CATALYSIS INVESTIGATION FOR SYNTHESIS OF 2-AMINO-4*H*-PYRAN-3-CARBONITRILES HAVING PROPARGYL GROUP

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Abstract. Some different catalysts, such as organic and inorganic bases and basic ionic liquids were used for synthesis of 2-amino-4*H*-pyran-3-carbonitriles containing propargyl group. Efficient catalysts of these substances were estimated. The structures of the obtained compounds were confirmed by the modern spectroscopic methods (IR, ^{1}H NMR, ^{13}C NMR).
Keywords: catalysis, ionic liquid, 4*H*-pyran

1. INTRODUCTION

2-Amino-3-cyano-4*H*-pyran are an important class of pharmacologically active organic compounds. These compounds have the wide range of biological activities and therapeutics. 4*H*-pyran derivatives well distributed in many naturally occurring compounds [1]. Organic compounds containing 4*H*-pyran ring shown biologically activities, such as antimicrobial [2], anti-inflammatory [3], anticancer [4], etc…The synthesis of some propargylic ethers of 2-amino-4*H*-chromene-3-carbonitriles was reported in our previous paper [5] from resorcinol, malononitrile and benzaldehydes by three-component one-pot reaction. In continuation of our work, herein a green approach for the one pot synthesis of propargyl ester of 2-amino-3-cyano-4*H*-pyran derivatives has been reported. These esters will be used in our further research in click reaction with tetra-*O*-acetyl-β-D-glucopyranosyl azide [6,7].

2. RESULTS AND DISCUSSIONS

Propargyl acetoacetate (**3**) was prepared in our lab from 2,2,6-trimethyl-1,3-dioxen-4-one (**1**) and propargyl alcohol (**2**) in large scale with yield of 73% (*Scheme 1, top*). A series of different substituted propargyl 6-amino-5-cyano-2-methyl-4-aryl-4*H*-pyran-3-carboxylates ((**5a-f**)) were synthesized from propargyl acetoacetate (**3**) by three-component reaction with malononitrile and corresponding substituted benzaldehydes (**4a-l**) (*Scheme 1, bottom*). The reactions performed by mixing malononitrile with propargyl acetoacetate in 96% ethanol, and then appropriated substituted benzaldehyde was added.

We have investigated initially some different catalysts for synthesis of compounds **5a-f**. Some substances were used as catalyst, such as 25-28% ammonium hydroxide, some ionic liquids such as [Bmim]OH, [Et_3N]OAc and [Et_3N]For [8,9]. Results were shown in Table 1.

The obtained mixture was stirred at room temperature and 25-28% ammonium hydroxide solution was added dropwise. In other cases The solids appeared after 3-5-minute stirring in some cases (benzaldehydes having nitro, chloro), meanwhile, the precipitate only separated for 1-2 hrs at room temperature. The increasing of reaction temperature led to form oily or tar substances having indefinite structures. The reaction yields were 40-63%. These obtained propargyl esters of 4*H*-pyrans were in white or pale yellow crystalline forms, soluble easily in

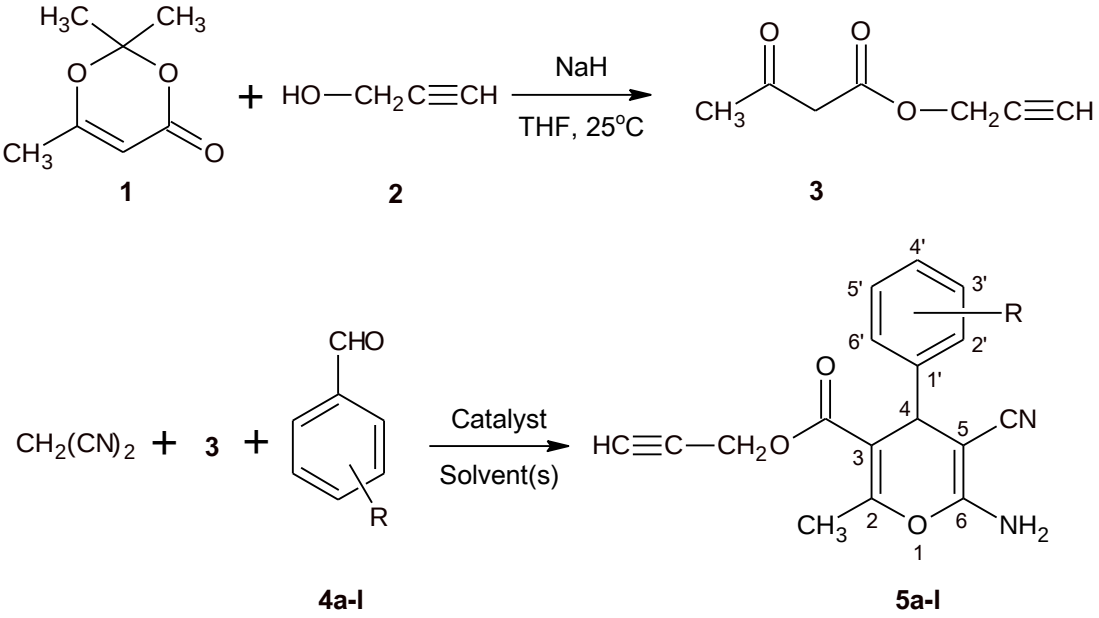
organic solvents (ethanol, methanol, DMF, DMSO, acetone, toluene…), insoluble in water, having high melting points.

Table 1. Reaction conditions optimisation for the synthesis of 5a

Catalyst*	Solvent	Temperature/°C	Time/h	Yield (%)
NH_4OH solution (25−28%)	96%-Ethanol	25	3	63
$[Et_3N]OAc$	96%-Ethanol:water (1:1)	Refluxing	2	No
$[Et_3N]For$	96%-Ethanol:water (1:1)	Refluxing	2	No
[Bmim]Br	96%-Ethanol:water (1:1)	Refluxing	2	No
[Bmim]OH	96%-Ethanol:water (1:1)	Refluxing	2	70

Note: Ac=acetyl, For=formyl, Bmim=*N*-butylimidazole. * Amounts of catalysts were 5mmol%.

The IR spectra of these esters of acid 6-amino-5-cyano-2-methyl-4-aryl-4*H*-pyran-3-carboxylic had three absorption bands in region of 3429-3393, 3337-3337 and 3264-3204 cm^{-1} belonged to two stretching vibrations and Fermi resonance band of amino group, respectively.



Scheme 1. Synthesis path for substituted propargyl 2-methyl-5-cyano-6-amino-3-carboxylates, where, **4a-l** & (**5a-f**): R= H (**a**), 4′-NO_2 (**b**), 4′-Cl (**c**), 4′-Me (**d**), 4′-iPr (**e**), 4′-OMe (**f**).

The presence of propargylic group was confirmed by following evidence. Strong band at 3333-3284 cm^{-1} belonged to stretching vibration of terminal alkyne; other weak band in region at 2147-2126 cm^{-1} belonged to carbon-carbon triple bond. Strong absorption band in range of 2203-2187 cm^{-1} belonged to nitrile group. Ester functional group was confirmed by absorption bands in regions at 1728-1695 cm^{-1} (C=O ester), 1267-1225 and 1065-1057 cm^{-1} (C-O-C ester). The carbon-carbon double bonds of benzene ring had some absorption bands in regions at 1611-1490 cm^{-1}. Two alkene bonds of pyran ring had absorption bands in regions at 1684-1674 and 1649-1620 cm^{-1}.

The ^{1}H and ^{13}C NMR spectral data of substituted propargyl 6-amino-5-cyano-2-methyl-4-aryl-4*H*-pyran-3-carboxylates (**5a-f**) shown that protons and carbon-13 atoms in these molecules have proper chemical shifts in corresponding spectral regions which are characteristic for each type of atoms (*Figs. 1 and 2*). The formation of propargyl ester of above 4*H*-pyran-carbonitriles (**5a-f**) was confirmed by the NMR spectral data. In ^{1}H NMR of these 4*H*-pyran (**5a-f**), the present of chemical shifts in region at δ = 7.14-6.81 ppm appeared in singlet and with integral height of 2 protons. This signal belonged to amino group on position 6 of pyran ring in compounds (**5a-f**). Chemical shift that occurred in region of δ = 120.24-119.35 ppm was chemical shift of nitrile functional group on position 5. Carboxyl group of ester had chemical shift in range of δ = 165.42-164.74 ppm. The following evidences confirmed the presence of propargylic group. The protons in propargylic group had chemical shifts at δ = 3.52-3.43 ppm, usually in triplet coupling pattern due to the coupling interactions with protons of methylene group in this group. The coupling constants in these cases were *J* = 2.0-2.5 Hz. Proton H-4 on pyran ring had chemical shift in region of δ = 5.03-4.24 ppm in singlet. Methyl substituent had signal at δ = 2.37-2.27 ppm in singlet pattern. Protons on benzene ring had magnetic chemical shifts in region of δ = 8.20-6.87 ppm with multiplicities changed in depending on substituted patterns of benzene ring.

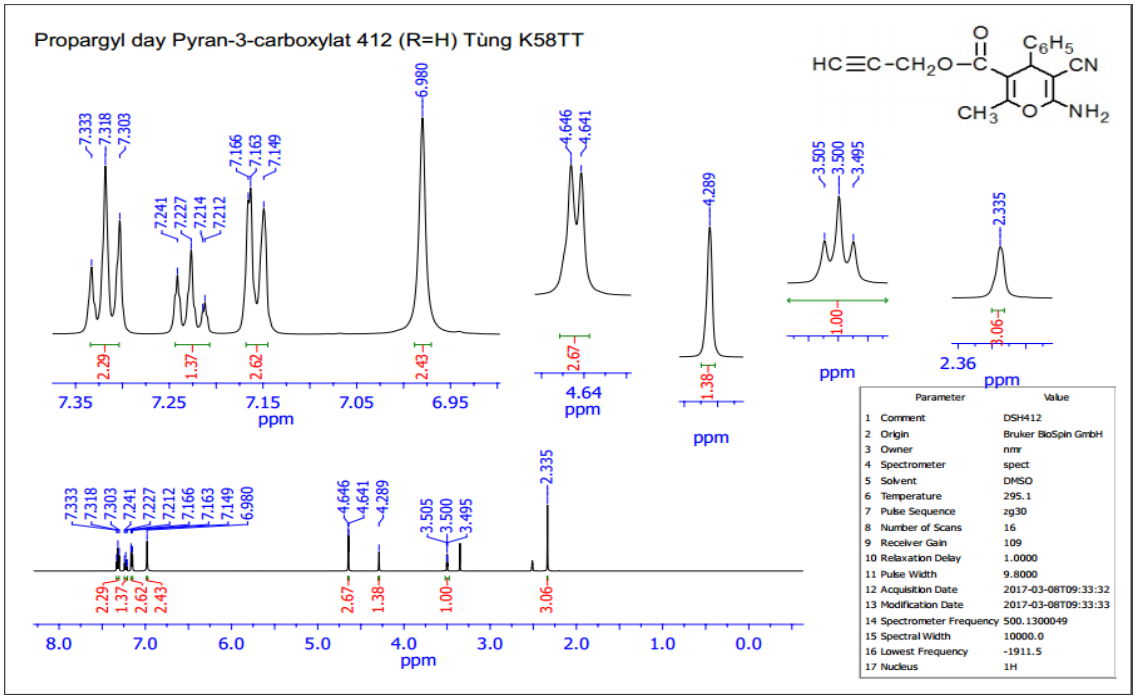


Figure 1. *^{1}H NMR spectrum of propargyl 6-amino-5-cyano-2-methyl-4-phenyl-4H-pyran-3-carboxylate (**5a**).*

Table 2. Meting point, IR Spectra of Some Propargyl 6-Amino-5-cyano-2-methyl-4-aryl-4*H*-pyran-3-carboxylate

Entry	m.p. (°C)	Yield (%)	IR (KBr, cm^{-1})						
			ν_{NH2}		ν_{C-O-C}	$\nu_{C=C}$	$\nu_{C\equiv N}$	$\nu_{C\equiv C}$	$\nu_{C=O}$
5a	152-154	63	3406; 3265	3331	1260; 1061	1676, 1609	2189	2137	1695
5b	162-164	61	3416, 3302	3333	1267, 1063	1678, 1620, 1607, 1522	2129	2197	1701
5c	168-170	53	3420; 3300	3337	1267; 1061	1674, 1643, 1605	2191	2131	1707
5d	167-169	42	3414, 3298	3331	1263, 1063	1676, 1645, 1607,	2129	2191	1709
5e	170-172	40	3414, 3229	3335	1263, 1061	1678, 1649, 1607	2137	2191	1697
5f	172-174	53	3393; 3298	3329	1225; 1057	1684, 1611, 1510	2196	2147	1724

Table 3. ^{1}H NMR Spectra of Some Propargyl 6-Amino-5-cyano-2-methyl-4-aryl-4*H*-pyran-3-carboxylate

Proton	Entry					
	5a	**5b**	**5c**	**5d**	**5e**	**5f**
H-3′ & H-5′	7.31 (d, *J* = 7.5 Hz, 2H)	8.20 (d, *J* = 8.5 Hz, 2H)	7.38 (d, *J* = 8.0 Hz, 2H)	7.04 (d, *J* = 8.0 Hz, 2H)	7.18 (d, *J* = 8.0 Hz, 2H)	6.87 (d, *J* = 8.75 Hz, 2H)
H-4′	7.22 (t, *J* = 7.5 Hz, 1H)	-	-	-	-	-
H-2′ & H-6′	7.15 (d, *J* = 7.5 Hz, 2H)	7.46 (dd, *J* = 8.5, 1.5 Hz, 2H)	7.19 (d, *J* = 8.0 Hz, 2H)	7.12 (d, *J* = 8.0 Hz, 2H, H-2′ & H-6′)	7.06 (d, *J* = 8.0 Hz, 2H)	7.06 (d, *J* = 8.75 Hz, 2H)
6-NH$_2$	6.98 (s, 2H)	7.14 (s, 2H)	7.03 (s, 2H)	6.94 (s, 2H)	6.96 (s, 2H)	6.93 (s, 2H)
H-4	4.29 (s, 1H)	4.48 (s, 1H)	4.32 (s, 1H)	4.25 (s, 1H)	4.25 (s, 1H)	4.24 (s, 1H)
2-CH$_3$	2.34 (s, 3H)	2.37 (s, 3H)	2.34 (s, 3H)	2.27 (s, 3H)	2.32 (s, 3H)	2.31 (s, 3H)
Other Protons	4.64 (d, *J* = 2.5 Hz, 2H, O**CH$_2$**C≡CH), 3.50 (t, *J* = 2.5 Hz, 1H, OCH$_2$C≡**CH**)	4.63 (qd, *J* = 15.5, 2.0 Hz, 2H, O**CH$_2$**C≡CH, 3.48 (t, *J* = 2.0 Hz, 1H, OCH$_2$C≡**CH**).	4.65 (t, *J* = 2.5 Hz, 2H, O**CH$_2$**C≡CH), 3.49 (t, *J* = 2.5 Hz, 1H, OCH$_2$C≡**CH**)	4.64 (d, *J* = 2.5 Hz, 2H, O**CH$_2$**C≡CH), 3.36 (s, 1H, OCH$_2$C≡**CH**), 2.32 (s, 3H, 4′-Me).	4.66 (d, J = 2.5 Hz, 2H, O**CH$_2$**C≡CH), 3.51 (t, J = 2.5 Hz, 4H, OCH$_2$C≡**CH**; 2.85 [septet, J = 7.0 Hz, 1H, **CH**(CH$_3$)$_2$]; 1.19 (d, J = 7.0 Hz, 6H, CH(**CH$_3$**)$_2$	4.65 (d, *J* = 2.5 Hz, 2H, O**CH$_2$**C≡CH), 3.52 (t, *J* = 2.5 Hz, 2H, OCH$_2$C≡**CH**), 3.73 (s, 3H, 4′-OMe)

Table 4. ^{13}C NMR Spectra of Some Propargyl 6-Amino-5-cyano-2-methyl-4-aryl-4*H*-pyran-3-carboxylate

Carbon	Entry					
	5a	**5b**	**5c**	**5d**	**5e**	**5f**
C-1'	145.07	152.69	144.14	142.11	142.47	137.12
C-3'	129.00	129.01	128.97	129.56	127.43	114.34
C-5'						
C-2'	127.50	124.33	129.53	127.49	125.93	128.70
C-6'						
C-4'	127.38	146.92	131.94	136.48	125.93	157.53
C≡N	120.12	119.70	119.95	120.15	120.24	120.18
C-2	158.10	158.98	158.17	157.79	157.97	158.62
C-3	107.21	105.94	106.72	107.37	107.47	107.54
C-4	39.17	39.10	38.66	38.77	38.72	38.37
C-5	57.65	56.58	57.28	57.77	57.73	57.88
C-6	158.99	159.34	158.94	158.95	159.10	158.89
2-CH_3	18.82	19.01	18.98	18.78	18.83	18.77
C=O ester	165.26	164.92	165.12	165.31	165.31	165.34
Other Carbons	78.52 (OCH_2**C**≡CH) 78.18 (OCH_2C≡**CH**) 52.40 (O**CH_2**C≡CH)	78.38 (OCH_2**C**≡CH), 78.20 (OCH_2C≡**CH**), 56.58 (O**CH_2**C≡CH).	78.48 (OCH_2**C**≡CH) 78.17 (OCH_2C≡**CH**) 52.42 (O**CH_2**C≡CH)	78.55 (OCH_2**C**≡CH), 78.20 (OCH_2C≡**CH**) 52.39 (O**CH_2**C≡CH) 21.10 (4′-Me).	78.56 (OCH_2C≡CH) 78.22 (OCH_2C≡CH) 33.49 [$CH(CH_3)_2$], 24.34 and 24.30 [$CH(CH_3)_2$]	78.57 (OCH_2**C**≡CH) 78.22 (OCH_2C≡**CH**, 52.37 (O**CH_2**C≡CH) 55.49 (4′-OMe)

The triple carbon-carbon bond was also confirmed by the chemical shift of the acetylenic carbon atoms in ^{13}C NMR spectra. The ^{13}C chemical shifts of propargylic group were located in region at δ = 78.18-77.99 ppm and δ = 78.59-78.17 ppm, belonged to the terminal and internal carbon atoms, respectively, in triple carbon-carbon bond. Methyl group had signal in region of δ = 19.06-18.74 ppm, and carbon atom in methylene-oxy bridge CH_2O had chemical shifts at δ = 52.46-52.28 ppm. The carbon atom on position 2 of pyran ring had downfield chemical shift at δ = 159.38-157.10 ppm due to electron-withdrawing influence of oxygen atom in pyran ring and of and nitrogen atom of amino group. The presence of the aromatic rings was confirmed by signals of the aromatic carbon resonances which located in range of δ = 148.30-111.96 ppm.

All above discursions on spectroscopic characteristics asserted the structure of obtained (**5a-f**).

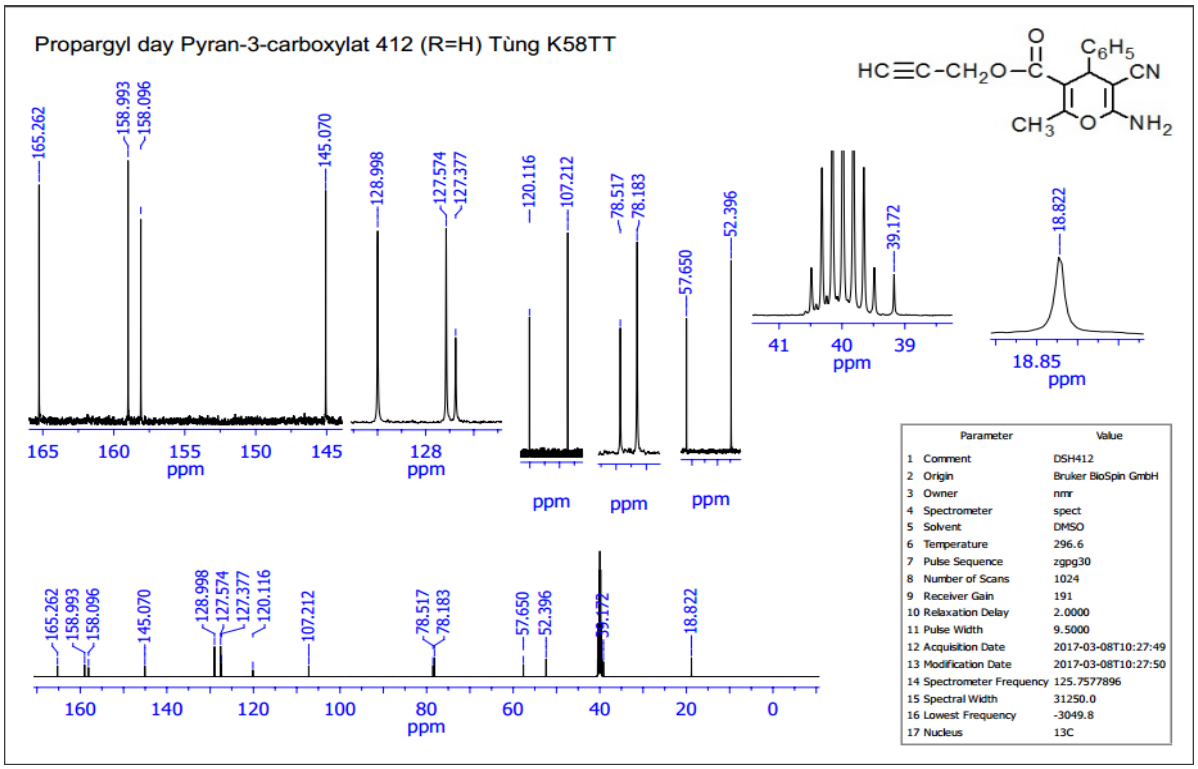


Figure 2. *Spectrum ^{13}C NMR of propargyl 6-amino-5-cyano-2-methyl-4-phenyl-4H-pyran-3-carboxylate (**5a**).*

3. CONCLUSIONS

In briefly, the precursors for click reaction, substituted propargyl 6-amino-5-cyano-2-methyl-4-aryl-4*H*-pyran-3-carboxylates, were synthesized by using three-component reaction using a cheap catalyst. Their structures were confirmed by using modern spectroscopic methods.

4. EXPERIMENTAL

Melting points (uncorrected) were measured on instrument STUART SMP3 (BIBBY STERILIN-UK). The IR spectra were recorded on FT-IR Affinity-1S Spectrometer (Shimadzu, Japan) in KBr pellet. The ^{1}H NMR and ^{13}C NMR spectra were recorded on an Avance Spectrometer AV500 (Bruker, Germany) at 500.13 MHz and 125.77 MHz, respectively, using DMSO-d_6 as solvent and TMS as an internal reference. Mass spectra were recorded on Mass Spectrometter LTQ Orbittrap XL^{TM} (Thermo SCIENTIFIC Co., USA), mode ESI,M-H (for **5a-k**) or M+H (for **5l**). Thin-layer chromatography was performed on silica gel plates $60F_{254}$ No. 5715 (Merck, Germany) with *n*-hexane:ethyl acetate = 1:2 by volume as solvent system, and spots were visualized with UV light or iodine vapor.

2.1. Procedure for synthesis of propargyl acetoacetate (3)

To a suspension of 80% sodium hydride (2.14 g; 0.071 mol) in 50 mL of anhydrous dioxane was added dropwise propargyl alcohol (**2**, 0.071mol, 3.98 g, 4.1 mL) in dioxane (150 mL) at room temperature. After being stirred for 1 h, a solution of 2,2,6-trimethyl-1,3-dioxen-4-one (**1**, 0.071 mol, 10 g, 9.3 mL) in THF (100 mL) was added dropwise. After 4 h, the solution was partitioned between ether (50 mL) and saturated solution of NH_4Cl (300 mL). The organic

layer was separated, washed with brine (2×400 mL), dried (by $CaCl_2$), and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel with eluent system ether:*n*-hexane (40/60 v/v) to afford the keto ester **3**. Yield 7.2 g (77%). The crude residue was propargyl acetoacetate that was pure enough for the further conversions [7]. **IR (neat) ν (cm^{-1})**: 3281, 2951, 2920, 2852, 2129, 1746, 1712, 1668, 1626, 1562, 1454, 1392, 1358, 1271, 1146.

2.2. General procedure for synthesis of substituted propargyl 6-amino-5-cyano-2-methyl-4-aryl-4*H*-pyran-3-carboxylates (5a-l)

To a solution of propargyl acetoacetate (5 mmol, 0.77g, 0.7 mL), malononitrile (5 mmol, 0.33 g, 0.31 mL) and appropriate substituted benzaldehyde **4** (5 mmol) in 96% ethanol (10 mL) was added appropriate catalyst (see Table 1). The reaction mixture was stirred at room temperature for 3 h, and monitored by TLC on silica gel plates. When the starting materials were disappeared, the separated solid product was filtered, washed by cold 96% ethanol, crystallized from 96% ethanol to afford the title propargyl ester of substituted 4*H*-pyran-3-carbonitriles **5a-l**.

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