Copper Salt Catalyzed Synthesis of Functionalized 2*H*-Pyranes

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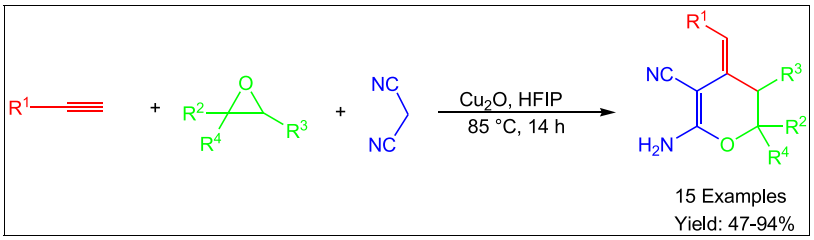
Received December 16, 2018
DOI 10.1002/jhet.3570
Published online 00 Month 2019 in Wiley Online Library (wileyonlinelibrary.com).



A copper-catalyzed reaction between terminal alkynes, oxiranes, and malonitrile has been described. In this transformation, copper acetylide was attacked on oxiranes to form homopropargyl alkoxy-copper intermediate that was further transferred to 2*H*-pyrane skeletons by reaction with malonitrile. We found that the reaction was not productive without hexafluoroisopropanol.

J. Heterocyclic Chem., **00,** 00 (2019).

INTRODUCTION

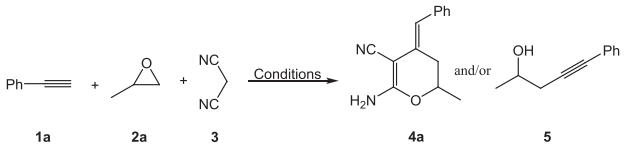
Terminal alkynes exhibited good reactivity both as nucleophiles and as electrophiles using appropriate catalytic systems [1–3]. Moreover, conversion of terminal alkynes to the corresponding acetylides and subsequent reactions with C-electrophiles is an important carbon–carbon bond-forming reaction. Accordingly, there are many reports in literature featuring the additions of metal-alkynylides to Michael acceptors [4–9]. In most of these transformations, metal acetylides formation occurred using equimolar amounts of pre-catalyst sources. During the last decade, *in situ* formations of metal acetylides offered an opportunity for the catalytic reactions of metal acetylides in C—C bond formations [10–12]. Additionally, there are many reports in literature featuring synthesis of heterocycle compounds catalysis in coinage metals [13]. Due to the high activity of Cu, metal acetylides synthesis has been extensively studied on Cu-based catalysts [14–17]. Since the pioneering work of Knöpfel and Carreira in catalytic conjugate addition reaction of terminal alkynes [18], the additions of metal acetylides on carbonyl, imine, and α-imino ester moieties for the construction of C—C bonds have been well explored [19–21]. Importantly, alkynylation of oxiranes with ring opening with metal acetylides is among the most versatile methods for the C—C bond formation [22–24]. As far as we could ascertain, the regioselectivity in the ring opening reactions of three-membered heterocycles depends on electronic and steric parameters on the substrates structures [25]. When the activated three-membered heterocycle is stable enough, metal acetylides reacted with the intermediate to give the ring-opened product. Whereas when the activated three-membered heterocycle is relatively unstable, Meinwald rearrangement occurred instantaneously to give the corresponding product, which reacted with the metal acetylides to give the product. While the importance of such reports cannot be overstated, the transformation suffered from the limitations such as low yields and regioselectivity. Recently, regioselective ring opening of oxiranes with lithium alkynyl ate complex has been reported [26]. Based on these finding, we decided to examine the feasibility of the oxiranes alkynylation strategy for the synthesis of 2*H*-pyrane motif.

RESULTS AND DISCUSSION

To examine the efficiency of the proposed reaction, phenyl acetylene (**1a**), 2-methyloxirane (**2a**), and malonitrile (**3**) were selected as reaction partners using AgOAc and $(i\text{-Pr})_2$EtN in hexafluoroisopropanol (HFIP) at 85°C. Our optimization results are shown in Table 1. The targeted product **4a** was achieved only in 25% yield together with the direct coupling by-product **5** in 42% yield (Table 1, entry 1). This compound must be generated by the direct attack of the silver acetylide to **2a**. It could be deduced that the reaction did not proceed through the S_N1-like pathway as no products arising from the Meinwald rearrangement are detected in crude reaction mixture analysis. The examination of other silver pre-catalysts showed that silver salts were inefficient in these transformations (Table 1, entries 2–7). $Pd(OAc)_2$ resulted

Table 1

Optimization of the reaction conditions[a].



1a 2a 3 4a 5

Entry	Catalyst	Base	Solvent	Yield (%)
1	AgOAc	$(i\text{-Pr})_2$EtN	HFIP	25 (42)[b]
2	AgI	$(i\text{-Pr})_2$EtN	HFIP	19 (53)
3	AgCl	$(i\text{-Pr})_2$EtN	HFIP	31 (29)
4	$AgNO_3$	$(i\text{-Pr})_2$EtN	HFIP	38 (25)
5	AgF	$(i\text{-Pr})_2$EtN	HFIP	50 (34)
6	$AgBF_4$	$(i\text{-Pr})_2$EtN	HFIP	13 (22)
7	Ag_2CO_3	$(i\text{-Pr})_2$EtN	HFIP	24 (16)
8	$Pd(OAc)_2$	$(i\text{-Pr})_2$EtN	HFIP	46 (25)
9	$AuCl_3$	$(i\text{-Pr})_2$EtN	HFIP	70
10	(IPr)CuCl	$(i\text{-Pr})_2$EtN	HFIP	68
11	CuOTf	$(i\text{-Pr})_2$EtN	HFIP	80
12	Cu_2O	$(i\text{-Pr})_2$EtN	HFIP	85
13	CuBr	$(i\text{-Pr})_2$EtN	HFIP	65
14	CuCl	$(i\text{-Pr})_2$EtN	HFIP	73
15	CuI	$(i\text{-Pr})_2$EtN	HFIP	80
16	$Cu(OTf)_2$	$(i\text{-Pr})_2$EtN	HFIP	55
17	Cu_2O	Et_3N	HFIP	68
18	Cu_2O	K_2CO_3	HFIP	16
19	Cu_2O	Cs_2CO_3	HFIP	38
20	Cu_2O	LiO^{t}Bu	HFIP	13
21	Cu_2O	$(i\text{-Pr})_2$EtN	MeCN	21
22	Cu_2O	$(i\text{-Pr})_2$EtN	DMF	26
23	Cu_2O	$(i\text{-Pr})_2$EtN	PEG 200	40
24	Cu_2O	$(i\text{-Pr})_2$EtN	PEG 400	70
25	Cu_2O	—	HFIP	31

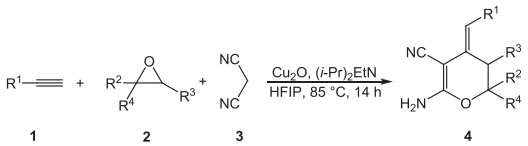
DMF, dimethylformamide; HFIP, hexafluoroisopropanol; PEG, polyethylene glycol.
[a]Reaction conditions: **1a** (1.2 mmol), **2** (1.0 mL), **3a** (1.0 mmol), catalyst (0.1 mmol), base (1.2 mmol), and Linde-type 3-Å molecular sieves (250 mg) in solvent (3 mL) at 85°C for 14 h.
[b]The digit in parentheses refer to the yield of **5**.

in a moderate yield of the targeted product, which might arise from the protonolysis of palladium acetylide, while the reaction conducted with $AuCl_3$ proceeded with good successes (Table 1, entries 8 and 9). It was delightedly found that 10 mol % loading of *N*-heterocyclic carbene copper(I) catalyst (IPr)CuCl (IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene) was turned out to effectively suppress the direct coupling by-product formation (Table 1, entry 10). The yield was highly improved upon using of CuOTf as the catalyst source (Table 1, entry 11). A copper pre-catalyst screen showed that Cu_2O gave superior yield in comparison with other copper catalysts (Table 1, entries 11–16). The superior catalytic activity of Cu_2O is likely due to its good solubility in HFIP. Importantly, no direct coupling by-product **5** was formed when the reaction was conducted with copper salts. The reactions conducted with Et_3N or inorganic bases formed lower yields than $(i\text{-Pr})_2$EtN (Table 1, entries 17–20). Replacing HFIP with MeCN or dimethylformamide resulted in inferior yields of **4a** (Table 1, entries 21 and 22). Polyethylene glycol 200 and 400 (known solvents for activating oxiranes and aziridines) resulted lower productivity (Table 1, entries 23 and 24). The control experiment showed that extremely low yield of **4a** was obtained in the absence of $(i\text{-Pr})_2$EtN, testifying the vital roles of base in this catalytic system (Table 1, entry 25).

Afterwards, we examined the scope of the transformation with different terminal alkynes and oxiranes (Table 2). Methyl oxirane **3a** afforded the corresponding 2*H*-pyrane motif **4a** with good success (Table 2, entry 1). It was delightedly found that oxiranes with longer chains gave the products in diminished yields, which might arise from the steric hindrance of alkyl branches (Table 2, entries 2 and 3). The reaction proceeded smoothly with phenoxy methyl-substituted oxirane (Table 2, entry 4). Oxirane possessing an ester motif was also tolerated (Table 2, entries 5 and 6). The transformation is sensitive

Table 2

Scope of terminal alkynes and oxiranes[a].



Entry	Alkyne	R^1	Epoxide	R^2, R^3, R^4	**4**, Yield (%)
1	**1a**	Ph	**2a**	CH_3, H, H	**4a**, 85
2	**1a**	Ph	**2b**	*n*-Pr, H, H	**4b**, 80
3	**1a**	Ph	**2c**	*n*-Pr, H, CH_3	**4c**, 71
4	**1a**	Ph	**2d**	$PhOCH_2$, H, H	**4d**, 84
5	**1a**	Ph	**2e**	CH_3, H, CH_3OCO	**4e**, 69
6	**1a**	Ph	**2f**	$CH_2CMeCO_2CH_2$, H, H	**4f**, 88
7	**1a**	Ph	**2g**	$(CH_3)_3$, H, H	**4g**, 60
8	**1a**	Ph	**2h**	$-(CH_2)_4-$, H	**4h**, 95
9	**1a**	Ph	**2i**	$-(CH_2)_5-$, H	**4i**, 47
10	**1a**	Ph	**2j**	Me_2CHOCH_2, H, H	**4j**, 78
11	**1a**	Ph	**2k**	H, Ph, H	**4k**, 90[b]
12	**1a**	Ph	**2l**	Ph, Ph, H (*trans 2S, 3S*)	**4l**, 94
13	**1a**	Ph	**2m**	4-NO_2-C_6H_4, H, H	**4m**, 58
14	**1b**	CH_3OCH_2	**2d**	H, Ph, H	**4n**, 63[b]
15	**1c**	TMS	**2d**	H, Ph, H	**4o**, 60[b]

[a]For all entries except stated otherwise: **1** (1.2 mmol), **2** (1.0 mmol), **3** (1.0 mmol), Cu_2O (0.1 mmol), $(i\text{-Pr})_2EtN$ (1.2 mmol), and 250 mg of Linde-type 3-Å molecular sieves, in hexafluoroisopropanol (HFIP) (3 mL) at 85°C for 14 h.
[b]The yield of internal-attacked product.

to steric hindrance of substrate as 2-(*tert*-butyl)oxirane (**2g**) yielded the targeted product in 60% yield (Table 2, entry 7). The *meso* oxirane derived from cyclohexene furnished the *trans*-configuration product **4h** in excellent yield (Table 2, entry 8). Cycloheptene oxide (**2i**) was less reactive in this developed transformation (Table 2, entry 9). This coupling reaction was also extended to phenyl-substituted oxiranes. As expected, 2-phenyloxirane (**2k**) was attacked by silver acetylide at the internal carbon (Table 2, entry 11). 2,3-Diphenyloxirane (**2l**) also afforded a good yield (Table 2, entry 12). Oxirane bearing 4-nitrophenyl **2m** underwent the transformation in different manners and give the terminal-attacked product exclusively (Table 2, entry 13). An obvious decrease in reaction outcome was observed when aliphatic terminal alkyne (**1b**) was used as the substrate, likely due to the lower acidity of aliphatic alkyne than that of phenyl acetylene (Table 2, entry 14). Trimethylsilylacetylene provided the 2*H*-pyrane skeleton in 60% yield, which could participate in organosilicon chemistry (Table 2, entry 15).

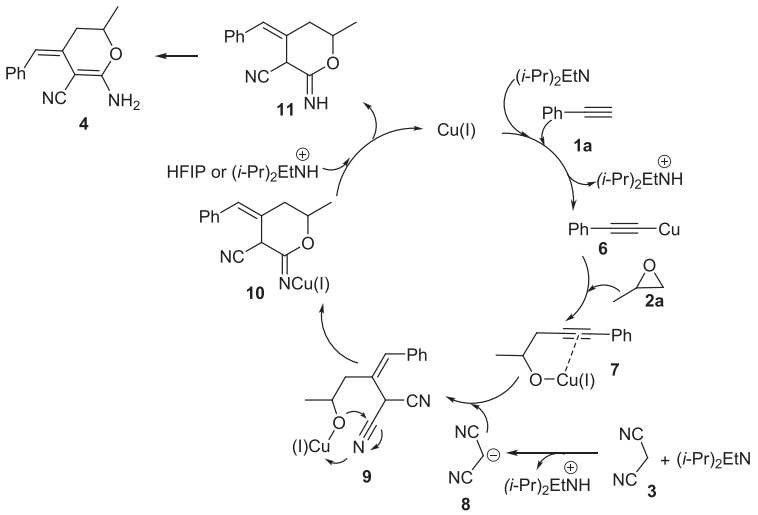
Mechanistically, copper(I) coordinates with the phenyl acetylene activating the alkyne carbon–hydrogen bond. The abstraction of the terminal proton easily by $(i\text{-Pr})_2EtN$ leads to the formation of copper acetylide nucleophile **6**. Copper acetylide was attacked on oxiranes to form homopropargyl alkoxy-copper intermediates **7**, which were further attacked by dicyanocarbanion **8**, generated from malinitrile and DIEPA, followed by cyclization and tautomerization, affording 2*H*-pyrane derivatives **4**. The investigation indicated that HFIP is necessary to furnish the reaction in acceptable yields (Scheme 1).

In this report, we attempt to develop a novel catalytic one-pot reaction involving *in situ* generated copper acetylides, oxiranes, and malonitrile. The control experiments showed that the choice of catalyst and the reaction medium had great impact in furnishing the desired transformation. Copper salts exhibited unique reactivity and selectivity in this transformation. We found that the efficiency and regioselectivity of the ring opening reaction of oxiranes depend on electronic and steric properties of substrates. Alkyl terminal alkynes required longer reaction times to furnish the reaction with good success. Gratifyingly, the reaction was proved to be general under the optimized conditions, performing well in most of the cases examined.

EXPERIMENTAL

Substrates and metal salts were purchased from commercial sources. All the solvents were purchased from PALACHEM Chemical Industries. Solvents were dried over molecular sieves before the use. Molecular sieves were activated at 260°C for 6 h and stored in desiccator in the presence of P_2O_5. The copper(I) salts were typically weighted in a glovebox and were stored in

Scheme 1. Proposed reaction progress path for the synthesis 2*H*-pyranes.



a desiccator while being utilized. All reactions were carried out in Schlenk tube (25 mL) using oven-dried glassware under a dry Ar atmosphere. All reactions were monitored by TLC analyses that were performed on silica gel 60 (Merck, item number 116835). Column chromatography was performed on silica gel 60 (particle size 63–200 μm) (Merck, item number 7734-3) on a glass column. Melting points (mp) were recorded with Electrothermal-9100 apparatus and are uncorrected. ^{1}H NMR spectra were recorded with Bruker DRX-500 AVANCE instrument, at 500 MHz (using TMS, as a reference), and ^{13}C NMR spectra were recorded at 125 MHz (using the $CDCl_3$ triplet as reference) in $CDCl_3$ as solvent at ambient temperature. Chemical shifts were reported as δ in parts per million (ppm), and coupling constant (*J*) values are given in Hertz. Mass data were recorded with EIMS (70 eV): Finnigan-MAT-8430 mass spectrometer, in *m/z*. IR spectra were recorded with Shimadzu IR-460 FTIR spectrometer as KBr pellets. Elemental analyses (C, H, N) were performed with a Heraeus CHN-O-Rapid analyzer. The results agreed favorably with the calculated values.

General procedure for the preparation of 4. A Schlenk tube (25 mL) was charged with Cu_2O (0.1 mmol, 14 mg), $(i\text{-Pr})_2$EtN (1.2 mmol), alkyne (1.2 mmol), and HFIP (3.0 mL). The mixture was stirred for 30 min at ambient conditions and then warmed up to 85°C. Oxirane (1.0 mmol) was then injected to the reaction vessel. The reaction mixture was then stirred for an additional 30 min at 85°C, followed by addition of a solution of malonitrile (1.0 mmol, 66 mg) in HFIP (1.0 mL). After consuming the starting material (TLC monitoring, 14 h), the resulting slurry was quenched with saturated aqueous NH_4Cl (5 mL) and extracted with EtOAc (3 × 10 mL). The organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was subjected to flash chromatography (silica gel, hexane:EtOAc) to give the pure targeted product **4**.

6-Amino-4-benzylidene-2-methyl-3,4-dihydro-2H-pyran-5-carbonitrile (4a, $C_{14}H_{14}N_2O$). The crude product was purified by column chromatography (SiO_2; hexane/EtOAc 3/1, R_f: 0.52) affording 0.19 g (85%) of **4a**. Colorless oil. IR (KBr): $\overline{V}$ = 3441, 3427, 3074, 2934, 2236, 1615, 1440, 1120. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ_H = 1.23 (3H, d, ^3J = 5.9 Hz, Me), 2.31 (1H, dd, ^2J = 11.4, ^3J = 8.8 Hz, CH), 2.49 (1H, dd, ^2J = 11.4, ^3J = 5.1 Hz, CH), 4.01–4.14 (1H, m, CH), 6.44 (1H, t, ^4J = 2.0 Hz, CH), 7.01 (2H, br s, NH_2), 7.29 (1H, t, ^3J = 6.5 Hz, CH), 7.42 (2H, t, ^3J = 6.5 Hz, 2CH), 7.65 (2H, d, ^3J = 6.6 Hz, 2CH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C = 19.8 (Me), 46.8 (CH_2), 76.5 (C), 79.6 (CH), 114.2 (CN), 125.1 (CH), 126.8 (CH), 128.2 (2CH), 130.0 (2CH), 137.6 (C), 143.4 (C), 184.1 (C). EI-MS (70 eV): *m/z* (%) = 226 (M^+, 2), 210 (15), 136 (34), 121 (56), 77 (100). *Anal*. Calcd (%) for (226.28): C, 74.31; H, 6.24; N, 12.38. Found: C, 74.66; H, 6.45; N, 12.61.

6-Amino-4-benzylidene-2-propyl-3,4-dihydro-2H-pyran-5-carbonitrile (4b, $C_{16}H_{18}N_2O$). The crude product was purified by column chromatography (SiO_2; hexane/EtOAc 4/1, R_f: 0.34) affording 0.20 g (80%) **4b**. Colorless oil. IR (KBr): $\overline{V}$ = 3422, 3411, 3043, 2966, 2273, 1611, 1376, 1052. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ_H = 0.92 (3H, t, ^3J = 6.2 Hz, Me), 1.36–1.57 (4H, m, $2CH_2$), 2.24 (1H, dd, ^2J = 12.0, ^3J = 4.9 Hz, CH), 2.47 (1H, dd, ^2J = 12.0, ^3J = 10.1 Hz, CH), 3.96–4.08 (1H, m, CH), 6.48 (1H, t, ^4J = 1.8 Hz, CH), 7.03 (2H, br s, NH_2), 7.28 (1H, t, ^3J = 6.6 Hz, CH), 7.41 (2H, t, ^3J = 6.6 Hz, 2CH), 7.63 (2H, d, ^3J = 6.6 Hz, 2CH). ^{13}C NMR

(125.7 MHz, $CDCl_3$): 13.1 (Me), 23.4 (CH_2), 40.14 (CH_2), 43.8 (CH_2), 76.1 (CH), 79.5 (C), 114.1 (CN), 126.3 (CH), 128.1 (CH), 129.5 (2CH), 130.8 (2CH), 136.1 (C), 144.8 (C), 182.2 (C). EI-MS (70 eV): *m/z* (%) = 254 (M^+, 7), 211 (12), 164 (40), 121 (67), 91 (38), 77 (100). *Anal*. Calcd (%) for (254.33): C, 75.56; H, 7.13; N, 11.01. Found: C, 75.88; H, 7.45; N, 11.14.

6-Amino-4-benzylidene-2-methyl-2-propyl-3,4-dihydro-2H-pyran-5-carbonitrile (4c, $C_{17}H_{20}N_2O$). The crude product was purified by column chromatography (SiO_2; hexane/EtOAc 4/1, R_f: 0.49) affording 0.19 g (71%) **4c**. Yellow oil. IR (KBr): $\overline{V}$ = 3420, 3411, 2936, 2182, 1609, 1448, 1222. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ_H = 0.95 (3H, t, ^3J = 6.6 Hz, Me), 1.30–1.48 (7H, m, $2CH_2$, Me), 2.26 (1H, dd, ^2J = 11.7, ^3J = 9.2 Hz, CH), 2.45 (1H, dd, ^2J = 11.7, ^3J = 5.1 Hz, CH), 6.40 (1H, t, ^4J = 1.8 Hz, CH), 6.98 (2H, br s, NH_2), 7.31 (1H, t, ^3J = 6.9 Hz, CH), 7.45 (2H, t, ^3J = 6.7 Hz, 2CH), 7.66 (2H, d, ^3J = 6.7 Hz, 2CH). ^{13}C NMR (125.7 MHz, $CDCl_3$): 13.93 (Me), 19.7 (CH_2), 27.2 (CH_3), 45.7 (CH_2), 49.1 (CH_2), 78.2 (C), 89.7 (C), 114.3 (CN), 125.3 (CH), 128.2 (CH), 130.0 (2CH), 132.6 (2CH), 136.8 (C), 145.02 (C), 183.6 (C). EI-MS (70 eV): *m/z* (%) = 268 (M^+, 4), 225 (11), 134 (38), 135 (68), 77 (100). *Anal*. Calcd (%) for (268.36): C, 76.09; H, 7.51; N, 10.44. Found: C, 76.36; H, 7.83; N, 10.54.

6-Amino-4-benzylidene-2-(phenoxymethyl)-3,4-dihydro-2H-pyran-5-carbonitrile (4d, $C_{20}H_{18}N_2O_2$). The crude product was purified by column chromatography (SiO_2; hexane/EtOAc 4/1, R_f: 0.31) affording 0.27 g (84%) **4d**. Pale yellow oil. IR (KBr): $\overline{V}$ = 3384, 3362, 2949, 2172, 1617, 1466, 1046. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ_H = 2.22 (1H, dd, ^2J = 10.5, ^3J = 8.9 Hz, CH), 2.45 (1H, dd, ^2J = 10.5, ^3J = 5.0 Hz, CH), 3.93–4.12 (2H, m, 2CH), 4.56–4.67 (1H, m, CH), 6.51 (1H, t, ^4J = 1.9 Hz, CH), 6.85 (2H, br s, NH_2), 6.90–7.05 (3H, m, 3CH), 7.29 (2H, t, ^3J = 6.3 Hz, 2CH), 7.35 (1H, t, ^3J = 6.4 Hz, CH), 7.43 (2H, t, ^3J = 6.4 Hz, 2CH), 7.65 (2H, d, ^3J = 6.3 Hz, 2CH). ^{13}C NMR (125.7 MHz, $CDCl_3$): 40.1 (CH_2), 76.0 (CH_2), 79.2 (C), 85.2 (CH), 114.1 (CN), 114.9 (2CH), 121.3 (CH), 125.2 (CH), 128.3 (CH), 129.2 (2CH), 130.2 (2CH), 132.73 (2CH), 137.2 (C), 144.1 (C), 159.2 (C), 184.2 (C). EI-MS (70 eV): *m/z* (%) = 318 (M^+, 6), 211 (14), 217 (17), 121 (82), 107 (68), 77 (100), 54 (46). *Anal*. Calcd (%) for (318.38): C, 75.45; H, 5.70; N, 8.80. Found: C, 75.71; H, 75.98; N, 8.93.

Methyl-6-amino-4-benzylidene-5-cyano-2-methyl-3,4-dihydro-2H-pyran-2-carboxylate (4e, $C_{16}H_{16}N_2O_3$). The crude product was purified by column chromatography (SiO_2; hexane/EtOAc 6/1, R_f: 0.30) affording 0.20 g (69%) **4e**. Yellow oil. IR (KBr): $\overline{V}$ = 3432, 3421, 3006, 2968, 2244, 1731, 1611, 1415, 1016. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ_H = 1.53 (3H, s, CH_3), 2.70 (1H, dd, ^2J = 10.9 Hz, ^4J = 1.9 Hz, CH), 2.96 (1H, dd, ^2J = 10.9 Hz, ^4J = 1.9 Hz, CH), 3.71 (3H, s, OCH_3), 6.70 (1H, t, ^4J = 1.9 Hz, CH), 6.94 (2H, br s, NH_2), 7.35 (1H, t, ^3J = 6.8 Hz, CH), 7.44 (2H, t, ^3J = 6.8 Hz, 2CH), 7.67 (2H, d, ^3J = 6.7 Hz, 2CH). ^{13}C NMR (125.7 MHz, $CDCl_3$): 23.5 (CH_3), 44.1 (CH_2), 57.2 (OCH_3), 79.5 (C), 84.1 (C), 114.1 (CN), 126.1 (CH), 127.1 (CH), 128.8 (2CH), 130.4 (2CH), 136.5 (C), 143.2 (C), 174.5 (C), 183.1 (C). EI-MS (70 eV): *m/z* (%) = 284 (M^+, 4), 269 (14), 210 (33), 121 (76), 91 (44), 77 (100) 54 (38). *Anal*. Calcd (%) for (284.32): C, 67.59; H, 5.67; N, 9.85. Found: C, 67.93; H, 5.96; N, 9.94.

6-Amino-4-benzylidene-5-cyano-3,4-dihydro-2H-pyran-2-yl-methyl methacrylate (4f, $C_{18}H_{18}N_2O_3$). The crude product was purified by column chromatography (SiO_2; hexane/EtOAc 4/1, R_f: 0.30) affording 0.25 g (81%) **4f**. Yellow oil. IR (KBr): $\overline{V}$ = 3408, 3385, 2934, 2181, 1713, 1415, 1167. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ_H = 2.17 (3H, t, ^3J = 1.7 Hz, CH_3), 2.39 (1H, d, ^2J = 11.1 Hz, ^3J = 9.5 Hz, CH), 2.62 (1H, d, ^2J = 11.1 Hz, ^3J = 4.9 Hz, CH), 4.35–4.46 (1H, m, CH), 4.59–4.76 (2H, m, 2CH), 6.40 (1H, t, ^4J = 1.7 Hz, CH), 6.52 (1H, d, ^2J = 4.5 Hz, CH), 6.68 (1H, d, ^2J = 4.5 Hz, CH), 6.89 (2H, br s, NH_2), 7.38 (1H, t, ^3J = 6.7 Hz, CH), 7.42 (2H, t, ^2J = 6.6 Hz, 2CH), 7.68 (2H, d, ^2J = 6.7 Hz, 2CH). ^{13}C NMR (125.7 MHz, $CDCl_3$): 18.6 (CH_3), 38.3 (CH_2), 73.3 (CH_2), 79.2 (C), 86.1 (CH), 114.3 (CN), 125.9 (CH), 126.9 (CH_2), 126.5 (CH), 129.2 (2CH), 131.5 (2CH), 136.2 (C), 138.0 (C), 143.1 (C), 169.2 (C), 182.8 (C). EI-MS (70 eV): *m/z* (%) = 310 (M^+, 8), 269 (14), 212 (34), 121 (69), 91 (45), 77 (100). *Anal*. Calcd (%) for (310.35): C, 69.66; H, 5.85; N, 9.03. Found: C, 69.87; H, 6.07; N, 9.24.

6-Amino-4-benzylidene-2-(tert-butyl)-3,4-dihydro-2H-pyran-5-carbonitrile (4g, $C_{17}H_{20}N_2O$). The crude product was purified by column chromatography (SiO_2; hexane/EtOAc 4/1, R_f: 0.49) affording 0.16 g (60%) **4g**. Yellow oil. IR (KBr): $\overline{V}$ = 3415, 3398, 2975, 2186, 1610, 1427, 1118. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ_H = 0.92 (9H, s, $3CH_3$), 2.42–2.60 (2H, m, 2CH), 3.78–3.89 (1H, m, CH), 6.56 (1H, t, ^4J = 1.7 Hz, CH), 6.89 (2H, br s, NH_2), 7.35 (1H, t, ^3J = 6.7 Hz, CH), 7.46 (2H, t, ^3J = 6.8 Hz, 2CH), 7.62 (2H, d, ^3J = 6.7 Hz, 2CH). ^{13}C NMR (125.7 MHz, CDCl3): 27.3 ($3CH_3$), 36.9 (CH_2), 38.1 (C), 78.1 (C), 84.9 (CH), 114.5 (CN), 126.7 (CH), 127.6 (CH), 129.9 (2CH), 131.2 (2CH), 136.1 (C), 145.2 (C), 181.9 (C). EI-MS (70 eV): *m/z* (%) = 268 (M^+, 4), 211 (17), 196 (34), 121 (67), 77 (100), 57 (89). *Anal*. Calcd (%) for (268.36): C, 76.09; H, 7.51; N, 10.44. Found: C, 76.31; H, 67.83; N, 10.62.

2-Amino-4-benzylidene-4a,5,6,7,8,8a-hexahydro-4H-chromene-3-carbonitrile (4h, $C_{17}H_{18}N_2O$). The crude product was purified by column chromatography (SiO_2; hexane/EtOAc 3/1, R_f: 0.44) affording 0.25 g (95%) **4h**. Yellow oil. IR (KBr): $\overline{V}$ = 3433, 3346, 2896, 2181, 1622,

1460, 1115. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ_H = 1.31–1.97 (8H, m, 4CH_2), 2.62–2.74 (1H, m, CH), 3.48–3.60 (1H, m, CH), 6.72 (1H, d, ^4J = 1.9 Hz, CH), 7.04 (2H, br s, NH_2), 7.33 (1H, t, ^3J = 6.8 Hz, CH), 7.42 (2H, t, ^3J = 6.8 Hz, 2CH), 7.65 (2H, d, ^3J = 6.8 Hz, 2CH). ^{13}C NMR (125.7 MHz, $CDCl_3$): 26.7 (CH_2), 28.1 (CH_2), 32.6 (CH_2), 35.4 (CH_2), 47.6 (CH), 79.5 (C), 83.4 (CH), 114.1 (CN), 125.9 (CH), 126.4 (CH), 128.9 (2CH), 131.2 (2CH), 136.1 (C), 144.3 (C), 182.7 (C). EI-MS (70 eV): *m*/*z* (%) = 266 (M^+, 7), 210 (14), 184 (35), 96 (80), 91 (44), 77 (100). *Anal*. Calcd (%) for (266.34): C, 76.66; H, 6.81; N, 10.52. Found: C, 76.95; H, 7.04; N, 10.73.

2-Amino-4-benzylidene-4,4a,5,6,7,8,9,9a-octahydrocyclohepta[b]pyran-3-carbonitrile (4i, $C_{18}H_{20}N_2O$). The crude product was purified by column chromatography (SiO_2; hexane/EtOAc 4/1, R_f: 0.21) affording 0.13 g (47%) **4i**. Pale yellow solid, mp: 57–59°C. IR (KBr): $\overline{V}$ = 3419, 3403, 2930, 2216, 1611, 1445, 1029. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ_H = 1.31–1.97 (10H, m, 5CH_2), 2.45–2.56 (1H, m, CH), 3.37–3.48 (1H, m, CH), 6.68 (1H, d, ^4J = 1.8 Hz, CH), 7.01 (2H, br s, NH_2), 7.32 (1H, t, ^3J = 6.8 Hz, CH), 7.40 (2H, t, ^3J = 6.8 Hz, 2CH), 7.51 (2H, d, ^3J = 6.8 Hz, 2CH). ^{13}C NMR (125.7 MHz, $CDCl_3$): 26.7 (CH_2), 27.5 (CH_2), 29.2 (CH_2), 31.4 (CH_2), 35.2 (CH_2), 37.1 (CH), 71.1 (CH), 79.4 (C), 114.2 (CN), 125.2 (CH), 127.1 (CH), 129.4 (2CH), 130.8 (2CH), 136.5 (C), 143.7 (C), 181.6 (C). EI-MS (70 eV): *m*/*z* (%) = 280 (M^+, 12), 210 (15), 195 (29), 170 (44), 81 (76), 91 (43), 77 (100). *Anal*. Calcd (%) for (280.37): C, 77.11; H, 7.19; N, 9.99. Found: C, 77.32; H, 7.38; N, 10.16.

6-Amino-4-benzylidene-2-(isopropoxymethyl)-3,4-dihydro-2H-pyran-5-carbonitrile (4j, $C_{17}H_{20}N_2O_2$). The crude product was purified by column chromatography (SiO_2; hexane/EtOAc 4/1, R_f: 0.53) affording 0.22 g (78%) **4j**. Colorless solid, mp: 82–84°C. IR (KBr): $\overline{V}$ = 3362, 3339, 3001, 2206, 1603, 1428, 1123. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ_H = 1.23 (6H, d, ^3J = 6.1 Hz, 2CH_3), 2.37 (1H, dd, ^2J = 11.2 Hz, ^3J = 9.5 Hz, CH), 2.62 (1H, dd, ^2J = 11.2 Hz, ^3J = 5.1 Hz, CH), 4.11–4.66 (4H, m, 4CH), 6.47 (1H, ^4J = 1.8 Hz, CH), 6.89 (2H, br s, NH_2), 7.35 (1H, t, ^3J = 6.5 Hz, CH), 7.44 (2H, t, ^3J = 6.6 Hz, 2CH), 7.64 (2H, d, ^3J = 6.6 Hz, 2CH). ^{13}C NMR (125.7 MHz, $CDCl_3$): 24.7 (2CH_3), 39.1 (CH_2), 69.1 (CH_2), 74.6 (CH), 79.1 (C), 86.1 (CH), 115.1 (CN), 126.1 (CH), 127.1 (CH), 129.3 (2CH), 130.8 (2CH), 137.1 (C), 143.5 (C), 181.9 (C). EI-MS (70 eV): *m*/*z* (%) = 284 (M^+, 5), 211 (15), 196 (41), 121 (78), 77 (100), 73 (64). *Anal*. Calcd (%) for (284.36): C, 71.81; H, 7.09; N, 9.85. Found: C, 72.06; H, 7.38; N, 9.98.

6-Amino-4-benzylidene-3-phenyl-3,4-dihydro-2H-pyran-5-carbonitrile (4k, $C_{19}H_{16}N_2O$). The crude product was purified by column chromatography (SiO_2; hexane/EtOAc 3/1, R_f: 0.27) affording 0.26 g (90%) **4k**. Pale yellow solid, mp: 76–78°C. IR (KBr): $\overline{V}$ = 3412, 3400, 2948, 2189, 1613, 1382, 1022. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ_H = 3.81 (1H, dd, ^3J = 10.0 Hz, ^3J = 7.1 Hz, CH), 4.40 (1H, dd, ^2J = 12.0 Hz, ^3J = 10.0 Hz, CH), 4.69 (1H, dd, ^2J = 12.0 Hz, ^3J = 7.1 Hz, CH), 6.59 (1H, t, ^3J = 1.8 Hz, CH), 6.89 (2H, br s, NH_2), 7.32–7.50 (8H, m, 8CH), 7.65 (2H, d, ^3J = 6.5 Hz, 2CH). ^{13}C NMR (125.7 MHz, $CDCl_3$): 47.1 (CH), 71.3 (CH_2), 78.2 (C), 114.3 (CN), 125.1 (CH), 126.1 (CH), 127.4 (CH), 127.9 (2CH), 129.8 (2CH), 130.7 (2CH), 132.5 (2CH), 135.1 (C), 140.1 (C), 142.7 (C), 181.9 (C). EI-MS (70 eV): *m*/*z* (%) = 288 (M^+, 3), 211 (24), 196 (36), 171 (50), 121 (74), 77 (100), 54 (36). *Anal*. Calcd (%) for (288.35): C, 79.14; H, 5.59; N, 9.72. Found: C, 79.42; H, 5.85; N, 9.94.

6-Amino-4-benzylidene-2,3-diphenyl-3,4-dihydro-2H-pyran-5-carbonitrile (4l, $C_{25}H_{20}N_2O$). The crude product was purified by column chromatography (SiO_2; hexane/EtOAc 2/1, R_f: 0.44) affording 0.34 g (94%) **4l**. Yellow solid, mp: 127–129°C. IR (KBr): $\overline{V}$ = 3376, 3348, 2962, 2235, 1643, 1432, 1176, 1007. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ_H = 4.49 (1H, d, ^3J = 9.1 Hz, CH), 5.23 (1H, d, ^3J = 9.1 Hz, CH), 6.55 (1H, d, ^3J = 1.8 Hz, CH), 6.88 (2H, br s, NH_2), 7.21–7.49 (13H, m, 13CH), 7.63 (2H, d, ^3J = 6.8 Hz, 2CH). ^{13}C NMR (125.7 MHz, $CDCl_3$): 49.1 (CH), 78.1 (C), 83.9 (CH), 114.0 (CN), 126.1 (CH), 126.1 (CH), 127.0 (CH), 127.8 (2CH), 128.2 (2CH), 128.7 (CH), 129.0 (2CH), 129.4 (2CH), 130.1 (2CH), 132.6 (2CH), 136.1 (C), 139.1 (C), 142.5 (C), 144.1 (C), 183.2 (C). EI-MS (70 eV): *m*/*z* (%) = 364 (M^+, 5), 287 (14), 210 (34), 185 (41), 170 (43), 121 (83), 77 (100). *Anal*. Calcd (%) for (364.45): C, 82.39; H, 5.53; N, 7.69. Found: C, 82.64; H, 5.86; N, 7.81.

6-Amino-4-benzylidene-2-(4-nitrophenyl)-3,4-dihydro-2H-pyran-5-carbonitrile (4m, $C_{19}H_{15}N_3O_3$). The crude product was purified by column chromatography (SiO_2; hexane/EtOAc 1/1, R_f: 0.58) affording 0.19 g (58%) **4m**. Yellow solid, mp: 153–155°C. IR (KBr): $\overline{V}$ = 3447, 3411, 2963, 2191, 1605, 1594, 1368, 1221, 1080. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ_H = 2.650–2.85 (2H, m, 2CH), 4.78–4.89 (21H, m, CH), 6.62 (1H, t, ^4J = 1.8 Hz, CH), 6.81 (2H, br s, NH_2), 7.31–7.43 (3H, m, 3CH), 7.61 (2H, d, ^3J = 6.7 Hz, 2CH), 7.70 (2H, d, ^3J = 6.9 Hz, 2CH), 8.21 (2H, d, ^3J = 6.9 Hz, 2CH). ^{13}C NMR (125.7 MHz, $CDCl_3$): 45.1 (CH_2), 79.1 (C), 89.2 (CH), 114.5 (CN), 126.0 (CH), 126.7 (2CH), 127.1 (CH), 128.8 (2CH), 129.2 (2CH), 129.9 (2CH), 136.3 (C), 140.5 (C), 146.1 (C), 147.3 (C), 183.7 (C). EI-MS (70 eV): *m*/*z* (%) = 333 (M^+, 11), 211 (18), 196 (25), 171 (34), 121 (78), 77 (100). *Anal*. Calcd (%) for (333.35): C, 68.46; H, 4.54; N, 12.61. Found: C, 68.69; H, 4.82; N, 12.80.

6-Amino-4-(2-methoxyethylidene)-3-phenyl-3,4-dihydro-2H-pyran-5-carbonitrile (4n, $C_{15}H_{16}N_2O_2$). The crude product was purified by column chromatography (SiO_2; hexane/EtOAc 4/1, R_f: 0.39) affording 0.16 g (63%) **4n**.

Colorless solid, mp: 78–80°C. IR (KBr): $\overline{V}$ = 3413, 3400, 2924, 2211, 1611, 1459, 1381, 1250, 1103. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ_H = 3.48 (3H, s, OMe), 4.03–4.25 (3H, m, 3CH), 4.45–4.61 (2H, m, 2CH), 5.81 (1H, t, ^3J = 6.7 Hz, CH), 6.87 (2H, br s, NH_2), 7.310 (1H, t, ^3J = 6.7 Hz, CH), 7.35–7.42 (4H, m, 4CH). ^{13}C NMR (125.7 MHz, $CDCl_3$): 40.3 (CH), 57.4 (OMe), 69.1 (CH_2), 76.4 (CH_2), 79.1 (C), 114.2 (CN), 126.5 (CH), 128.5 (2CH), 129.1 (CH), 130.5 (2CH), 141.3 (C), 144.7 (C), 182.5 (C). EI-MS (70 eV): *m/z* (%) = 256 (M^+, 2), 179 (15), 164 (28), 139 (40), 121 (79), 77 (100). *Anal*. Calcd (%) for (256.21): C, 70.29; H, 6.29; N, 10.93. Found: C, 70.48; H, 6.46; N, 11.16.

6-Amino-3-phenyl-4-((trimethylsilyl)methylene)-3,4-dihydro-2H-pyran-5-carbonitrile (4o, $C_{16}H_{20}N_2OSi$). The crude product was purified by column chromatography (SiO_2; hexane/EtOAc 5/1, R_f: 0.28) affording 0.17 g (60%) **4o**. Colorless solid, mp: 60–62°C. IR (KBr): $\overline{V}$ = 3345, 3303, 3066, 2924, 2260, 1613, 1539, 1447, 1331, 1083. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ_H = 0.11 (9H, s, 3 Me), 3.90–3.98 (1H, m, CH), 4.41 (1H, dd, ^2J = 12.0 Hz, ^3J = 5.9 Hz, CH), 4.63 (1H, dd, ^2J = 12.0 Hz, ^3J = 9.1 Hz, CH), 5.95 (1H, d, ^4J = 1.7 Hz, CH), 6.87 (2H, br s, NH_2), 7.30 (1H, t, ^3J = 6.4 Hz, CH), 7.35–7.44 (4H, m, 4CH). ^{13}C NMR (125.7 MHz, $CDCl_3$): 1.9 ($3CH_3$), 49.5 (CH), 74.7 (C), 76.19 (CH_2), 114.6 (CN), 125.1 (CH), 127.9 (2CH), 128.9 (2CH), 129.8 (CH), 142.7 (C), 160.1 (C), 183.7 (C). EI-MS (70 eV): *m/z* (%) = 284 (M^+, 7), 207 (15), 192 (27), 167 (41), 121 (73), 77 (100). *Anal*. Calcd (%) for (284.43): C, 67.56; H, 7.09; N, 9.85. Found: C, 67.82; H, 7.33; N, 10.04.

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