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Alkyl alk-1-enyl alanes in Reissert like reaction

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Abstract

1,2-Dihydro-1-acyl-2-((*E*)-alk-1′-enyl)-pyridine, -quinoline and isoquinoline derivatives are prepared in good yields via an efficient procedure involving di-alkyl alk-1-enyl alanates. This simple one pot protocol affords useful and interesting poly functionalised intermediates in organic synthesis.

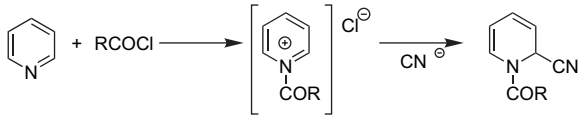
Keywords: Amides; Heterocycles; Alkenylation; Organoalanes

1. Introduction

Following our recent work employing di-alkyl alk-1-enyl aluminium–pyridine complexes with arylsulfonyl chlorides to obtain aryl alk-1-enyl sulfoxides,[1] we could extend the study by employing acyl chlorides in order to verify if we could access α,β-unsaturated carbonyl compounds.

Considering the differences between the polarity and hardness of sulfonyl and acyl moieties, a Reissert like reactivity was expectable too.

Reissert, in 1905, proposed an efficient method to alkylate pyridines, quinolines and isoquinolines[2–4] derivatives (Scheme 1).



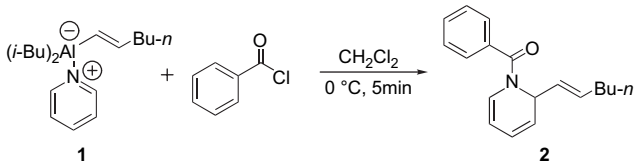
Scheme 1. The Reissert reaction.

Related methods to this reaction have been widely employed[3] also using Grignard reagents,[5–8] lithium derivatives,[9] alkenyl stannanes,[10–14] silyl derivatives[15] and more recently aluminium alkynes[16] as organometallic reagents in the alkylation of nitrogen bases.

Moreover taking into account that the reactivity of alkenyl alane–pyridine complexes towards acyl chlorides has not been thoroughly studied until now, it was interesting to investigate in the matter.

2. Results and discussion

In a preliminary attempt, benzoyl chloride was added to a CH_2Cl_2 solution of a preformed (*E*) di-*i*-butyl hex-1-enyl aluminium–pyridine complex **1**, in the same reaction conditions adopted for arylsulfonyl chlorides (Scheme 2).[1]



1 2

Scheme 2. Reaction of di-*i*-butyl hex-1-enyl aluminium-pyridine complex **1** with benzoyl chloride.

After few minutes the analyses (GC, NMR and GC–MS) of the reaction mixture showed the presence of 1,2-dihydro-1-benzoyl-2-((*E*)-hex-1′-enyl)pyridine (**2**) that was recovered in a nearly quantitative yield (94%, Table 1, run 1).

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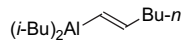
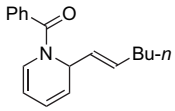
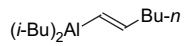
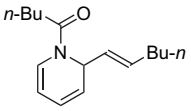
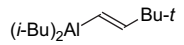
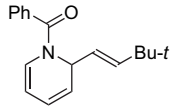
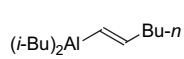
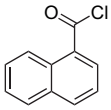
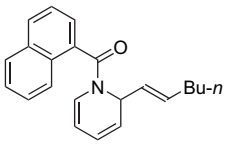
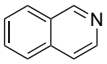
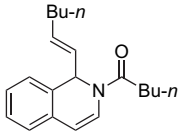
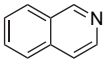
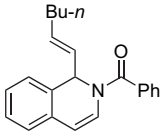
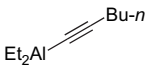
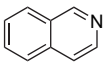
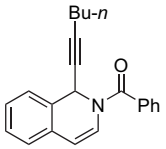
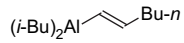
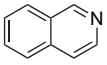
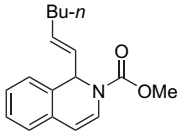
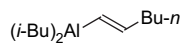
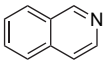
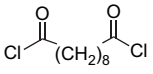
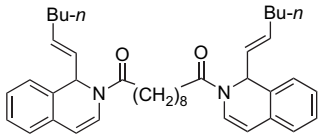
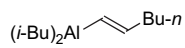
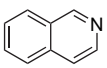
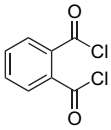
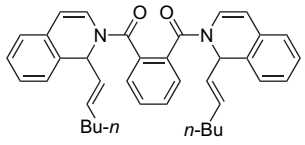
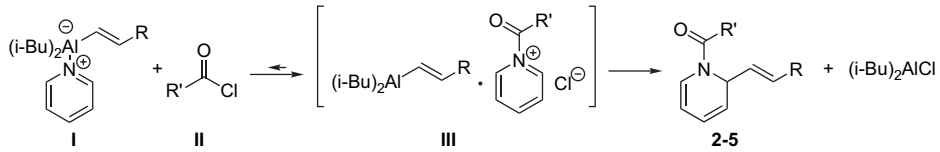
Table 1
N-acylation and C-alkenylation of pyridine and isoquinoline

Run[a]	R_2AlR''	Heterocycle	R′COCl	Product		Yield[b] (%)
1					**2**	94
2					**3**	94
3					**4**	94
4					**5**	90
5					**6**	93[c]
6					**7**	93[c,d]
7					**8**	92[c]
8					**9**	65[c]
9					**10**	61[c]
10					**11**	63[c]
11					**12**	60[c]

[a] All reaction were performed at 0 °C in CH_2Cl_2 solutions, using an organoalane/pyridine/acyl chloride 1:1:0.9 ratio.
[b] Evaluated on the isolated, chemically pure product.
[c] Reaction carried out at −20 °C.
[d] At 0 °C, an appreciable (10%) amount of (1-*i*-butylisoquinolin-2(1*H*)-yl)(phenyl)methanone was obtained.



Scheme 3. Suggested reaction pathway.

The reaction is effective even when different acyl chlorides are employed, affording products in good to excellent yields (Table 1).

The data collected in Table 1 show the applicability of the reaction to different nitrogen containing heterocyclic moieties, different acyl halides, alkenyl alanes and one acetylenic derivative such as 1-(hex-1-ynyl) alane (Table 1, run 7).

It must be underlined that large decreases in the yield occur when reaction conditions are changed. This is especially true when the sequence of addition is modified.

In our opinion the reaction between aluminium piridinate ***I*** and the opportune acyl chloride ***II***, occurs via the preliminary formation of a small amount of *N*-acylpyridinum chloride–organoalane complex ***III*** that, in the presence of free di-alkyl alk-1-enylalane, quickly reacts at the *C*2 position of the heterocyclic ring (Scheme 3).

This reaction could be easily employed in the synthesis of bicyclenes with nitrogen and oxygen as heteroatoms. These are interesting molecules in the treatment of disorder of calcium metabolism.[17–23]

In this view, 8-trimethylsilyloxy quinoline, firstly complexed with di-*i*-butyl hex-1-enylaluminium, reacted with bromoacetyl bromide at −20 °C, to give the expected product **13**[24] (Scheme 4).

Intermediate **13** can lead to tricyclic product **14** (80% yield) either slowly spontaneously or through a faster pathway in the presence of KF under phase transfer conditions.

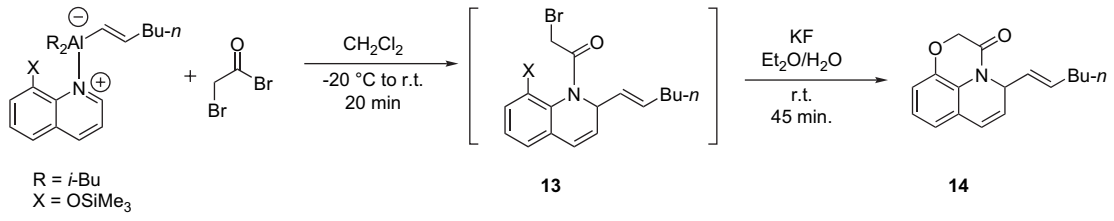
3. Conclusions

In conclusion, a new one pot N-acylation, C-alkenylation of pyridine, quinoline and isoquinoline ring, with complete chemo and regioselectivity, has been reported.

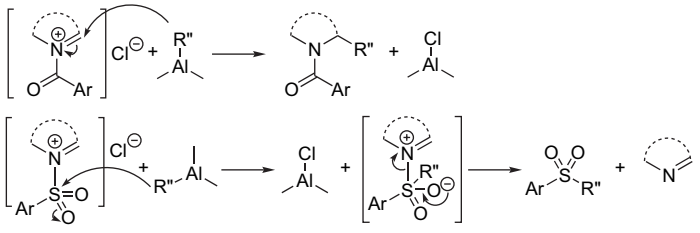
The products can be obtained with a simple work-up procedure and promise to give valuable intermediates in the synthesis of natural and biologically active products.[25,26]

The described reactions highlight the difference in the reactivity between acyl or sulfonyl halide–pyridine complexes towards alkenyl alanes that, as shown in the Scheme 5, react at the C_2 pyridine carbon atom in the first case but with the sulfonyl group in the second one[27] due to the different hardness of the two substrates employed.

Studies are in progress in order to investigate the biological and pharmacological activity of the synthesized compounds and to extend the reactivity[27] to the synthesis of aryl alk-1-enyl sulfones.



Scheme 4. Synthesis of a tricyclic compound starting from 8-trimethylsilyloxy quinoline.



Scheme 5. Reactivity of alkenyl alanes with sulfonyl or acyl pyridinate.

4. Experimental section

4.1. General procedures and materials

Dichloromethane was refluxed on, and distilled from, P_2O_5. Acid halides were purified by distillation and stored under inert atmosphere until their use. Di-*i*-butyl aluminium hydride (DIBAL-H) was synthesized starting from Al(*i*-Bu)$_3$. Quinoline and isoquinoline were purified by distillation and stored under inert atmosphere until their use. Alkynes were distilled immediately before the use. GLC analyses were performed on a Perkin–Elmer 8500 instrument [ZB1 capillary column (15 m×0.25 mm), film 0.25 μm] equipped with a flame ionization detector and a split–splitless injector, with He as carrier gas. Thin layer chromatography (TLC) analyses were performed on silica gel 60 plates (Fluka) and flash chromatography purifications were carried out on silica gel 60 (Fluka, 230–400 mesh) using the eluting mixtures (v/v) reported for each case. Melting points were determined using a Kofler hot stage apparatus and are not corrected. ^{1}H and ^{13}C NMR (300 and 75 MHz, respectively) spectra were recorded on a Varian Infinity 300 spectrometer; all NMR data were obtained using $CDCl_3$ solutions. Chemical shifts (δ, ppm) are referred to tetramethylsilane (TMS) (^{1}H NMR) or $CDCl_3$ (^{13}C NMR) as internal standard. Mass spectra (*m/z*, I%) were taken on a 5980 Hewlett–Packard GC instrument, equipped with an HP-5MS column (30 m×0.25 mm, film 0.25 μm) interfaced with an Hewlett–Packard 5995A instrument, with He as carrier gas. Indicated yields are reported on the isolated, chemically pure products.

4.2. Hydroalumination of alkynes

In a typical run, a hexane solution of DIBAL-H (1.0 mL, 1 mmol) was slowly added to a cooled (0 °C) hexane solution (25 mL) of the suitable alkyne (1.1 mmol). The mixture was then refluxed for 5 h, cooled to room temperature, the hexane was removed in vacuo (15 mmHg), replaced with CH_2Cl_2 (25 mL) and the solution was used without further purifications.

4.3. Preparation of unsolvated diethyl hex-1-ynyl alane[28]

In a typical procedure, freshly distilled triethylamine (5.5 μL, 0.075 mmol,) and an hexane solution (25 mL) of hex-1-yne (0.6 mL, 1 mmol) were added to a cooled (0 °C) hexane solution (25 mL) of DIBAL-H (1.0 mL, 1 mmol). After stirring for 2 h at 0 °C the mixture was allowed to warm at room temperature, the solvent was removed at reduced pressure (15 mmHg), replaced with CH_2Cl_2 (25 mL) and the solution was used without further purifications.

4.4. 8-Trimethylsilyloxy quinoline[29]

To a solution of 8-hydroxyquinoline (4.79 g, 33 mmol), imidazole (2.36 g, 35 mmol) in 50 ml of dry CH_2Cl_2, 4.62 ml (36 mmol) of trimethylsilyl chloride was added. The mixture was stirred overnight, then diethyl ether (100 ml) was added and then filtered. The organic layer was dried over Na_2SO_4 and the solvent evaporated under reduced pressure (18 mmHg), affording the chemically pure product as a yellowish oil (6.32 g, 88%); GC–MS (*m/z*, I%): 216 ($M^{\bullet+}-1$, 3), 204 (5), 203 (20), 202 (100), 186 (2), 172 (34), 142 (4), 128 (5), 101 (5), 94 (4); ^{1}H NMR: 0.20 (s, 9H, $-Si(CH_3)_3$), [7.21 (dd, J=7.5 Hz, J'=1.5 Hz, 1H), 7.36 (dd, J=7.5 Hz, J'=7.5 Hz, 1H), 7.45 (dd, J=7.5 Hz, J'=1.5 Hz, 1H), 7.48 (dd, J=7.5 Hz, J'=1.5 Hz, 1H), 8.18 (dd, J=7.5 Hz, J'=7.5 Hz, 1H), 8.81 (dd, J=7.5 Hz, J'=1.5 Hz, 1H), Ar–]; ^{13}C NMR: 5.4, 110.4, 118.0, 121.9, 127.9, 128.7, 136.3, 138.4, 148.1, 152.4.

4.5. 1,2-Dihydro-1-acyl-2-((*E*)-alk-1′-enyl)-pyridine, -quinoline and isoquinoline derivatives (**2–12**, **14**)

In a typical reaction, the appropriate heteroaromatic substrate (3.0 mmol) was added to the CH_2Cl_2 solution (30 mL) of the unsaturated alane (3.0 mmol), prepared as described above. The solution was cooled to 0 or −20 °C (depending on the nature of the heteroaromatic precursor used) and the acid halide (2.7 mmol) was quickly added. After stirring (30 min) the reaction mixture was siphoned onto a short column of silica gel and eluted with 200 ml of CH_2Cl_2. The solution was dried over anhydrous Na_2SO_4 and then the solvent removed at reduced pressure (18 mmHg). Flash chromatography was sometimes needed to obtain the pure products **2–12**, **14**.

4.6. 5-((*E*)-Hex-1-enyl)-2H-[1,4]oxazino[2,3,4-ij]-quinolin-3(5H)-one (**14**)

Crude 1,2-dihydro-1-(2-bromoacetyl)-2-(hex-1-enyl)-8-trimethylsilyloxy quinoline (**13**) arising from the previously described procedure was dissolved in Et_2O (30 mL). This solution was added to 30 ml of an aqueous solution of KF (5% w/v). The mixture was vigorously stirred at room temperature (45 min) until complete conversion of the product (GLC). The recovered organic layer was washed with water (20 mL) and dried. After evaporation of the solvent at reduced pressure the chemically pure **14** was recovered.

4.7. Characterization of products **2–12** and **14**

For each of the synthesized compounds the following characterizations are reported: eluting mixture for the flash chromatography, physical state, mass spectrum, ^{1}H and ^{13}C NMR, IR spectrum.

4.7.1. (2-((*E*)-Hex-1-enyl)pyridin-1(2H)-yl)(phenyl)-methanone (**2**)

Hexane/ethyl acetate 85:15; yellowish oil; GC–MS (*m/z*, I%): 267 ($M^{\bullet+}$, 7), 224 (1), 210 (2), 184 (18), 162 (22), 132 (1), 118 (3), 105 (100), 77 (32); ^{1}H NMR: 0.88 (t, J=7.0 Hz, 3H, CH_3), 1.20–1.40 (m, 4H, $CH_3-CH_2-CH_2-$), 2.03 (tdd, J=7.0 Hz, J'=6.6 Hz, J''=1.0 Hz, 2H, $-CH=CH-CH_2-$), 5.25 (br t, J=7.0 Hz, 1H, $>CH-N<$),

5.50–5.80 (m, 4H, –CH=C*H*–CH=C*H*–CH(N)–C*H*=C*H*–), 6.03 (dd, *J*=9.2 Hz, *J′*=5.4 Hz, 1H, –C*H*=CH–CH(N)–), 6.30 (br s, 1H, –CH=C*H*–N<), 7.40–7.70 (m, 5H, Ph–); ^{13}C NMR: 14.1, 22.4, 31.4, 32.1, 51.4, 109.1, 121.7, 123.1, 125.6 (2C), 128.6 (2C), 129.2, 130.7, 133.5, 134.3, 135.1, 169.3; IR (cm^{-1}): 3061, 3030, 2956, 2928, 2871, 2859, 1719, 1637, 1578, 1530, 1489, 1448, 1413, 1358, 1263, 1109, 1071, 1027, 970, 790, 755, 712. Anal. Calcd for $C_{18}H_{21}NO$: C, 80.86; H, 7.92; N, 5.24%. Found: C, 80.83; H, 7.94; N, 5.25%.

4.7.2. 1-(2-((*E*)-Hex-1-enyl)pyridin-1(2*H*)-yl)pentan-1-one (**3**)

Hexane/ethyl acetate 85:15; yellowish oil; GC–MS (*m*/*z*, I%): 247 (M$^{\bullet+}$, 14), 218 (1), 204 (1), 190 (3), 162 (40), 132 (2), 120 (16), 106 (11), 93 (4), 80 (100), 67 (2), 57 (10); ^{1}H NMR: 0.90, 0.93 (2t, *J*=*J′*=7.0 Hz, 6H, 2C*H*$_3$), 1.20–1.40, 1.55–1.75 (2m, 8H, 2-C*H*$_2$–C*H*$_2$–CH$_3$), 1.97 (td, *J*=6.6 Hz, *J′*=7.0 Hz, 2H, –CH=CH–C*H*$_2$–), 2.41 (t, *J*=7.7 Hz, 2H, –CH$_2$–C*H*$_2$–CO–), 4.92 (br t, *J*=7.0 Hz, 1H, >C*H*–N<), 5.2–5.7 (m, 4H, –CH=C*H*–CH=C*H*–CH(N)–C*H*=C*H*–), 5.95 (dd, *J*=8.4 Hz, *J′*=5.5 Hz, 1H, –C*H*=CH–CH(N)–), 6.49 (d, *J*=7.7 Hz, 1H, >N–C*H*=CH–); ^{13}C NMR: 14.1(2C), 22.4, 22.7, 27.1, 31.4, 32.0, 33.3, 51.5, 107.2, 121.2, 123.7, 124.7, 126.0, 133.2, 171.9; IR (cm^{-1}): 3023, 2957, 2930, 2871, 1672, 1625, 1569, 1491, 1456, 1412, 1379, 1290, 1218, 1105, 966, 920, 775, 752. Anal. Calcd for $C_{16}H_{25}NO$: C, 77.68; H, 10.19; N, 5.66%. Found: C, 77.66; H, 10.17; N, 5.69%.

4.7.3. (2-((*E*)-3,3-Dimethylbut-1-enyl)pyridin-1(2*H*)-yl)(phenyl)methanone (**4**)

Hexane/ethyl acetate 85/15; yellowish oil; GC–MS (*m*/*z*, I%): 267 (M$^{\bullet+}$, 7), 224 (2), 184 (22), 162 (5), 131 (15), 118 (14), 105 (100), 77 (38), 55 (6); ^{1}H NMR: 0.91 (s, 9H, -C(C*H*$_3$)$_3$), 5.28 (br t, *J*=7.0 Hz, 1H, >C*H*–N<) 5.50–5.80 (m, 4H, –CH=C*H*–CH=C*H*–CH(N)–C*H*=C*H*–), 5.98 (dd, *J*=9.0 Hz, *J′*=5.6 Hz, 1H, –C*H*=CH–CH(N)–), 6.35 (br s, 1H, –CH=C*H*–N<), 7.40–7.70 (m, 5H, Ph–); ^{13}C NMR: 23.0 (3C), 31.4, 51.8, 109.0, 121.6, 123.3, 125.5 (2C), 128.7 (2C), 129.2, 130.2, 133.4, 134.3, 135.0, 169.0; IR (cm^{-1}): 3058, 3027, 2960, 2930, 2864, 2845, 1725, 1638, 1585, 1532, 1484, 1450, 1412, 1314, 1262, 1111, 1073, 1024, 967, 787, 754, 711. Anal. Calcd for $C_{18}H_{21}NO$: C, 80.86; H, 7.92; N, 5.24%. Found: C, 80.83; H, 7.96; N, 5.22%.

4.7.4. (2-((*E*)-Hex-1-enyl)pyridin-1(2*H*)-yl)(naphthalen-1-yl)methanone (**5**)

Hexane/ethyl acetate 85:15; yellowish oil; GC–MS (*m*/*z*, I%): 317 (M$^{\bullet+}$, 3), 289 (1), 260 (1), 234 (2), 232 (2), 219 (1), 162 (15), 156 (17), 155 (100), 127 (47), 118 (2), 101 (2), 91 (1), 77 (3); ^{1}H NMR: 0.91 (t, *J*=7.0 Hz, 3H, –CH$_3$), 1.20–1.40 (m, 4H, –C*H*$_2$–C*H*$_2$–CH$_3$), 2.10 (tdd, *J*=6.7 Hz, *J′*=7.1 Hz, *J″*=1.1 Hz, 2H, –C*H*$_2$–CH=CH–), 5.27 (br t, *J*=7.1 Hz, 1H, >C*H*–N<), 5.50–5.80 (m, 4H, –CH=C*H*–CH=C*H*–CH(N)–C*H*=C*H*–), 6.07 (dd, *J*=9.2 Hz, *J′*=5.4 Hz, 1H, –C*H*=CH–CH(N)–), 6.30 (br s, 1H, –CH=C*H*–N<), 7.40–7.80 (m, 7H, Np–), 9.05 (dd, *J*=8.4 Hz, *J′*=1.1 Hz, 1H, Np–); ^{13}C NMR: 14.1, 22.4, 31.4, 32.1, 51.4, 109.1, 120.3, 121.7, 123.1, 125.6 (2C), 128.6, 129.2, 130.7, 131.1, 132.4, 133.1, 133.5, 134.7 (2C), 135.1, 169.3; IR (cm^{-1}): 3048, 2956, 2928, 2870, 2858, 1713, 1635, 1592, 1579, 1509, 1463, 1414, 1351, 1255, 1214, 1196, 1132, 1027, 970, 780, 737, 634. Anal. Calcd for $C_{22}H_{23}NO$: C, 83.24; H, 7.30; N, 4.41%. Found: C, 83.23; H, 7.27; N, 4.39%.

4.7.5. 1-(1-((*E*)-Hex-1-enyl)isoquinolin-2(1*H*)-yl)pentan-1-one (**6**)

Hexane/ethyl acetate 85:15; yellowish oil; GC–MS (*m*/*z*, I%): 297 (M$^{\bullet+}$, 18), 282 (7), 275 (9), 268 (45), 254 (25), 240 (7), 230 (8), 214 (32), 212 (14), 195 (18), 168 (39), 154 (3), 129 (12), 85 (4); ^{1}H NMR: 0.90, 0.99 (2t, *J*=*J′*=7 Hz, 6H, 2-CH$_3$), 1.30–1.60 (m, 8H, 2-CH$_2$–C*H*$_2$–C*H*$_2$–CH$_3$), 2.01 (tdd, *J*=6.6 Hz, *J′*=7.0 Hz, *J″*=1.0 Hz, 2H, –CH=CH–C*H*$_2$–), 2.35 (t, *J*=7.1 Hz, 2H, –CH$_2$–CO–), 5.52 (dt, *J*=14.1 Hz, *J′*=7.0 Hz, 1H, –CH=C*H*–CH$_2$–), 5.98 (br s, 1H, >N–C*H*<), 6.10–6.80 (m, 3H, –C*H*=C*H*–(N)–CH–C*H*=CH–), 7.20–7.40 (m, 4H, Ar–); ^{13}C NMR: 12.9, 13.5, 18.4, 19.0, 21.5, 22.4, 31.2, 32.3, 47.0, 110.2, 125.9, 127.6, 128.9, 129.4, 130.0, 131.2, 131.7, 134.3, 135.5, 169.2; IR (cm^{-1}): 3067, 2958, 2917, 2215, 1772, 1661, 1618, 1583, 1451, 1337, 1260, 1241, 1163, 1102, 921, 752, 722, 685. Anal. Calcd for $C_{20}H_{27}NO$: C, 80.76; H, 9.15; N, 4.71%. Found: C, 80.74; H, 9.13; N, 4.73%.

4.7.6. (1-((*E*)-Hex-1-enyl)isoquinolin-2(1*H*)-yl)(phenyl)methanone (**7**)

Hexane/ethyl acetate 85:15; yellowish oil; GC–MS (*m*/*z*, I%): 317 (M$^{\bullet+}$, 15), 288 (5), 275 (18), 274 (22), 260 (37), 242 (4), 230 (13), 212 (25), 168 (21), 154 (1), 129 (17), 105 (100), 83 (19) 77 (56); ^{1}H NMR: 0.96 (t, *J*=7 Hz, 3H, –CH$_3$), 1.30–1.60 (m, 4H, –C*H*$_2$–C*H*$_2$–CH$_3$), 2.27 (td, *J*=7.0 Hz, *J′*=6.9 Hz, 2H, –CH=CH–C*H*$_2$–), 5.48 (dt, *J*=13.8 Hz, *J′*=6.9 Hz, 1H, –CH=C*H*–CH$_2$–), 6.10 (br s, 1H, >N–C*H*<), 6.20–6.80 (m, 3H, –C*H*=C*H*–(N)–CH–C*H*=CH–), 7.20–7.40 (m, 4H, Ar–), 7.50–7.80 (m, 5H, Ph); ^{13}C NMR: 13.5, 19.0, 22.4, 31.2, 47.0, 110.2, 125.9, 126.2, 127.6 (2C), 128.2, 128.9 (2C), 129.4, 129.7, 130.0, 131.1, 131.7, 134.0, 134.3, 135.5, 169.2; IR (cm^{-1}): 3056, 2946, 2929, 2223, 1784, 1673, 1629, 1573, 1444, 1343, 1265, 1238, 1159, 1098, 910, 760, 729, 699. Anal. Calcd for $C_{22}H_{23}NO$: C, 83.24; H, 7.30; N, 4.41%. Found: C, 83.22; H, 7.33; N, 4.43%.

4.7.7. (1-(Hex-1-ynyl)isoquinolin-2(1*H*)-yl)-(phenyl)methanone (**8**)

Hexane/ethyl acetate 85:15; yellowish oil; GC–MS (*m*/*z*, I%): 315 (M$^{\bullet+}$, 14), 286 (7), 273 (13), 272 (24), 258 (21), 244 (9), 230 (4), 210 (33), 180 (5), 168 (12), 154 (4), 129 (10), 105 (100), 77 (45); ^{1}H NMR: 0.92 (t, *J*=7 Hz, 3H, –CH$_3$), 1.30–1.60 (m, 4H, –C*H*$_2$–C*H*$_2$–CH$_3$), 2.20 (t, *J*=7 Hz, 2H, –C≡C–C*H*$_2$–), 6.07 (br s, 1H, >N–CH<), 6.40–6.80 (m, 2H, –C*H*=C*H*–(N)–CH–C≡C–), 7.20–7.40 (m, 4H, Ar–), 7.50–7.80 (m, 5H, Ph–); ^{13}C NMR: 13.8, 18.7, 22.1,

30.7, 47.2, 78.4, 84.7, 110.3, 125.4, 126.4, 127.9 (2C), 128.5 (2C), 128.7, 129.0, 129.3, 131.3, 131.6, 134.3, 135.6, 169.0; IR (cm^{-1}): 3061, 2957, 2931, 2216, 1773, 1664, 1625, 1569, 1455, 1349, 1272, 1231, 1154, 1102, 919, 773, 726, 701. Anal. Calcd for $C_{22}H_{21}NO$: C, 83.78; H, 6.71; N, 4.44%. Found: C, 83.75; H, 6.73; N, 4.42%.

*4.7.8. Methyl 1-((E)-hex-1-enyl)isoquinoline-2(1H)-carboxylate (**9**)*

Hexane/ethyl acetate 80:20; yellowish oil GC–MS (*m/z*, I%): 271 ($M^{\bullet+}$, 20), 214 (2), 188 (100), 168 (5), 156 (1), 144 (25), 129 (8), 115 (5), 103 (6), 77 (2), 59 (3); ^1H NMR: 0.83 (t, J=7.3 Hz, 3H, $-CH_3$), 1.20–1.40 (m, 4H, $-CH_2-CH_2-CH_3$), 1.93 (dt, J=6.2 Hz, J'=6.6 Hz, 2H, $-CH=CH-CH_2-$), 3.82 (s, 3H, $-O-CH_3$), 5.40–5.55 (m, 3H, $-CH=CH-(N)-CH-CH=CH-$), 5.75–5.90 (m, 1H, $-CH=CH-CH_2-$), 6.75–6.95 (br s, 1H, >N–CH<), 7.00–7.25 (m, 4H, Ar–); ^{13}C NMR: 13.9, 22.2, 31.2 31.7, 53.2, 57.3 (broad), 108.3, 124.8, 126.1, 126.7, 127.0, 127.7, 128.0, 130.4, 131.7, 132.1, 149.2; IR (cm^{-1}): 2955, 2927, 2871, 2856, 1718, 1633, 1571, 1456, 1441, 1413, 1352, 1235, 1193, 1121, 1101, 968, 923, 771. Anal. Calcd for $C_{17}H_{21}NO_2$: C, 75.25; H, 7.80; N, 5.16%. Found: C, 75.26; H, 7.82; N, 5.17%.

*4.7.9. 1,10-Bis(1-((E)-hex-1-enyl)isoquinolin-2(1H)-yl)-decane-1,10-dione (**10**)*

Hexane/ethyl acetate 85:15; yellowish oil; GC–MS (*m/z*, I%): could not be recorded due to the low volatility of the product; ^1H NMR: 0.82, 0.88 (2t, 6H, $J=J'$=7.0 Hz, 2-CH_3), 1.10–1.50 (m, 8H, 2 ($-CH_2-CH_2-CH_3$)), 1.60–1.80 (m, 12H, $-(CH_2)_6-$), 1.92 (2t, J=5.8 Hz, J'=5.6 Hz, 4H, 2 ($-CH_2-CO-$)), 2.20–2.60 (m, 4H, ($-CH=CH-CH_2-$)), 5.30–6.00 (m, 8H, 2 ($-CH=CH-(N)-CH-CH=CH-$)), 6.65–6.69 (m, 2H, 2 ($-CH=CH-(N)-CH-CH=CH-$)), 7.00–7.30 (m, 8H, 2 Ar–), 7.60–8.10 (m, 2H); ^{13}C NMR: 13.9 (2C), 22.2 (2C), 24.9 (2C), 29.2 (2C), 31.7 (2C), 34.1 (2C), 44.5 (2C), 54.9 (2C), 109.9 (2C), 124.7 (2C), 126.0 (2C), 126.7 (2C), 127.3 (2C), 127.7 (2C), 129.8 (2C), 130.2 (2C), 131.1 (2C), 132.4 (2C), 132.6 (2C), 171.2 (2C); IR (cm^{-1}): 3062, 3018, 2946, 2921, 2864, 2852, 1724, 1664, 1613, 1578, 1562, 1449, 1405, 1352, 1286, 1227, 1157, 1113, 925, 754, 712, 685. Anal. Calcd for $C_{40}H_{52}N_2O_2$: C, 81.04; H, 8.84; N, 4.73%. Found: C, 81.07; H, 8.82; N, 4.69%.

*4.7.10. 1,2-Bis-2–1-[(E)-hex-1-enyl]isoquinolin-2(1H)-ylbenzene-1,2-dione (**11**)*

Hexane/ethyl acetate 85:15; yellowish oil GC–MS (*m/z*, I%): could not be recorded due to the low volatility of the product; ^1H NMR: 0.84 (2t, $J=J'$=7.0 Hz, 6H, 2-CH_3), 1.10–1.30 (m, 8H, 2 ($-CH_2-CH_2-CH_3$)), 1.80–2.00 (m, 4H, 2 ($-CH=CH-CH_2-$)), 5.30–5.60 (m, 4H, 2 (>N–$CH-CH=CH-$)), 5.60–6.60 (m, 6H, 2 ($-CH=CH-(N)-CH-CH=CH-$)), 6.90–7.80 (m, 12H, 2-Ar, Ph–); ^{13}C NMR: 14.0, 22.2 (2C), 31.2 (2C), 31.7 (2C), 55.5 (2C), 109.4 (2C), 124.9 (2C), 125.8 (2C), 127.2 (2C), 127.7 (2C), 128.1 (2C), 128.5 (2C), 128.7 (2C), 129.8 (2C), 130.1 (2C), 132.0 (2C), 132.3 (2C), 134.8 (2C), 167.5 (2C); IR (cm^{-1}): 3058, 3023, 2956, 2927, 2870, 2857, 1720, 1660, 1625, 1595, 1569, 1489, 1455, 1413, 1359, 1290, 1234, 1198, 1157, 1118, 1090, 967, 919, 774, 749, 722, 709, 695. Anal. Calcd for $C_{38}H_{40}N_2O_2$: C, 81.98; H, 7.24; N, 5.03%. Found: 81.95; H, 7.27; N, 5.06%.

*4.7.11. 2-Bromo-1-(1-((E)-hex-1-enyl)isoquinolin-2(1H)-yl)ethanone (**12**)*

Hexane/ethyl acetate 80:20; yellowish oil GC–MS (*m/z*, I%): 334 ($M^{\bullet+}$, 12), 333 (12), 254 (33), 252 (38), 250 (39), 212 (9), 196 (3), 182 (3), 168 (14), 156 (4), 154 (4), 143 (6), 130 (100), 115 (7), 102 (5), 89 (1), 77 (3); ^1H NMR: 0.86 (t, J=7.0 Hz, 3H, $-CH_3$), 1.20–1.40 (m, 4H, $-CH_2-CH_2-CH_3$), 1.90–2.05 (m, 2H, $-CH=CH-CH_2-$), 3.98 (s, 2H, $-CH_2-Br$), 5.40–6.03 (m, 3H, $-CH=CH-(N)-CH-CH=CH-$), 6.13 (m, 1H, $-CH=CH-CH_2-$), 6.69 (dd, J=7.7 Hz, J'=1.0 Hz, 1H, >N–CH<), 7.10–7.35 (m, 4H, Ar–); ^{13}C NMR: 13.9, 22.2, 25.6, 31.1, 31.7, 55.5, 111.7, 123.9, 125.2, 126.4, 127.0, 127.8, 127.9, 129.6, 132.5, 133.0, 164.3; IR (cm^{-1}): 2960, 2930, 2865, 2850, 1707, 1621, 1561, 1432, 1423, 1408, 1360, 1231, 1187, 1112, 1098, 972, 920, 765. Anal. Calcd for $C_{17}H_{20}BrNO$: C, 61.09; H, 6.03; Br, 23.91; N, 4.19%. Found: C, 61.12; H, 6.05; Br, 23.87; N, 4.16%.

*4.7.12. 5-((E)-Hex-1-enyl)-2H-[1,4]-oxazino-[2,3,4-ij]quinolin-3(5H)-one (**14**)*

Yellowish oil; GC–MS (*m/z*, I%): 269 ($M^{\bullet+}$, 38), 252 (2), 240 (9), 227 (19), 212 (14), 198 (12), 186 (99), 167 (6), 158 (100), 128 (28), 115 (6), 101 (5), 89 (5), 77 (7); ^1H NMR: 0.86 (t, J=7.3 Hz, 3H, $-CH_3$), 1.10–1.40 (m, 4H, $-CH_2-CH_2-CH_3$), 1.98 (dt, J=6.6 Hz, J'=7.3 Hz, 2H, $-CH=CH-CH_2-$), 4.48 (s, 2H, $-O-CH_2-$), 4.72 (d, J=5.5 Hz, 1H, $-CH=CH-CH(N)-$), 5.45 (dt, J=15 Hz, J'=6.6 Hz, 1H, $-CH=CH-CH_2-$), 5.60–5.80 (m, 1H, $-CH=CH-CH_2-$), 5.86 (dd, J=10 Hz, J'=5.5 Hz, 1H, $C-CH=CH-CH(N)-$), 6.47 (d, J=10.0 Hz, 1H, $C-CH=CH-CH(N)-$), 6.75–7.00 (m, 3H, Ar–); ^{13}C NMR: 14.0, 22.3, 31.1, 31.8, 51.7, 68.0, 116.6, 120.8, 122.8, 123.3, 123.7, 125.9, 126.1, 131.2, 134.2, 144.5, 163.9; IR (cm^{-1}): 3045, 2957, 2927, 2871, 2857, 1688, 1580, 1477, 1386, 1358, 1311, 1277, 1252, 1181, 1085, 1055, 1035, 967, 802, 726, 705. Anal. Calcd for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11; N, 5.20%. Found: C, 75.84; H, 7.13; N, 5.18%.

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