensive and reusable solid catalyst. The ¹H NMR spectra of other pairs of O-alkylated aryl amino nitriles **7c,d** and **7e,f** showed a characteristic pattern for the aliphatic chain, in addition to a CH-N proton singlet at δ 5.22-5.30 ppm and an O-CH₂R methylene triplet ($J = 4.7$ Hz) at δ 3.99-4.03 ppm

Table 3. Properties and yields of synthesized α -amino nitriles **7a-f**.^a

Product	R ₁	R ₅	Yield, %	Mp, °C	MW, g/mol	cLogP ^b	TPSA ^c	pKa
7a	H	Allyl	50	84-86	256.35	3.318	36.264	5.72
7b	OMe	Allyl	67	83-85	286.37	2.908	45.498	5.63
7c	H	n-Bu	52	86-88	272.39	4.112	36.264	5.72
7d	OMe	n-Bu	55	97-99	302.41	3.702	46.498	5.64
7e	H	n-Octyl	51	120-122	328.25	6.133	35.264	5.72
7f	OMe	n-Octyl	70	132-135	358.52	5.723	45.498	5.64

^a Theoretical values cLogP, TPSA and pKa were calculated using commercially available ChemDraw 15.0 program; ^bcLogP = *n*-octanol/water partition coefficient; ^cTPSA = Topological polar surface area.

Taking into consideration that the field of agrochemical discovery could benefit from treatment of pesticide-likeness (agrochemical-likeness)^{30,31}, we realized a small *in silico* calculation study evaluating some parameters (cLogP, TPSA and pKa) that can predict membrane permeability, lipophilicity and basicity of the synthetic molecule. From Table 3, it should be noted that 1. All compounds obtained possess favorable values of TPSA (36.26 - 45.49) and pKa for agrochemical substances; 2.

The values of calculated partition coefficient (cLog P) are above the lipophilicity optimum interval (0 < cLog P < 3). This means that all synthesized

α -amino nitriles molecules have a low water solubility character (cLog P > 2.90-6.13) that could compromise the absorption properties of these compounds. However, according to these parameters, the α -amino nitriles obtained **7a-f** could penetrate the cuticle of insects, especially the compounds **7e,f** with the hydrophobic portion.

Conclusion

Studying chemical transformations of diverse allyl(alkyl)-aryl ethers, prepared using Williamson reaction, it was shown that thermal aromatic

Claisen rearrangement of allyl-aryl ethers to obtain *ortho*-allyl phenols (naphthols) can be promoted considerably by propylene carbonate, green, nontoxic and biodegradable medium. The use of this green solvent allowed to enhance notably product yields and reduce significantly the reaction time comparing with the use of 1,2-dichlorobenzene. Also it demonstrated that simple three-component Strecker reaction of selected substituted benzaldehydes, piperidine and potassium cyanide in the presence of sulfuric acid supported on silica gel (SSA, SiO₂-O-SO₃H) under mild green reaction conditions allowed preparing easily new α -amino nitriles, analogues of alkaloid girsengohnine, interesting molecules in the search for new insecticidal agrochemicals against *Aedes aegypti*. According to the *in-silico* calculation study, all almost the α -amino nitriles obtained are moderate lipophilic compounds with favorable values of TPSA for agrochemical substances. Biological tests of these compounds are currently under study in our laboratories and their results will be published elsewhere in near future.

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Experimental

The melting points (uncorrected) were determined on a Fisher-Johns melting point apparatus. Infrared (FT-IR) spectra were recorded on a Lumex Infracum FT-02 spectrometer, γ_{\max} in cm⁻¹. Bands are characterized according to the functional group. ¹H-NMR spectra were obtained with a Bruker AM-400 spectrometer (400 MHz). Data were reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, dd = doublet of doublets, dt = doublet of triplets, ddd = doublet of doublet of doublets, td = triplet of doublets, qd = quartet of doublets, m = multiplet), coupling constants (Hz) and proton assignment. ¹³C-NMR spectra were obtained with a Bruker AM-400 (100 MHz) spectrometer with complete proton decoupling. Chemical shifts were reported in ppm (δ) relative to the solvent peak (CDCl₃, 7.24 ppm for ¹H and 77.23 ppm for ¹³C). A Hewlett Packard 5890a Series II Gas Chromatograph interfaced to an HP 5972 Mass Selective Detector (MSD) with an HP MS ChemStation Data system was used for MS identification at 70 eV using a 60 m capillary column coated with HP-5 [5%-phenylpoly(dimethylsiloxane)]. Elemental analyses were performed on a PerkinElmer 2400 Series II analyzer with theoretical values of ± 0.4 . The work-up for the reactions, extraction, and purification procedures in column chromatography were carried out using reactants and reagent grade solvents (purchased from Merck, Sigma-Aldrich and J.T.

Baker). Thin-layer chromatography (TLC) was performed using Silufol UV254 precoated plates (0.25 mm). UV light of 254 nm was used to observe components and iodine vapor was used for revealing. Column chromatography was performed using silica gel column as solid support (Merck, silica gel 60 (0.063 - 0.200 mm) 70-230 mesh) using as eluents solvent mixtures of petroleum ether and ethyl acetate.

Typical Procedure for Synthesis of Allyl(alkyl)-Aryl Ethers 4 and 5

A mixture of phenol **1** (1 mmol), allyl bromide **2** or alkyl bromides **3** (1 mmol) and Na₂CO₃ (2 mmol) in ethanol (10 mL) was heated to reflux for the required time as indicated in Table 1. The progress of the reaction was monitored by TLC. Standard work-up with filtration of reaction mixture, ethanol evaporation and ethyl acetate extraction followed by simple column chromatography provided the pure product. All products listed in Table 1 were known in the literature and were identified by comparison of their GC-MS, FT-IR, and ¹H NMR with literature data.

Typical Procedure for Thermal Aromatic Claisen rearrangement of Allyloxyarenes 4a-i

A solution of allyl compound **4a-4i** (10.00 mmol) in 1,2-dichlorobenzene (10 mL) or in propylene carbonate (5 mL) was subjected to heating (190 °C for DCB and 140 °C for PC). The progress of the reaction was monitored by TLC. Upon completion of the reaction, the solvent was evaporated and the reaction crude was purified by column chromatography (CC) on silica gel using a mixture of hexane and ethyl acetate as the eluent to obtain the rearranged product **5a-5i**. All products listed in Table 2 were known in the literature and were identified by comparison of their GC-MS, FT-IR, and ¹H NMR with literature data.

Typical Procedure for Synthesis of α -Amino nitriles 7a-f

Using a 50 mL round-bottom flask, benzaldehyde ethers **4h,i**, **5a-d** (3 mmol) and piperidine (1.5 mmol) were dissolved with a magnetic stirrer in acetonitrile (10 mL) and kept stirring for 30 minutes at room temperature. Subsequently, KCN (100 mg, 3 mmol) and 0.80 g of SSA catalyst were added to the flask. Then, the resulting suspension was stirred for 60 min (TLC control) and filtered. The resulting filtrate was quenched with saturated sodium bicarbonate solution (10 mL, 1 M), extracted with ethyl acetate (3 \times 10 mL), dried (Na₂SO₄) and concentrated. The obtained crude product was purified with silica gel column chromatography (SiO₂) eluting with different concentrations of petroleum ether:ethyl acetate to

obtain pure α -amino nitrile compounds **7a-f** as white stable solid with well-defined melting points (Table 3).

2-(4-(Allyloxy)phenyl)-2-(piperidin-1-yl)

acetoneitrile 7a. Evaluated by hexane: ethyl acetate (10:1) system. Yield 50%. White solid, mp. 84-86 °C. IR (KBr), ν cm^{-1} : 2854, 2298, 1604, 1511, 1465, 1249.

^1H NMR (400 MHz, CDCl_3), $\delta_{(\text{ppm})}$: 7.17 (2H, d, $J = 7.5$ Hz, H_{Ar}), 6.87 (2H, d, $J = 7.5$ Hz, H_{Ar}), 5.86 (1H, m, $-\text{CH}=\text{}$), 5.20 (1, s, $-\text{CH}-\text{CN}$), 5.16 (2H, m, $=\text{CH}_2$), 4.60 (2H, m, $-\text{O}-\text{CH}_2-$), 3.09 (4H, m, H_{Pipe}), 1.67 (4H, m, H_{Pipe}), 1.58 (2H, m, H_{Pipe}).

^{13}C NMR (101 MHz, CDCl_3), $\delta_{(\text{ppm})}$: 155.6, 134.5, 128.5, 128.4, 123.7, 117.5, 116.7, 115.7, 115.71, 70.1, 64.7, 51.3 (2C), 24.7 (2C), 23.4.

GC-MS: m/z (EI, %): 256 (M^+ , 30), 172 (90), 84 (30), 41 (100).

Anal. Calcd for $\text{C}_{16}\text{H}_{20}\text{N}_2\text{O}$: C, 74.97; H, 7.86; N, 10.93. Found: C, 74.68; H, 7.97; N, 10.76.

2-(4-(Allyloxy)-3-methoxyphenyl)-2-(piperidin-1-yl)acetoneitrile 7b.

Evaluated by hexane: ethyl acetate (5:1) system. Yield 67%. White solid, mp. 83-85 °C. IR (KBr), ν cm^{-1} : 2931, 2215, 1589, 1511, 1465, 1265.

^1H NMR (400 MHz, CDCl_3), $\delta_{(\text{ppm})}$: 6.85 (1H, d, $J = 6.8$ Hz, $5-\text{H}_{\text{Ar}}$), 6.84 (1H, s, $2-\text{H}_{\text{Ar}}$), 6.81 (1H, d, $J = 6.9$ Hz, $6-\text{H}_{\text{Ar}}$), 5.86 (1H, m, $-\text{CH}=\text{}$), 5.16 (2H, m, $=\text{CH}_2$), 4.88 (1H, s, $-\text{CH}-\text{CN}$), 4.60 (2H, d, $J = 6.3$ Hz, $-\text{O}-\text{CH}_2-$), 3.81 (3H, s, OMe), 2.54 (4H, m, H_{Pipe}), 1.66 (4H, m, H_{Pipe}), 1.61 (2H, m, H_{Pipe}).

^{13}C NMR (101 MHz, CDCl_3), $\delta_{(\text{ppm})}$: 149.6, 142.6, 134.7, 123.7, 121.0, 118.2, 117.5, 116.7, 109.2, 71.2, 65.5, 56.8, 51.3 (2C), 24.7 (2C), 23.42.

GC-MS: m/z (EI, %): 286 (M^+ , 10), 202 (60), 162 (25), 84 (100).

Anal. Calcd for $\text{C}_{17}\text{H}_{22}\text{N}_2\text{O}_2$: C, 71.30; H, 7.74; N, 9.78. Found: C, 71.17; H, 7.94; N, 9.63

2-(4-Butoxyphenyl)-2-(piperidin-1-yl)acetoneitrile

7c. Evaluated by hexane: ethyl acetate (10:1) system. Yield 52%. White solid, mp. 86-88 °C. IR (KBr), ν cm^{-1} : 2933, 1523, 1465, 1265.

^1H NMR (400 MHz, CDCl_3), $\delta_{(\text{ppm})}$: 7.27 (2H, d, $J = 7.3$ Hz, H_{Ar}), 6.92 (2H, d, $J = 7.5$ Hz, H_{Ar}), 5.22 (1H, s, $-\text{CH}-\text{CN}$), 3.99 (2H, t, $J = 4.7$ Hz, $-\text{OCH}_2-$), 2.65 (4H, dt, $J = 5.3$ Hz, H_{Pipe}), 1.73 (2H, m, CH_2 butyl), 1.65 (4H, m, H_{Pipe}), 1.63 (2H, m, H_{Pipe}), 1.44 (2H, m, CH_2 butyl), 0.99 (3H, m, $-\text{CH}_3$ butyl).

^{13}C NMR (101 MHz, CDCl_3), $\delta_{(\text{ppm})}$: 155.8, 128.8 (2C), 123.66, 116.7, 115.14 (2C), 69.8, 64.7, 51.25 (2C), 30.5, 24.7 (2C), 23.4, 19.9, 14.0.

GC-MS: m/z (EI, %): 272 (M^+ , 20), 188 (45), 132 (100), 84 (20).

Anal. Calcd for $\text{C}_{17}\text{H}_{24}\text{N}_2\text{O}$: C, 74.96; H, 8.88; N, 10.28. Found: C, 74.76; H, 8.97; N, 10.05.

2-(4-Butoxy-3-methoxyphenyl)-2-(piperidin-1-yl)acetoneitrile 7d.

Evaluated by hexane: ethyl acetate (10:1) system. Yield 55%. White solid, mp.

97-99 °C. IR (KBr), ν cm^{-1} : 2945, 1511, 1465, 1265.

^1H NMR (400 MHz, CDCl_3), $\delta_{(\text{ppm})}$: 7.07 (1H, s, $2-\text{H}_{\text{Ar}}$), 7.03 (1H, d, $J = 6.7$, $5-\text{H}_{\text{Ar}}$), 7.02 (1H, d, $J = 6.6$ Hz, $6-\text{H}_{\text{Ar}}$), 5.25 (1H, s, $-\text{CH}-\text{CN}$), 4.01 (2H, t, $J = 4.4$ Hz, $-\text{OCH}_2$ butyl), 3.83 (3H, s, OMe), 2.54 (4H, dt, $J = 5.5$ Hz, H_{Pipe}), 1.75 (2H, m, CH_2 butyl), 1.67 (4H, m, H_{Pipe}), 1.58 (2H, m, H_{Pipe}), 1.42 (2H, m, CH_2 butyl), 1.00 (3H, t, $J = 6.5$ Hz, $-\text{CH}_3$ butyl).

^{13}C NMR (101 MHz, CDCl_3), $\delta_{(\text{ppm})}$: 149.5, 142.8, 123.8, 121.1, 118.1, 116.7, 108.9, 70.6, 65.5, 56.8, 51.3 (2C), 30.5, 24.7 (2C), 23.4, 19.9, 14.0.

GC-MS: m/z (EI, %): 302 (M^+ , 1), 272 (30), 188 (55), 132 (100), 84 (25).

Anal. Calcd for $\text{C}_{18}\text{H}_{26}\text{N}_2\text{O}_2$: C, 71.49; H, 8.67; N, 9.26. Found: C, 71.23; H, 8.98; N, 9.35.

2-(4-(Octyloxy)phenyl)-2-(piperidin-1-yl)

acetoneitrile 7e. Evaluated by hexane: ethyl acetate (10:1) system. Yield 51%. White solid, mp. 120-122 °C. IR (KBr), ν cm^{-1} : 2932, 1532, 1265.

^1H NMR (400 MHz, CDCl_3), $\delta_{(\text{ppm})}$: 7.27 (2H, d, $J = 7.6$ Hz, H_{Ar}), 6.92 (2H, d, $J = 7.4$ Hz, H_{Ar}), 5.24 (1, s, $-\text{CH}-\text{CN}$), 3.95 (2H, t, $J = 7.5$ Hz, $-\text{OCH}_2$ octyl), 2.52 (4H, dt, $J = 5.3$ Hz, H_{Pipe}), 1.73 (2H, m, $-\text{CH}_2$ octyl), 1.66 (4H, m, H_{Pipe}), 1.57 (2H, m, H_{Pipe}), 1.31 (10H, m, $-\text{CH}_2$ octyl), 0.99 (3H, t, $J = 6.5$ Hz, $-\text{CH}_3$ octyl).

^{13}C NMR (101 MHz, CDCl_3), $\delta_{(\text{ppm})}$: 155.8, 128.8 (2C), 123.7, 116.7, 115.1 (2C), 69.6, 64.7, 51.25 (2C), 31.7, 29.1, 28.9, 28.7, 26.5, 24.7 (2C), 23.4, 22.9, 14.0.

GC-MS: m/z (EI, %): 328 (M^+ , 1), 272 (30), 188 (55), 132 (100), 84 (25).

Anal. Calcd for $\text{C}_{21}\text{H}_{32}\text{N}_2\text{O}$: C, 76.78; H, 9.82; N, 8.53. Found: C, 76.56; H, 9.61; N, 8.79.

2-(3-Methoxy-4-(octyloxy)phenyl)-2-(piperidin-1-yl)acetoneitrile 7f.

Evaluated by hexane: ethyl acetate (10:1) system. Yield 70%. White solid, mp. 132-135 °C. IR (KBr), ν cm^{-1} : 2931, 2215, 1511, 1465, 1265.

^1H NMR (400 MHz, CDCl_3), $\delta_{(\text{ppm})}$: 7.03 (3H, m, H_{Ar}), 5.30 (1, s, $-\text{CH}-\text{CN}$), 4.01 (2H, t, $J = 4.6$ Hz, $-\text{OCH}_2$ octyl), 3.83 (3H, s, OMe), 2.65 (4H, dt, $J = 5.2$ Hz, H_{Pipe}), 1.75 (2H, m, $-\text{CH}_2$ octyl), 1.65 (4H, m, H_{Pipe}), 1.63 (2H, m, H_{Pipe}), 1.34 (10H, m, $-\text{CH}_2$ octyl), 0.99 (3H, t, $J = 6.6$ Hz, $-\text{CH}_3$ octyl).

^{13}C NMR (101 MHz, CDCl_3), $\delta_{(\text{ppm})}$: 149.5, 142.7, 123.8, 121.1, 118.1, 116.7, 108.9, 70.3, 65.5, 56.8, 51.3 (2C), 31.6, 29.1, 28.9, 28.7, 26.5, 24.7 (2C), 23.4, 22.9, 14.0.

GC-MS: m/z (EI, %): 358 (M^+ , 1), 272 (30), 188 (55), 132 (100), 84 (25).

Anal. Calcd for $\text{C}_{22}\text{H}_{34}\text{N}_2\text{O}_2$: C, 73.70; H, 9.56; N, 7.81; O, 8.92. Found: C, 73.85; H, 9.34; N, 7.96.

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