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PAPER

Copper(II)-mediated oxidative cyclization of enamides to oxazoles†

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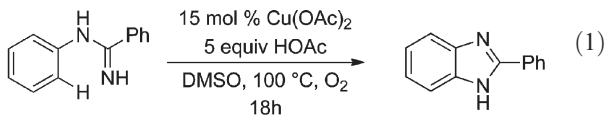
The copper(II)-mediated oxidative cyclization of enamides to oxazoles is reported. A range of 2,5-disubstituted oxazoles were prepared in moderate to good yields in two steps from simple amide and alkyne precursors.

Introduction

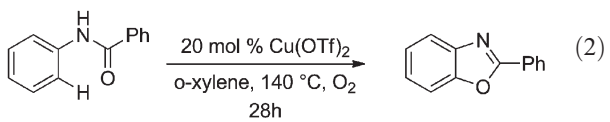
Copper(II)-mediated C–H oxidation reactions have been the focus of extensive attention in recent years.[1,2] Many applications of these reactions are oxidative cyclizations involving heterofunctionalization of arene C–H bonds.[3] Two early examples, reported by the groups of Buchwald[3a] and Nagasawa,[3b,c] feature copper-catalyzed oxidative cyclization of substituted benzamidines and benzanilides to benzimidazoles (eqn (1)) and benzoxazoles (eqn (2)), respectively. In connection with our broader interest in the oxidative functionalization of alkenes,[4] we wondered whether analogous C–H oxidation reactions could be achieved with enamides (eqn (3)). Here, we present a method for the synthesis of 2,5-disubstituted oxazoles *via* sequential anti-Markovnikov hydroamidation of terminal alkynes, followed by Cu-mediated cyclization of the resulting enamides.

Buchwald et al.

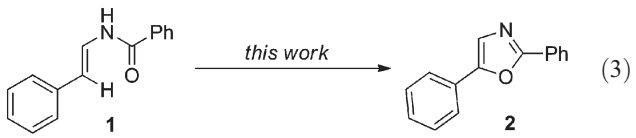


(1)

Nagasawa et al.



(2)



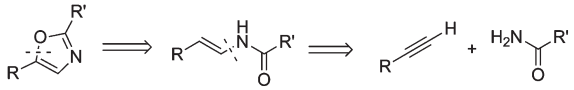
(3)

Oxazoles are an important class of heterocycles that are ubiquitous in biologically active molecules, including pharmaceuticals and natural products.[5] Annulation methods are among numerous approaches used in the preparation of substituted oxazoles. Recent examples include multicomponent coupling reactions,[6] intramolecular additions to alkynes,[7] and oxidative and non-oxidative condensation and substitution reactions.[8] Several methods are particularly relevant to the work described here. Yoshimura and coworkers[8a] developed a heterocyclization method involving base-mediated *O*-vinylation *via* *O*-addition/HBr-elimination of β-bromoenamides. A similar method was later implemented by Pattenden *et al.*[8b] Glorius and coworkers have reported a method for copper-catalyzed coupling of primary amides with 1,2-dihalogenated olefins, which affords mixtures of 2,4- and 2,5-disubstituted oxazoles.[8c] Buchwald *et al.* have developed a two-step, one-pot method for copper-catalyzed cross-coupling of vinyl halides with primary amides, followed by intramolecular *O*-vinylation *via* iodine-mediated *O*-addition to the alkene and elimination of HI.[8d]

Each of the methods just noted requires access to vinyl halide precursors. We envisioned a complementary route to oxazoles originating from readily available terminal alkynes and primary amides (Scheme 1). This strategy draws upon recent work of Goossen and coworkers, who have shown that enamides may be accessed efficiently *via* Ru-catalyzed anti-Markovnikov hydroamidation of alkynes.[9]

Results and discussion

Our efforts to develop Cu-mediated methods for oxidative cyclization of enamides were initiated with *N*-[(*E*)-2-phenylethenyl] benzamide **1** as the substrate. Use of the catalytic conditions reported previously for oxidative cyclization of aromatic substrates (eqn (1) and (2)) were not successful with **1**. These



Scheme 1 Retrosynthetic strategy for the synthesis of oxazoles.

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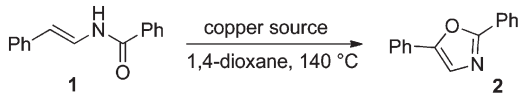
†Electronic supplementary information (ESI) available: Additional reaction screening data, experimental procedures and product characterization data. See DOI: 10.1039/c2ob25310k

Table 1 Optimization of copper-mediated annulation of enamides[a]



1 **2**

Entry	Copper source	Additive	Yield[b] (%)
1	2.0 equiv $CuCl_2$	—	8[c]
2	2.0 equiv $CuCl_2$	0.5 equiv pyridine	23
3	2.0 equiv $CuCl_2$	0.5 equiv Et_3N	26
4	2.0 equiv $CuCl_2$	0.5 equiv DMAP[d]	22
5	2.0 equiv $CuCl_2$	0.5 equiv DBU[e]	24
6	2.0 equiv $CuCl_2$	0.5 equiv imidazole	31
7	2.0 equiv $CuCl_2$	2.0 equiv imidazole	59
8	2.0 equiv $Cu(OAc)_2$	2.0 equiv imidazole	6.8
9	2.0 equiv $Cu(OTf)_2$	2.0 equiv imidazole	10
10	**2.0 equiv $CuCl_2$**	**2.0 equiv NMI[f]**	**67 (74)[g]**
11	1.0 equiv $CuCl_2$	1.0 equiv NMI	56
12	0.5 equiv $CuCl_2$	0.5 equiv NMI	40

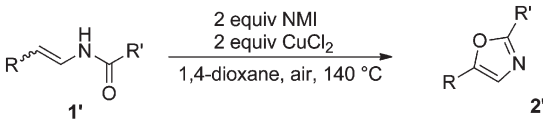
[a] Reaction conditions: reactions were run on 0.05 mmol scale, at 0.1 M in a sealed vessel at 140 °C under air. [b] GC yield. [c] In toluene. [e] 4-Dimethylaminopyridine. [e] 1,8-Diazabicyclo[5.4.0]undec-7-ene. [g] *N*-Methylimidazole. [g] NMR yield, 0.2 mmol scale.

conditions led to complete consumption of **1**, but only trace quantities of the desired 2,5-diphenyloxazole product **2** (see ESI, Table S1†). Subsequent efforts to identify alternative conditions compatible with the use of catalytic quantities of Cu were similarly unsuccessful (see ESI†). Measurable yields of the desired product **2** were obtained, however, by using stoichiometric $CuCl_2$ in toluene (Table 1, entry 1). Further screening of reaction conditions revealed that higher product yields could be obtained with dioxane as the solvent. Addition of various amine bases significantly improved the reaction outcome (Table 1, entries 2–6), and imidazole was the optimal base in the initial experiments (31% yield, entry 6). The amine bases appear to serve as ligands for Cu^{II}, evidenced by significant color changes and improved Cu solubility upon their addition to the reaction mixture. Use of chelating ligands, such as 2,2′-bipyridine and 1,10-phenanthroline, led to lower yields of **2** relative to reactions with imidazole (Table S1†). Whereas a Cu : base stoichiometry of 4 : 1 was optimal for some bases (*e.g.*, DMAP; see ESI†) the best results with imidazole were obtained with a 1 : 1 Cu : base stoichiometry (59%, entry 7). Screening of alternative Cu sources [*e.g.*, $Cu(OAc)_2$, $Cu(OTf)_2$] failed to improve the yield (entries 8 and 9). Subsequent screening showed that replacement of imidazole with *N*-methylimidazole, NMI (Cu : NMI = 1 : 1) led to the highest observed yield of **2** (67%, entry 10).

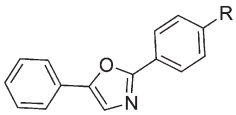
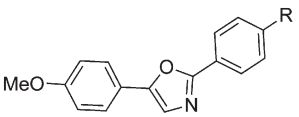
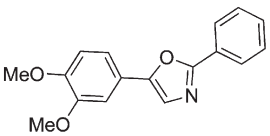
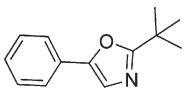
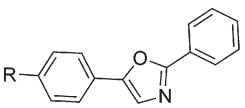
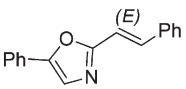
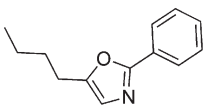
Efforts to lower the Cu loading and achieve catalytic turnover were not successful, despite the use of aerobic (ambient air) conditions in these reactions (entries 11 and 12). Nevertheless, the use of an air atmosphere is beneficial to the reaction. The product yield diminished to 54% when the reaction was performed under anaerobic (N_2) conditions, and the use of pure O_2 (1 atm) also led to a lower yield (50%). The latter result correlates with an increase in the formation of unidentified side-products in the reaction.

The optimized conditions were employed with a number of different substrates to explore the reaction scope (Table 2). The Ru-catalyzed hydroamidation protocol of Goossen *et al.* enabled

Table 2 Substrate scope of copper-mediated annulation of enamides[a]

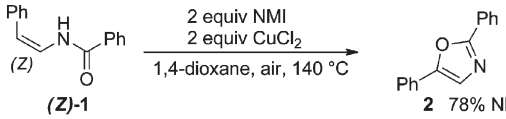


1' **2'**

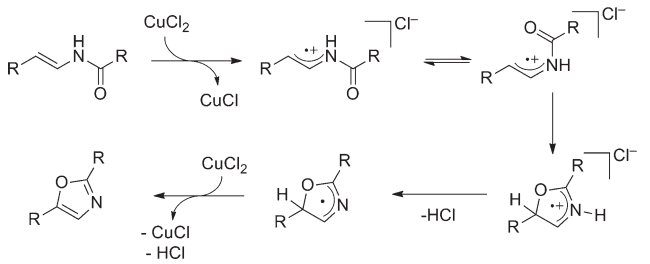
Entry	Product		Yield[b] (%)
1		R = H	67[c]
2		R = OMe	74[c]
3		R = H	72
4		R = OMe	69
5		R = NO_2	49
6			67
7			29
8		R = Cl	57 (52)[d]
9		R = Me	69
10		R = *t*Bu	73
11			38
12			58

[a] Reaction conditions: 0.4 mmol enamide, 0.8 mmol $CuCl_2$, and 0.8 mmol NMI in 0.1 M 1,4-dioxane in a sealed tube under air for 20 h at 140 °C. [b] Isolated yield. [c] Average of two runs. [d] 0.9 mmol enamide, 1.8 mmol $CuCl_2$, and 1.8 mmol NMI in a sealed tube under air for 20 h at 140 °C.

efficient access to diverse secondary enamide substrates.[9a,10] The enamides obtained from this method are obtained initially with (*Z*)-alkene stereochemistry, but (*E*)-enamides may be obtained by Et_3N-promoted isomerization of the crude hydroamidation product at elevated temperatures. The geometry of the starting enamide did not influence the outcome of the oxidative cyclization reactions; both (*Z*)- and (*E*)-**1** afforded the oxazole **2** in the same yield (78% and 74%, respectively; Table 1, entry 10 and eqn (4)). This result does not appear to have implications for the cyclization mechanism, however, because a control experiment showed that (*Z*)-**1** isomerizes to (*E*)-**1** in the absence of $CuCl_2$ under the cyclization conditions.



(4)

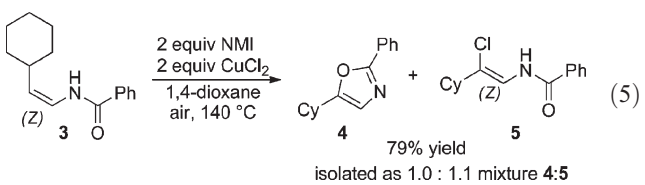


Scheme 2 Proposed mechanism for oxazole synthesis.

Substrates were varied at both the amide- or alkyne-derived portion of the molecule. In general, good yields were obtained with substrates bearing aromatic substituents, particularly electron-rich groups (Table 2, entries 1–6 and 8–10). A modest reduction in yield was observed for substrates bearing electron-deficient aromatic substituents (entries 5 and 8).

Poor yields were obtained with substrates derived from alkyl-substituted amides. For example, the pivalamide derivative (entry 7) led to only 29% yield of the oxazole, and no desired product was obtained with the corresponding *i*Pr derivative (not shown). In contrast, a β-*n*Bu-enamide derived from 1-hexyne underwent cyclization in moderate yield (58%, entry 12).

The β-cyclohexyl enamide **3** underwent cyclization to the desired oxazole **4** in 38% yield (eqn (5)); however, a significant amount of the vinylic chlorination product **5** was observed as a side product (41% yield). Vinylic chlorination is not a significant side-reaction with the other substrates in Table 2. Chlorination of the β C–H bond of **3** resembles $CuCl_2$-mediated chlorination of electron-rich arene C–H bonds, which are believed to be initiated by single-electron transfer from the arene to Cu^{II}.[1b,11] By analogy, we speculate that the present reactions involve initial Cu^{II}-mediated one-electron oxidation of the enamide. Addition of the amide oxygen to the radical-cation intermediate, followed by loss of two protons and another electron, affords the oxazole product (Scheme 2). This mechanism seems more plausible than an organometallic pathway involving directed C–H activation.[12] Single-electron-transfer mechanisms have also been proposed in another Cu^{II}-mediated arene annulation reaction.[3e] Partial support for this hypothesis was obtained from the observation that the β-deuterated enamide **1**-d_1 exhibits an identical time course relative to the reaction of **1**, KIE = 1.0 (±0.2).[13]



(5)

Conclusion

In summary, we have developed an efficient route for the preparation of 2,5-disubstituted oxazoles from simple alkyne and amide precursors. These methods, based on oxidative cyclization of enamides, complement the growing collection of Cu^{II}-based methods for heterofunctionalization of C–H bonds.

Experimental section

General

All commercially available compounds were purchased form Sigma-Aldrich, and used as received unless otherwise indicated. Solvents were dried over alumina columns prior to use; anhydrous 1,4-dioxane was used as received. ^{1}H and ^{13}C NMR spectra were recorded on Bruker AC-300 MHz, Varian Mercury-300 MHz, or Varian INOVA 500 MHz spectrometers. Chemical shift values are given in parts per million relative to residual solvent peaks or TMS internal standard. Exact mass measurements were obtained by the mass spectrometry facility at the University of Wisconsin. Melting points were taken on a Mel-Temp II melting point apparatus. Gas chromatography was done on a Shimadzu GC-17A using Shimadzu RTX-5MS (15 m) column and referenced to an internal standard (trimethoxybenzene). Flash chromatography was performed using SilicaFlash P60 (Silicycle, particle size 40–63 μm, 230–400 mesh) from Sigma Aldrich.

Typical procedure for oxazole formation

All products were synthesized in the following manner from either (*Z*) or (*E*) enamides: In a 6 dram vial equipped with a stir bar were added 1.0 equiv *Z* or *E* enamide and 2.0 equiv $CuCl_2$. 1,4-Dioxane was added to achieve 0.1 M substrate concentration, followed by 2.0 equiv NMI under an air atmosphere. The vial threadings were lined with Teflon tape and a Teflon cap was securely fastened. The sealed vial was allowed to stir at 140 °C behind a blast shield for 20 h, after which time the vial was removed from the bath and allowed to cool. The contents of the vial were concentrated, and then chromatographed directly – typically in 1 : 10 or 1 : 5 EtOAc–hexanes.

2,5-Diphenyl-1,3-oxazole, (Table 2, entry 1).[8g] Isolated as a white solid, mp = 65–66 C;^{1}H NMR (300 MHz, $CDCl_3$): δ 8.11 (m, 2H), 7.72 (m, 2H), 7.30–7.53 (m, 7H); ^{13}C NMR (300 MHz, CDCl3): δ 161.38, 151.49, 130.54, 129.15, 129.04, 128.65, 128.27, 127.71, 126.51, 124.42, 123.70; EMM (ESI) *m*/*z* calc for $C_{15}H_{11}NO$ $[M + H]^+$: 222.0914, meas: 222.0911.

2-(4-Methoxyphenyl)-5-phenyl-1,3-oxazole (Table 2, entry 2).[8g] Isolated as a white solid, mp = 94–96 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.05 (dt, 2H, J = 9, 2.1 Hz), 7.71 (complex d, 2H, J = 7.2 Hz), 7.45 (t, 2H, J = 7.5 Hz), 7.41 (s, 1H), 7.34 (t, 1H, J = 6.6 Hz), 7.00 (dt, 1H, J = 9, 1.8Hz); ^{13}C NMR (300 MHz, $CDCl_3$): δ 160.58, 159.84, 151.32, 130.09, 128.78, 127.60, 126.15, 125.76, 121.98, 120.91, 114.42, 55.38; EMM (ESI) *m*/*z* calc for $C_{16}H_{13}NO_2$ $[M + H]^+$: 252.1020, meas: 252.1025.

5-(4-Methoxyphenyl)-2-phenyl-1,3-oxazole (Table 2, entry 3).[8g] Isolated as a white solid, mp = 63–66 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.10 (m, 2H), (dt, 2H, J = 8.7, 1.8 Hz), 7.43–7.53 (m, 3H), 7.326 (s, 1H), 6.98 (dt, 2H, J = 9, 2.1 Hz); ^{13}C NMR (300 MHz, $CDCl_3$): δ 160.80, 160.05, 151.54, 130.32, 128.99, 127.82, 126.37, 125.97, 122.18, 121.13, 114.64, 55.59. EMM (ESI) *m*/*z* calc for $C_{16}H_{13}NO_2$ $[M + H]^+$: 252.1020, meas: 252.1015.

2,5-Bis(4-methoxyphenyl)-1,3-oxazole (Table 2, entry 4).[14a] Isolated as a cream-colored solid, mp = 139–141 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.02 (d, 2H, J = 8.7 Hz), 7.63 (d, 2H, J = 8.7 Hz), 7.27 (s, 1H), 6.95–7.00 (m, 4H), 3.87 (s, 3H), 3.81 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 161.42, 160.91, 159.89, 150.99, 128.02, 125.82, 121.98, 121.30, 120.68, 114.59, 114.42, 55.58; EMM (EI) m/z calc for $C_{17}H_{15}NO_3$ $[M]^+$: 281.1047, meas: 281.1046.

5-(4-Methoxyphenyl)-2-(4-nitrophenyl)-1,3-oxazole (Table 2, entry 5).[14a] Isolated as a yellow solid, mp = 205–206 °C with decomposition; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.34 (d, 2H, J = 9 Hz), 8.24 (d, 2H, J = 8.7 Hz), 7.68 (d, 2H, 8.7 Hz), 7.41 (s, 1H), 7.00 (d, 2H, J = 9 Hz), 3.87 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 159.37, 157.34, 151.92, 147.36, 131.94, 125.66, 125.09, 123.22, 121.86, 119.10, 113.56, 54.41; EMM (ESI) m/z calc for $C_{16}H_{12}N_2O_4$ $[M + H]^+$: 297.0870, meas: 297.0880.

5-(3,4-Dimethoxyphenyl)-2-phenyl-1,3-oxazole (Table 2, entry 6).[14b] Isolated as a white solid, mp = 95–97 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.10 (m, 2H), 7.48 (m, 3H), 7.45 (s, 1H), 7.33 (dd, 1H, J = 8.4, 2.1 Hz), 7.20 (d, 1H, 2.1 Hz), 3.99 (s, 3H) 3.93 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 160.88, 151.51, 149.69, 149.59, 130.38, 129.01, 127.77, 126.39, 122.49, 121.31, 117.50, 111.74, 107.71, 56.26, 56.23; EMM (ESI) m/z calc for $C_{17}H_{15}NO_3$ $[M]^+$: 281.1047, meas: 281.1059.

2-*tert*-Butyl-5-phenyl-1,3-oxazole (Table 2, entry 7).[14c] Isolated as a yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.63 (m, 2H), 7.40 (t, 2H, J = 7.8 Hz), 7.30 (m, 1H), 7.202 (s, 1H), 1.445 (s, 9H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 171.05, 150.82, 129.02, 128.62, 128.26, 124.19, 121.70, 34.05, 28.83; EMM (ESI) m/z calc for $C_{13}H_{15}NO$ $[M]^+$: Calc: 201.1149, meas: 201.1158.

5-(4-Chlorophenyl)-2-phenyl-1,3-oxazole (Table 2, entry 8).[8g] Isolated as an off-white solid, mp = 102–104 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.10 (m, 2H), 7.65 (dt, 2H, J = 8.7, 1.8 Hz), 7.49 (m, 6H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 161.61, 150.48, 134.40, 130.71, 129.43, 129.07, 127.50, 126.74, 126.55, 125.63, 124.08; EMM (ESI) m/z calc for $C_{15}H_{10}ClNO$ $[M]^+$: 255.0446, meas: 255.0442.

5-(4-Methylphenyl)-2-phenyl-1,3-oxazole (Table 2, entry 9).[8g] Isolated as a white solid, mp = 77–78 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.10 (m, 2H), 7.61 (d, 2H, J = 8.1 Hz), 7.47 (m, 3H), 7.39 (s, 1H), 7.25 (d, 2H overlaps with $CHCl_3$, J = 8.1 Hz), 2.38 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 161.05, 151.70, 138.71, 130.40, 129.84, 129.00, 127.79, 126.44, 125.53, 124.40, 123.04, 21.59; EMM (ESI) m/z calc for $C_{16}H_{13}NO$ $[M + H]^+$: 236.1070, meas: 236.1080.

5-(4-*tert*-Butylphenyl)-2-phenyl-1,3-oxazole (Table 2, entry 10).[14d] Isolated as an oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.11 (m, 2H), 7.65 (m, 2H), 7.47 (m, 4H), 7.39 (s, 1H), 1.34 (s, 9H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 161.12, 151.95, 151.66, 130.41, 129.02, 127.82, 126.45, 126.08, 125.51, 124.29, 123.17, 34.99, 31.44; EMM (ESI) m/z calc for $C_{19}H_{19}NO$ $[M + H]^+$: 278.1540, meas: 278.1551.

5-Phenyl-2-[(*E*)-2-phenylethenyl]-1,3-oxazole (Table 2, entry 11).[8e] Isolated as a white solid, mp = 97–100 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.72 (m, 2H), 7.55 (m, 3H), 7.10–7.48 (m, 7H), 7.00 (d, 1H, J = 16.5 Hz); ^{13}C NMR (300 MHz, $CDCl_3$): δ 166.66, 161.32, 151.13, 136.06, 135.82, 129.38, 129.16, 128.69, 128.17, 127.41, 124.45, 123.94, 114.147; EMM (ESI) m/z calc for $C_{17}H_{13}NO$ $[M + H]^+$: 248.1070, meas: 248.1073.

5-Butyl-2-phenyl-1,3-oxazole (Table 2, entry 12).[14e] Isolated as a clear oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.99 (m, 2H), 7.42 (m, 3H), 6.85 (t, 1H, J = 0.9 Hz), 2.72 (td, 2H, J = 8.1 Hz, J = 0.9 Hz), 1.67 (p, 2H, J = 7.5 Hz), 1.43 (m, 2H), 0.97 (t, 3H, J = 7.5 Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 160.80, 153.45, 130.04, 128.90, 128.09, 126.18, 123.75, 29.95, 25.54, 22.41, 13.95; EMM (EI) m/z calc for $C_{13}H_{15}NO$ $[M]^+$: 201.1149, meas: 201.1149.

***N*-[(*Z*)-2-Chloro-2-cyclohexylethenyl]benzamide, 5.** Assignment of (*Z*)-isomer made based on NOE observed between vinyl proton and cyclohexyl methine proton (500 MHz, $CDCl_3$): NOE of 4.42%, mix: 1.26 ms. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (br d, 1H, J = 9.6 Hz), 7.83 (d, 2H, J = 8.1 Hz), 7.46–7.58 (m, 3H), 7.18 (d, 1H, J = 10.5 Hz), 2.26 (m, 1H), 1.21–1.92 (m, 10H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 164.24, 133.52, 132.43, 129.04, 127.35, 125.00, 116.81, 44.64, 31.69, 26.22, 26.09; EMM (ESI) m/z calc for $C_{15}H_{18}ClNO$ $[M]^+$: 263.1072, meas: 263.1084.

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