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A nickel(0) catalyzed cycloaddition of alkynes and isocyanates that affords pyrimidine-diones

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Dedicated to Professor Günther Wilke for his contribution to the field of organonickel chemistry

Abstract—A Ni/*N*-heterocyclic carbene catalyzed cycloaddition of *one alkyne* and *two isocyanates* that affords pyrimidine-dione is described. The key to the success of this protocol is the use of unsymmetrically substituted alkynes that favors the formation of pyrimidine-diones over pyridones. A variety of pyrimidine-diones were prepared. A one-pot cycloaddition and Stille coupling were reported for tributyl(1-propynyl)tin. Competition studies also provide insights into the mechanism of the cycloaddition.

1. Introduction

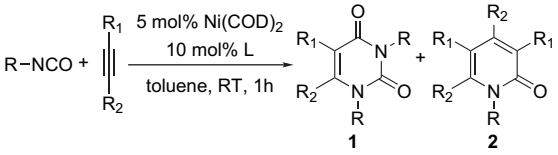
The transition metal catalyzed cycloaddition of unsaturated coupling partners has developed into a powerful and efficient method for the construction of heterocycles.[1] Such reactions generally involve the coupling of two alkynes with a heteroatom-containing substrate. For example, Co,[2] Ru,[3] and Ni[4] based systems catalyze cycloaddition reactions that yield pyrones, pyridones, pyrans, and pyridines. Any other combination of these coupling partners is rare.[5] We report that pyrimidine-diones can be prepared from the Ni-catalyzed cycloaddition of *one alkyne* and *two isocyanates*.

2. Results and discussion

We recently showed that the combination of Ni and IPr (or SIPr)[6] is an effective catalyst system for the cycloaddition of alkynes and isocyanates to afford pyridones in excellent yield.[4c] Included was the cycloaddition of 3-hexyne and phenyl isocyanate, which gave an excellent yield of tetraethylpyridone **2a** (entry 1, Table 1).[4c] During our investigations, we discovered that reactions run in excess of isocyanate led to the formation of a new heterocyclic product, pyrimidine-dione **1a**, in appreciable amounts (entry 2, Table 1).

A mechanism that diverges at a common intermediate and accounts for both pyridone and pyrimidine-dione products is shown in Scheme 1.[7] Initial oxidative coupling between

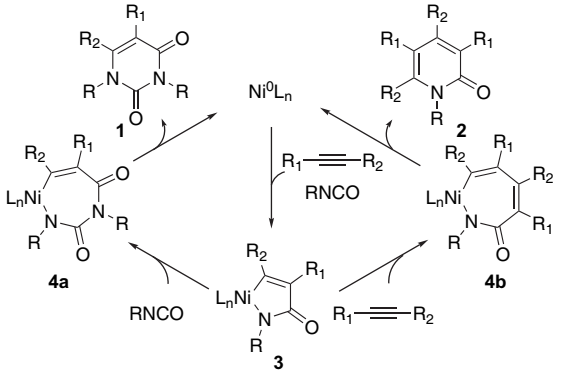
Table 1. Ni-catalyzed cycloaddition of alkynes and isocyanates



(1)

Entry	L	RNCO		Alkyne			% Alkyne conversion	1 (% Yield)	2 (% Yield)
		R	concn (M)	R_1	R_2	concn (M)			
1	IPr	Ph	0.2	Et	Et	0.1	100	**1a** (0)	**2a** (87)[a]
2	IPr	Ph	0.8	Et	Et	0.1	100	**1a** (30)[a]	**2a** (53)[a]
3	IPr	Ph	0.2	Ph	Ph	0.1	5	**1b** (0)[b]	**2b** (0)[b]
4	IPr	Ph	0.2	TMS	TMS	0.1	0	**1c** (0)[b]	**2c** (0)[b]
5	IPr	Ph	0.8	TMS	Me	0.1	100	**1d** (75)[a]	**2d** (0)[a]
6	None	Ph	0.2	TMS	Me	0.1	7	**1d** (0)[b]	**2d** (0)[b]

[a] Isolated yield.
[b] Determined by GC.



Scheme 1. Proposed mechanisms of the Ni-catalyzed cycloaddition.

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an alkyne and the isocyanate leads to nickelacycle **3**. When isocyanate concentrations are high, subsequent reaction with isocyanate, rather than alkyne, occurs and yields pyrimidine-dione products. This mechanism suggests that an increase in steric bulk on alkyne substrates would promote selective insertion of isocyanate rather than alkyne. Indeed, although diphenyl acetylene and bis(trimethylsilyl) acetylene failed to react (entries 3 and 4, Table 1), 1-trimethylsilyl propyne gave excellent yield of the pyrimidine-dione (**1d**) without the need for excess isocyanate concentrations (entry 5). Interestingly, the same reactants afforded only pyridone **2d** when Ni/PEt_3 was used as the catalyst.[4e] Thus, the steric hindrance of the IPr ligand may help to encourage isocyanate insertion over the insertion of another hindered alkyne. No cycloaddition occurred when $Ni(COD)_2$ was used in the absence of IPr ligand (entry 6).

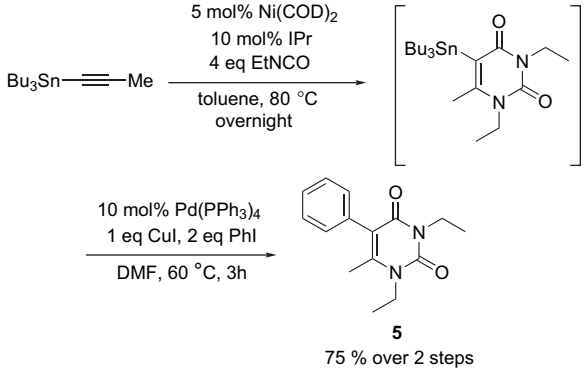
A variety of pyrimidine-diones were prepared via this procedure (Table 2). Pyrimidine-diones were obtained with aryl isocyanates although pyridone products were also observed in some cases (entries 2–4). Alkyl isocyanates were cleanly converted to the corresponding pyrimidine-dione (entries 5–7). Electron-withdrawing groups (such as $–CO_2Et$ and $–C_2H_3$) were also tolerated (entries 8, 9). Dialkyl-substituted acetylene such as 4,4-dimethyl-2-pentyne also worked well under the cyclization conditions to give the corresponding product in good yield (entry 10). Less sterically-encumbered alkynes such as 4-methyl-2-pentyne gave lower yields and selectivities (entry 11). A mixture of the pyrimidine-dione regioisomers and pyridone products were obtained (entry 11).

Tributyl(1-propynyl)tin cyclized to afford a pyrimidine-dione selectively (Scheme 2). Furthermore, exposure of the cycloaddition reaction mixture directly to standard Stille coupling conditions[8] resulted in the phenyl-substituted pyrimidine-dione **5** in 75% yield (Scheme 2). Thus, aryl pyrimidine-diones can be readily prepared through a two-step, one-pot reaction.

Table 2. Pyrimidine-diones prepared from Ni-catalyzed cycloaddition[a]

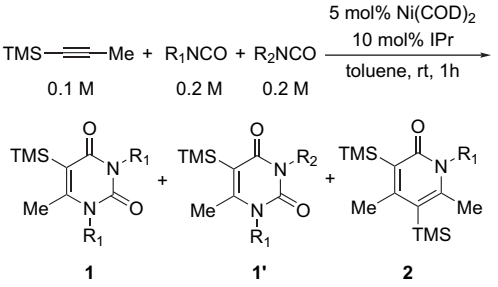
Entry	RNCO	Alkyne		Pyrimidine-dione **1** (% yield)[b]	Pyridone **2** (% yield)[b]
	R	R_1	R_2		
1	Ph	TMS	Me	**1d** (75)[c]	—
2	4-MeOPh	TMS	Me	**1e** (68)	**2e** (24)
3	3-MeOPh	TMS	Me	**1f** (49)	**2f** (24)
4	4-CF_3Ph	TMS	Me	**1g** (17)	**2g** (68)
5	Et	TMS	Me	**1h** (83)	—
6	Bn	TMS	Me	**1i** (72)[d]	—
7[e]	Cy	TMS	Me	**1j** (60)	—
8[f]	Cy	TMS	CO_2Et	**1k** (43)	—
9	Ph	TMS	C_2H_3	**1l** (38)[c]	**2l** (38)
10	Et	^{t}Bu	Me	**1m** (81)[d]	—
11	Ph	^{i}Pr	Me	**1n** (35)[g]	**2n** (18)

[a] Reaction conditions: 0.1 M diyne, 0.2 M isocyanate, 5 mol % $Ni(COD)_2$, 10 mol % IPr, toluene, rt.
[b] Isolated yields (average of two runs).
[c] Isocyanate (0.8 M) was used.
[d] Isocyanate (0.4 M) was used.
[e] Desilylated pyridone product was observed.
[f] Cyclotrimerized alkyne product (**3k**) was obtained in 45% yield.
[g] The other regioisomer (**1′n**) was also obtained in 14%.



Scheme 2. One-pot cycloaddition and Stille coupling.

Further insights into the mechanism of the cycloaddition were obtained through the competition reaction of 1-trimethylsilyl-1-propyne and two different isocyanates (Scheme 3). When 1-trimethylsilyl-1-propyne was exposed to equal concentrations of 4-CF_3PhNCO and 4-MeOPhNCO, a mixture of heterocyclic products was obtained (Table 3, entry 1). The product mixture included pyrimidine-dione **1g** (derived from the cycloaddition of only the electron-deficient isocyanate) as well as pyrimidine-dione **1′g** (derived from the cycloaddition of both isocyanates). Other pyrimidine-dione regioisomers were not observed. Similarly, when the same alkyne was subjected to equal mixtures of 4-MeOPhNCO and EtNCO, only two (out of the possible eight) pyrimidine-dione products were observed (entry 2). Only one pyridone was obtained in both competition reactions. Thus, the product distributions provide further evidence that hetero-oxidative coupling occurs (Scheme 1) and that nickelacycle **3** can react with either an alkyne or an isocyanate. The first step, oxidative coupling of the alkyne and an isocyanate, favors the more electron-deficient isocyanate (such as 4-CF_3PhNCO and 4-MeOPhNCO in entries 1 and 2, Table 3, respectively) and all observed heterocyclic products reflect this phenomenon. Nickelacycle **3** can insert either an alkyne or isocyanate to give pyridones or pyrimidine-diones, respectively.



Scheme 3. Cycloaddition with a mixture of isocyanates.

Table 3. Yields of pyrimidine-diones and pyridones

Entry	R_1	R_2	**1**	% Yield[a] **1′**	**2**
1	4-CF_3Ph	4-MeOPh	**1g** (11)	**1′g** (14)	**2g** (44)
2	4-MeOPh	Et	**1e** (28)	**1′e** (29)	**2e** (18)

[a] Isolated yields.

3. Conclusion

The combination of Ni and IPr catalyzes the cycloaddition of alkynes and isocyanates. When untethered alkynes that possess a large substituent are employed, coupling of two isocyanates and an alkyne affords pyrimidine-diones. Competition reactions suggest that initial hetero-oxidative coupling between an isocyanate and an alkyne occurs. Further application of this chemistry in the synthesis of other heterocycles is currently being investigated.

4. Experimental

4.1. General

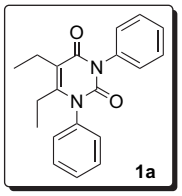
$Ni(COD)_2$ was purchased from Strem and used without further purification. 1,3-Bis(2,6-diisopropylphenyl)-imidazol-2-ylidene (IPr) was prepared according to literature procedure.[9] Phenyl isocyanate, ethyl isocyanate, benzyl isocyanate, 3-methoxyphenyl isocyanate, 4-methoxyphenyl isocyanate, α,α,α-trifluoro-*p*-tolyl isocyanate, cyclohexyl isocyanate, and butyl isocyanate were purchased from Aldrich, dried over phosphorous pentoxide, and degassed prior to use. 4-Methyl 2-pentyne (Aldrich), ethyl 3-(trimethylsilyl)propynoate (Aldrich), tributyl(1-propynyl)tin (Aldrich), and 4,4-dimethyl-2-pentyne (GFS) were purchased, dried over calcium hydride, and degassed prior to use. 1-Trimethylsilyl-pent-3-en-1-yne was prepared according to literature procedure.[10] ^1H and ^{13}C NMR spectra were recorded on a Varian VXL-300 spectrometer and a Varian VXR-500 spectrometer and referenced to residual protiated solvent (resonances downfield to the standard are reported as positive). All ^{13}C NMR spectra were proton decoupled. IR bands were measured as a thin film on a NaCl plate on a Bruker Tensor 27 FTIR spectrometer. The assignments of atom connectivity and spatial relationships are exclusively based on 2D NMR correlation (NOESY, $^1H/^{13}C$ HMBC, and $^1H/^{13}C$ HMQC) and 1D NOESY. Elemental analyses were performed at Midwest Microlab LLC., Indianapolis, IN.

4.2. General cycloaddition procedure of alkynes and isocyanates

A toluene solution of $Ni(COD)_2$ and IPr was prepared and allowed to equilibrate for at least 6 h.[4a] In a glove box, a solution of alkyne and isocyanate in toluene was added to an oven-dried vial equipped with a stir bar. To the stirring solution, a solution of $Ni(COD)_2$ and IPr was added and the reaction was stirred at room temperature for 1 h, unless otherwise stated. The mixture was then concentrated and purified by column chromatography with silica gel that was pre-treated with triethyl amine.

4.2.1. 5,6-Diethyl-1,3-diphenylpyrimidine-2,4(1*H*,3*H*)-dione (1a) and 3,4,5,6-tetraethyl-1-phenylpyridin-2(1*H*)-one (2a). The general procedure was used with 3-hexyne (28 mg, 0.34 mmol, 0.1 M), phenyl isocyanate (325 mg, 2.27 mmol, 0.8 M), $Ni(COD)_2$ (4.7 mg, 0.017 mmol, 5 mol %), IPr (13 mg, 0.034 mmol, 10 mol %), and 3.4 mL of toluene. The reaction mixture was purified first by column chromatography on silica gel (5:40:55 acetone/methylene chloride/hexane). Compound **1a** was further purified by column chromatography on silica gel (20% ethyl acetate/hexane then methylene chloride) to afford **1a** (33 mg, 30%) as a white solid. Compound **2a** was further purified by column chromatography on silica gel (10% acetone/methylene chloride) to afford **2a** (26 mg, 53%) as a white solid.[4c]

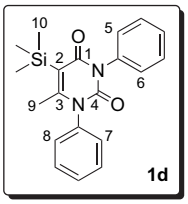
4.2.1.1. Analytical data for 1a.



^1H NMR (500 MHz, $CDCl_3$, ppm): δ 7.51–7.26 (m, 10H), 2.52 (q, 7.4 Hz, 2H), 2.37 (q, 7.4 Hz, 2H), 1.19 (t, 7.4 Hz, 3H), 1.03 (t, 7.4 Hz, 3H). ^{13}C {^1H} NMR (125 MHz, $CDCl_3$, ppm): δ 163.3, 152.5, 152.1, 137.5, 135.6, 129.7, 129.4, 129.3, 129.2, 128.6, 128.5, 113.6, 23.2, 19.9, 14.2, 13.3. IR ($CHCl_3$, cm^{-1}): 1707. Anal. Calcd for $C_{20}H_{20}N_2O_2$: C, 74.98; H, 6.29; N, 8.74, found: C, 74.88; H, 6.31; N, 8.69.

4.2.2. 6-Methyl-5-(trimethylsilyl)-1,3-diphenylpyrimidine-2,4(1*H*,3*H*)-dione (1d). The general procedure was used with 1-trimethylsilyl-1-propyne (35 mg, 0.31 mmol, 0.1 M), phenyl isocyanate (297 mg, 2.49 mmol, 0.8 M), $Ni(COD)_2$ (4.3 mg, 0.016 mmol, 5 mol %), IPr (12 mg, 0.032 mmol, 10 mol %), and 3.1 mL of toluene. The reaction mixture was purified by column chromatography on silica gel (20% acetone/hexane then 10% ethyl acetate/hexane) to afford **1d** as a white solid (82 mg, 75%).

4.2.2.1. Analytical data for 1d.

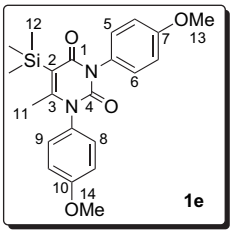


^1H NMR (300 MHz, CD_2Cl_2, ppm): δ 7.52–7.40 (m, 6H), 7.30–7.23 (m, 4H), 1.96 (s, 3H), 0.31 (s, 9H). ^{13}C {^1H} NMR (125 MHz, CD_2Cl_2, ppm): δ 165.6, 157.3, 152.5, 138.5, 136.5, 130.2, 129.6, 129.5, 129.3, 129.1, 128.7, 108.4, 21.9, 1.9. HMBC cross-peaks: H9 and C2, C3; H10 and C2 and other cross-peaks of aromatic protons and aromatic carbons. NOE was observed for aromatic protons and H9. IR (CH_2Cl_2, cm^{-1}): 1710, 1652, 1581. Anal. Calcd for $C_{20}H_{22}N_2O_2Si$: C, 68.54; H, 6.33; N, 7.99, found: C, 68.49; H, 6.52; N, 7.87.

4.2.3. 1,3-Bis(4-methoxyphenyl)-6-methyl-5-(trimethylsilyl)pyrimidine-2,4(1*H*,3*H*)-dione (1e) and 1-(4-methoxyphenyl)-4,6-dimethyl-3,5-bis(trimethylsilyl)pyridin-2(1*H*)-one (2e). The general procedure was used with

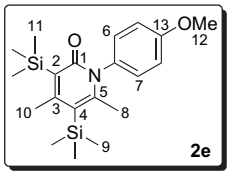
1-trimethylsilyl-1-propyne (35 mg, 0.31 mmol, 0.1 M), 4-methoxyphenyl isocyanate (93 mg, 0.62 mmol, 0.2 M), $Ni(COD)_2$ (4.3 mg, 0.016 mmol, 5 mol %), IPr (12 mg, 0.032 mmol, 10 mol %), and 3.1 mL of toluene. The reaction mixture was purified by column chromatography on silica gel (10% ethyl acetate/hexane then 10% acetone/hexane) to afford **1e** (87 mg, 68%) and **2e** (14 mg, 24%) as white solids.

4.2.3.1. Analytical data for 1e.



^1H NMR (300 MHz, $CDCl_3$, ppm): δ 7.21–7.16 (m, 4H), 7.04–7.00 (m, 4H), 3.87 (s, 3H), 3.85 (s, 3H), 2.00 (s, 3H), 0.34 (s, 9H). ^{13}C $\{^1H\}$ NMR (125 MHz, $CDCl_3$, ppm): δ 165.9, 160.4, 159.9, 157.8, 153.0, 131.1, 130.3, 130.0, 129.1, 115.3, 114.8, 108.2, 56.1, 56.0, 21.9, 1.9. HMBC cross-peaks: H11 and C2, C3; H12 and C2; H13 and C7; H14 and C10; and other cross-peaks of aromatic protons and aromatic carbons. NOE was observed for aromatic protons and H11. IR ($CHCl_3$, cm^{-1}): 1709, 1651. Anal. Calcd for $C_{22}H_{26}N_2O_4Si$: C, 64.36; H, 6.38; N, 6.82, found: C, 64.37; H, 6.41; N, 6.70.

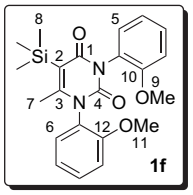
4.2.3.2. Analytical data for 2e.



^1H NMR (500 MHz, acetone, ppm): δ 7.08 (d, 8.8 Hz, 2H), 7.02 (d, 8.8 Hz, 2H), 3.86 (s, 3H), 2.40 (s, 3H), 2.06 (s, 3H), 0.38 (s, 9H), 0.28 (s, 9H). ^{13}C $\{^1H\}$ NMR (125 MHz, acetone, ppm): δ 166.4, 162.8, 160.2, 153.2, 133.7, 130.4, 125.5, 115.4, 114.8, 55.9, 26.5, 24.1, 4.0, 2.3. HMBC cross-peaks: H8 and C4, C5; H9 and C4; H10 and C2, C3, C4; H11 and C2; H12 and C13; and other cross-peaks of aromatic protons and aromatic carbons. IR (CH_2Cl_2, cm^{-1}): 1629. HRMS (*m*/*z*): calcd for $C_{20}H_{31}NO_2Si$ (M^+) 373.1893, found 373.1880.

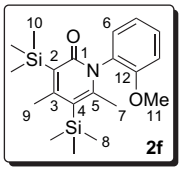
4.2.4. 1,3-Bis(3-methoxyphenyl)-6-methyl-5-(trimethylsilyl)pyrimidine-2,4(1*H*,3*H*)-dione (1f) and 1-(3-methoxyphenyl)-4,6-dimethyl-3,5-bis(trimethylsilyl)pyridin-2(1*H*)-one (2f). The general procedure was used with 1-trimethylsilyl-1-propyne (31 mg, 0.28 mmol, 0.1 M), 3-methoxyphenyl isocyanate (82 mg, 0.56 mmol, 0.2 M), $Ni(COD)_2$ (3.8 mg, 0.014 mmol, 5 mol %), IPr (11 mg, 0.028 mmol, 10 mol %), and 2.8 mL of toluene. The reaction mixture was purified first by column chromatography on silica gel (20% ethyl acetate/hexane). Compound **1f** was further purified by column chromatography on silica gel (methylene chloride) to afford **1f** as a white solid (56 mg, 49%). Compound **2f** was further purified by column chromatography on silica gel (1% acetone/methylene chloride) to afford **2f** as a white solid (12 mg, 24%).

4.2.4.1. Analytical data for 1f.



^1H NMR (300 MHz, $CDCl_3$, ppm): δ 7.42–7.33 (m, 2H), 7.01–6.81 (m, 6H), 3.83 (s, 3H), 3.80 (s, 3H), 2.05 (s, 3H), 0.36 (s, 9H). ^{13}C $\{^1H\}$ NMR (125 MHz, $CDCl_3$, ppm): δ 165.2, 160.7, 160.4, 156.7, 152.0, 138.7, 136.4, 130.5, 130.0, 121.0, 120.7, 115.1, 114.7, 114.5, 114.1, 108.3, 55.6, 55.4, 21.4, 1.9. HMBC cross-peaks: H7 and C2, C3; H8 and C2; H9 and C10; H11 and C12; and other cross-peaks of aromatic protons and aromatic carbons. NOE was observed for aromatic protons and H7. IR ($CHCl_3$, cm^{-1}): 1710, 1651, 1603, 1582. Anal. Calcd for $C_{22}H_{26}N_2O_4Si$: C, 64.36; H, 6.38; N, 6.82, found: C, 64.20; H, 6.29; N, 6.68.

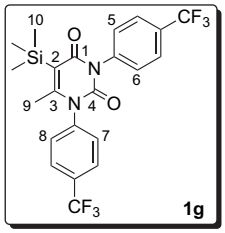
4.2.4.2. Analytical data for 2f.



^1H NMR (500 MHz, CD_2Cl_2, ppm): δ 7.44–7.41 (m, 1H); 7.00–6.98 (m, 1H), 6.76–6.69 (m, 2H), 3.85 (s, 3H), 2.41 (s, 3H), 2.07 (s, 3H), 0.41 (s, 9H), 0.33 (s, 9H). ^{13}C $\{^1H\}$ NMR (125 MHz, CD_2Cl_2, ppm): δ 166.1, 163.1, 161.2, 151.7, 141.9, 130.6, 125.7, 121.0, 115.2, 114.6, 114.2, 56.0, 26.7, 23.7, 4.0, 2.2. HMBC cross-peaks: H7 and C4, C5; H8 and C4; H9 and C2, C3, C4; H10 and C2; H11 and C12; and other cross-peaks of aromatic protons and aromatic carbons. IR (CH_2Cl_2, cm^{-1}): 1630, 1547. HRMS (*m*/*z*): calcd for $C_{20}H_{31}NO_2Si$ (M^+) 373.1893, found 373.1891.

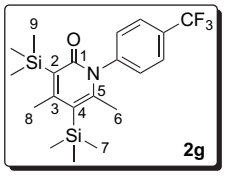
4.2.5. 1,3-Bis(4-(trifluoromethyl)phenyl)-6-methyl-5-(trimethylsilyl)pyrimidine-2,4(1*H*,3*H*)-dione (1g) and 1-(4-(trifluoromethyl)phenyl)-4,6-dimethyl-3,5-bis(trimethylsilyl)pyridin-2(1*H*)-one (2g). The general procedure was used with 1-trimethylsilyl-1-propyne (37 mg, 0.33 mmol, 0.1 M), α,α,α-trifluoro-*p*-tolyl isocyanate (123 mg, 0.66 mmol, 0.2 M), $Ni(COD)_2$ (4.5 mg, 0.016 mmol, 5 mol %), IPr (13 mg, 0.032 mmol, 10 mol %), and 3.3 mL of toluene. The reaction mixture was purified first by column chromatography on silica gel (5% ethyl acetate/hexane) to afford **2g** (46 mg, 68%) as a white solid. Compound **1g** was further purified by column chromatography on silica gel (10% acetone/hexane then 1:1 methylene chloride/hexane) to afford **1g** as a white solid (27 mg, 17%).

4.2.5.1. Analytical data for 1g.



^{1}H NMR (500 MHz, acetone, ppm): δ 7.91 (d, 8.3 Hz, 2H), 7.81 (d, 8.3 Hz, 2H), 7.75 (d, 8.3 Hz, 2H), 7.54 (d, 8.3 Hz, 2H), 2.08 (s, 3H), 0.33 (s, 9H). ^{13}C {^{1}H} NMR (125 MHz, acetone, ppm): δ 164.8, 156.9, 151.5, 142.0, 140.1, 130.61, (q, 32 Hz), 130.60, 130.2, 129.7 (q, 32 Hz), 126.8 (q, 3 Hz), 125.9 (q, 3 Hz), 124.5 (q, 271 Hz), 124.3 (q, 271 Hz), 107.5, 21.3, 1.21. HMBC cross-peaks: H9 and C2, C3; H10 and C2 and other cross-peaks of aromatic protons and aromatic carbons. NOE was observed for aromatic protons and H9. IR (CH_2Cl_2, cm^{-1}): 1712, 1657, 1586. HRMS (*m*/*z*): calcd for $C_{22}H_{20}N_2O_2SiF_6$ (M^+) 486.1198, found 486.1191.

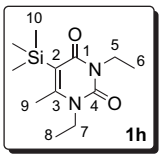
4.2.5.2. Analytical data for 2g.



^{1}H NMR (500 MHz, acetone, ppm): δ 7.87 (d, 8.3 Hz, 2H), 7.48 (d, 8.3 Hz, 2H), 2.43 (s, 3H), 2.08 (s, 3H), 0.40 (s, 9H), 0.29 (s, 9H). ^{13}C {^{1}H} NMR (125 MHz, acetone, ppm): δ 165.3, 162.8, 151.2, 144.3, 130.0–129.4 (m, 2C), 126.6 (m), 125.0, 124.5 (q, 271 Hz), 114.7, 25.9, 23.4, 3.2, 1.5. HMBC cross-peaks: H6 and C4, C5; H7 and C4; H8 and C2, C3; H9 and C2; and other cross-peaks of aromatic protons and aromatic carbons. IR (CH_2Cl_2, cm^{-1}): 1630, 1488. Anal. Calcd for $C_{20}H_{28}NOSi_2F_3$: C, 58.36; H, 6.86; N, 3.40, found: C, 58.74; H, 6.52; N, 3.51.

4.2.6. 1,3-Diethyl-6-methyl-5-(trimethylsilyl)pyrimidine-2,4(1*H*,3*H*)-dione (1h). The general procedure was used with 1-trimethylsilyl-1-propyne (51 mg, 0.45 mmol, 0.1 M), ethyl isocyanate (65 mg, 0.90 mmol, 0.2 M), Ni(COD)$_2$ (6.2 mg, 0.023 mmol, 5 mol %), IPr (17 mg, 0.046 mmol, 10 mol %), and 4.5 mL of toluene. The reaction mixture was purified by column chromatography on silica gel (5% acetone/methylene chloride) to afford **1h** as a colorless oil (96 mg, 83%).

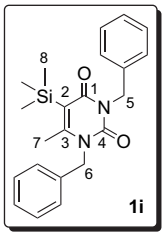
4.2.6.1. Analytical data for 1h.



^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 3.94 (m, 4H), 2.31 (s, 3H), 1.27 (t, 7.0 Hz, 3H), 1.19 (t, 7.0 Hz, 3H), 0.30 (s, 9H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$, ppm): δ 165.0, 155.5, 151.9, 107.9, 40.4, 36.5, 19.5, 14.3, 13.0, 2.1. HMBC cross-peaks: H5 and C1, C4, C6; H6 and C5; H7 and C3, C4, C8; H8 and C7; H9 and C2, C3; H10 and C2. IR ($CHCl_3$, cm^{-1}): 1694, 1635, 1584. HRMS (*m*/*z*): calcd for $C_{12}H_{22}SiN_2O_2$ (M^+) 254.1451, found 254.1448.

4.2.7. 1,3-Dibenzyl-6-methyl-5-(trimethylsilyl)pyrimidine-2,4(1*H*,3*H*)-dione (1i). The general procedure was used with 1-trimethylsilyl-1-propyne (35 mg, 0.31 mmol, 0.1 M), benzyl isocyanate (166 mg, 1.24 mmol, 0.4 M), Ni(COD)$_2$ (8.6 mg, 0.032 mmol, 10 mol %), IPr (24 mg, 0.064 mmol, 20 mol %), and 3.1 mL of toluene. After stirring overnight at 80 °C, the reaction mixture was purified by column chromatography on silica gel (10% ethyl acetate/hexane) to afford **1i** as a white solid (85 mg, 72%).

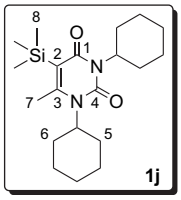
4.2.7.1. Analytical data for 1i.



^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.51–7.15 (m, 10H), 5.19–5.18 (m, 4H), 2.25 (s, 3H), 0.33 (s, 9H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$, ppm): δ 165.0, 156.3, 153.0, 137.5, 136.7, 129.2, 129.1, 128.5, 127.8, 127.6, 126.3, 108.5, 48.4, 44.7, 20.0, 2.0. HMBC cross-peaks: H5 and C1, C4; H6 and C3, C4; H7 and C2, C3; H8 and C2 and other cross-peaks of aromatic protons and aromatic carbons. NOE was observed for H7 and H6 and aromatic protons. IR ($CHCl_3$, cm^{-1}): 1695, 1638, 1584. Anal. Calcd for $C_{22}H_{26}N_2O_2Si$: C, 69.80; H, 6.92; N, 7.40, found: C, 69.84; H, 6.91; N, 7.47.

4.2.8. 1,3-Dicyclohexyl-6-methyl-5-(trimethylsilyl)pyrimidine-2,4(1*H*,3*H*)-dione (1j). To a solution of Ni(COD)$_2$ (4.7 mg, 0.016 mmol, 5 mol %) and IPr (13 mg, 0.032 mmol, 10 mol %) in 1.4 mL of toluene was added dropwise a solution of 1-trimethylsilyl-1-propyne (38 mg, 0.34 mmol, 0.1 M), and cyclohexyl isocyanate (85 mg, 0.90 mmol, 0.2 M) in 2.0 mL of toluene. After stirring at room temperature for 1 h, the reaction mixture was purified by column chromatography on silica gel (2:3 methylene chloride/hexane) to afford **1j** as a white solid (74 mg, 60%). Some decomposition product of a pyridone product was also observed by ^{1}H NMR.

4.2.8.1. Analytical data for 1j.

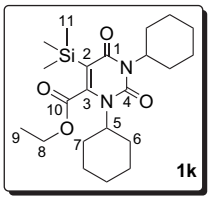


^{1}H NMR (500 MHz, CD_2Cl_2, ppm): δ 4.67–4.62 (m, 1H), 3.83 (m, 1H), 2.54–2.47 (m, 2H), 2.38–2.29 (m, 2H), 2.25 (s, 3H), 2.85–1.77 (m, 4H), 1.65–1.37 (m, 6H), 1.36–1.53 (m, 6H), 0.26 (s, 9H). ^{13}C {^{1}H} NMR (125 MHz, CD_2Cl_2,

ppm): δ 166.2, 156.4, 152.0, 108.4, 60.2, 29.8, 29.1, 27.1, 27.0, 26.1, 25.8, 20.9, 2.3. HMBC cross-peaks: H7 and C2, C3; H8 and C2, and other cross-peaks of cyclohexyl protons and cyclohexyl carbons. NOE was observed for cyclohexyl protons and H7. IR (CH_2Cl_2, cm^{-1}): 1697, 1637, 1582; Anal. Calcd for $C_{20}H_{34}N_2O_2Si$: C, 66.25; H, 9.45; N, 7.73, found: C, 66.36; H, 9.18; N, 7.60.

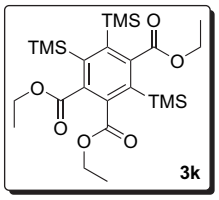
4.2.9. Triethyl 1,3-dicyclohexyl-1,2,3,6-tetrahydro-5-(trimethylsilyl)-2,6-dioxopyrimidine-4-carboxylate (1k) and triethyl 3,5,6-tris(trimethylsilyl)benzene-1,2,4-tricarboxylate (3k). The general procedure was used with ethyl 3-(trimethylsilyl)propynoate (46 mg, 0.27 mmol, 0.1 M), cyclohexyl isocyanate (68 mg, 0.54 mmol, 0.2 M), $Ni(COD)_2$ (3.7 mg, 0.013 mmol, 5 mol %), IPr (10 mg, 0.026 mmol, 10 mol %), and 2.7 mL of toluene. The reaction mixture was purified by column chromatography on silica gel (5% ethyl acetate/hexane) to afford **1k** (49 mg, 43%) and **3k** as white solids (21 mg, 45%).

4.2.9.1. Analytical data for 1k.



^1H NMR (500 MHz, $CDCl_3$, ppm): δ 4.71–4.67 (m, 1H), 4.38–4.36 (m, 2H), 3.24–3.20 (m, 1H), 2.52–2.45 (m, 2H), 2.40–2.32 (m, 2H), 1.87–1.77 (m, 6H), 1.60–1.59 (m, 4H), 1.40–1.11 (m, 9H), 0.19 (s, 9H). ^{13}C {^1H} NMR (125 MHz, $CDCl_3$, ppm): δ 166.0, 163.5, 150.8, 150.3, 107.0, 64.5, 62.7, 54.3, 29.4, 28.7, 26.7, 26.5, 25.4, 25.1, 14.0, −0.3. HMBC cross-peaks: H5 and C3, C4, C6, C7; H8 and C9, C10; H9 and C8; H11 and C2; other cross-peaks of cyclohexyl protons and cyclohexyl carbons. IR ($CHCl_3$, cm^{-1}): 1742, 1704, 1647, 1590. Anal. Calcd for $C_{22}H_{36}N_2O_4Si$: C, 62.82; H, 8.63; N, 6.66, found: C, 62.99; H, 8.46; N, 6.68.

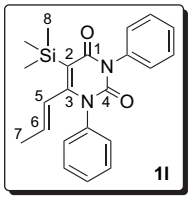
4.2.9.2. Analytical data for 3k.



^1H NMR (500 MHz, CD_2Cl_2, ppm): δ 4.33–4.21 (m, 6H), 1.39–1.29 (m, 9H), 0.36 (s, 9H), 0.33 (s, 9H), 0.26 (s, 9H). ^{13}C {^1H} NMR (125 MHz, CD_2Cl_2, ppm): δ 170.7, 170.0, 153.5, 151.4, 147.7, 139.4, 139.2, 139.0, 62.3 (m, 3C), 14.3 (m, 3C), 4.4, 3.9, 1.8. IR (CH_2Cl_2, cm^{-1}): 1726. HRMS (*m*/*z*): calcd for $C_{24}H_{42}O_6Si_3$ (M^+) 510.2289, found 510.2291.

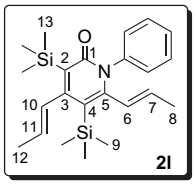
4.2.10. 5-(Trimethylsilyl)-1,3-diphenyl-6-((*Z*)-prop-1-enyl)pyrimidine-2,4(1*H*,3*H*)-dione (1l) and 3,5-bis(trimethylsilyl)-1-phenyl-4,6-di((*Z*)-prop-1-enyl)pyridin-2(1*H*)-one (2l). The general procedure was used with 1-trimethylsilyl-pent-3-en-1-yne (34 mg, 0.24 mmol, 0.1 M), phenyl isocyanate (234 mg, 1.96 mmol, 0.2 M), $Ni(COD)_2$ (3.4 mg, 0.012 mmol, 5 mol %), IPr (9 mg, 0.024 mmol, 10 mol %), and 2.4 mL of toluene. The reaction mixture was purified first by column chromatography on silica gel (methylene chloride) to afford **2l** (18 mg, 38%) as a white solid. **1l** was further purified by column chromatography on silica gel (5% ethyl acetate/hexane) to afford **1l** (35 mg, 38%) as a white solid.

4.2.10.1. Analytical data for 1l.



^1H NMR (500 MHz, CD_2Cl_2, ppm): δ 7.52–7.43 (m, 6H), 7.30–7.23 (m, 4H), 5.88–5.80 (m, 1H), 5.61 (dd, 1.5 and 15.7 Hz, 1H), 1.64 (dd, 1.5 and 7.0 Hz, 3H), 0.25 (s, 9H). ^{13}C {^1H} NMR (125 MHz, CD_2Cl_2, ppm): δ 166.3, 158.1, 152.3, 138.4, 137.0, 136.5, 130.0, 129.8, 129.6, 129.3, 129.2, 128.8, 126.3, 108.8, 18.4, 2.1. HMBC cross-peaks: H5 and C2, C3, C6, C7; H6 and C3, C5, C7; H7 and C5, C6; H8 and C2; and other cross-peaks of aromatic protons and aromatic carbons. NOE was observed for aromatic protons and H5. IR (CH_2Cl_2, cm^{-1}): 1711, 1653, 1569. Anal. Calcd for $C_{22}H_{24}N_2O_2Si$: C, 70.18; H, 6.42; N, 7.44, found: C, 70.15; H, 6.51; N, 7.41.

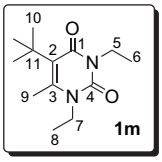
4.2.10.2. Analytical data for 2l.



^1H NMR (300 MHz, CD_2Cl_2, ppm): δ 7.47–7.34 (m, 3H), 7.09–7.06 (m, 2H), 6.59 (dq, 1.8 and 15.8 Hz, 1H), 5.77–5.55 (m, 3H), 1.84 (d, 6.6 Hz, 3H), 1.58 (d, 6.6 Hz, 3H), 0.22 (s, 9H), 0.15 (s, 9H). ^{13}C {^1H} NMR (125 MHz, CD_2Cl_2, ppm): δ 165.8, 164.9, 154.8, 140.2, 135.7, 135.3, 130.7, 129.7, 129.5, 128.4, 125.8, 114.8, 18.5, 18.3, 4.3, 2.0. HMBC cross-peaks: H8 and C6, C7; H9 and C4; H10 and C2, C3, C4, C11, C12; H12 and C10, C11; H13 and C2; and other cross-peaks of olefinic/aromatic protons and olefinic/aromatic carbons. IR (CH_2Cl_2, cm^{-1}): 1632. Anal. Calcd for $C_{23}H_{33}NOSi_2$: C, 69.81; H, 8.41; N, 3.54, found: C, 69.41; H, 8.25; N, 3.36.

4.2.11. 5-Tert-butyl-1,3-diethyl-6-methylpyrimidine-2,4(1*H*,3*H*)-dione (1m). The general procedure was used with 4,4-dimethyl-2-pentyne (34 mg, 0.35 mmol, 0.1 M), ethyl isocyanate (100 mg, 1.42 mmol, 0.4 M), $Ni(COD)_2$ (9.7 mg, 0.035 mmol, 10 mol %), IPr (27 mg, 0.070 mmol, 20 mol %), and 3.5 mL of toluene. After stirring at 80 °C overnight, the reaction mixture was purified by column chromatography on silica gel (20% ethyl acetate/hexane) to afford **1m** as a yellow solid (68 mg, 81%).

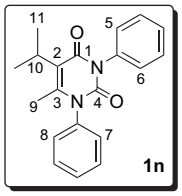
4.2.11.1. Analytical data for 1m.



^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 4.01–3.92 (m, 4H), 2.39 (s, 3H), 1.44 (s, 9H), 1.28 (t, 7.0 Hz, 3H), 1.21 (t, 7.0 Hz, 3H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$, ppm): δ 162.2, 151.1, 146.5, 120.2, 40.4, 36.9, 35.7, 32.0, 18.9, 14.5, 13.1. HMBC cross-peaks: H5 and C1, C4, C6; H6 and C5; H7 and C3, C4, C8; H8 and C7; H9 and C2, C3; H10 and C2, C11. IR ($CHCl_3$, cm^{-1}): 1693, 1644, 1587. Anal. Calcd for $C_{13}H_{22}N_2O_2$: C, 65.51; H, 9.30; N, 11.75, found: C, 65.69; H, 9.49; N, 11.64.

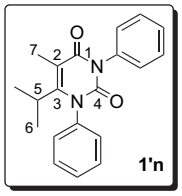
4.2.12. 5-Isopropyl-6-methyl-1,3-diphenylpyrimidine-2,4(1*H*,3*H*)-dione (1n), 6-isopropyl-5-methyl-1,3-diphenylpyrimidine-2,4(1*H*,3*H*)-dione (1′n), and 3,5-diisopropyl-4,6-dimethyl-1-phenylpyridin-2(1*H*)-one (2n). The general procedure was used with 4-methyl 2-pentyne (53 mg, 0.65 mmol, 0.1 M), phenyl isocyanate (154 mg, 1.30 mmol, 0.2 M), $Ni(COD)_2$ (8.9 mg, 0.032 mmol, 5 mol %), IPr (25 mg, 0.064 mmol, 10 mol %), and 6.5 mL of toluene. The reaction mixture was purified by column chromatography on silica gel (15–25% ethyl acetate/hexane) to afford **1n** (72 mg, 35%) and **1′n** (29 mg, 14%) as white solids. A fraction was also determined to be the impure pyridone **2n** (16 mg, 18%).

4.2.12.1. Analytical data for dione 1n.



^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 7.50–7.26 (m, 10H), 3.08–3.05 (sept, 7.0 Hz, 1H), 1.96 (s, 3H), 1.35 (d, 7.0 Hz, 6H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$, ppm): δ 162.3, 151.8, 146.9, 138.0, 135.5, 129.9, 129.3, 129.2, 129.0, 128.6, 128.5, 117.2, 28.5, 20.7, 18.1. HMBC cross-peaks: H9 and C2, C3; H10 and C1, C2, C3, C11; H11 and C10; and other cross-peaks of aromatic protons and aromatic carbons. IR ($CHCl_3$, cm^{-1}): 1708, 1656. Anal. Calcd for $C_{20}H_{20}N_2O_2$: C, 74.98; H, 6.29; N, 8.74, found: C, 75.0; H, 6.36; N, 8.73.

4.2.12.2. Analytical data for dione 1′n.



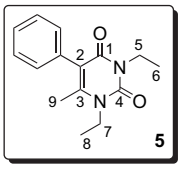
^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.54–7.35 (m, 6H), 7.29–7.26 (m, 4H), 2.74 (sept, 7.1 Hz, 1H), 2.17 (s, 3H), 1.26 (d, 7.1 Hz, 6H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$, ppm): δ 164.2, 155.7, 152.1, 138.3, 135.6, 130.0, 129.3, 129.2, 128.9, 128.6, 128.4, 108.2, 30.9, 19.7, 12.0. HMBC cross-peaks: H5 and C2, C3; H6 and C3, C5; H7 and C1, C2, C3; and other cross-peaks of aromatic protons and aromatic carbons. IR ($CHCl_3$, cm^{-1}): 1709, 1654. Anal. Calcd for $C_{20}H_{20}N_2O_2$: C, 74.98; H, 6.29; N, 8.74, found: C, 74.70; H, 6.46; N, 8.43.

4.2.12.3. Analytical data for 2n (impure). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.51–7.36 (3H); 7.18–7.14 (2H), 3.36–3.23 (m, 2H), 2.29 (s, 3H), 1.95 (s, 3H); 1.35–1.31 (m, 12H).

4.2.13. One-pot cycloaddition followed by Stille coupling: 1,3-diethyl-6-methyl-5-phenylpyrimidine-2,4(1*H*,3*H*)-dione. The general procedure for cycloaddition was used with tributyl(1-propynyl)tin (134 mg, 0.41 mmol, 0.1 M), ethyl isocyanate (116 mg, 1.64 mmol, 0.4 M), $Ni(COD)_2$ (5.6 mg, 0.020 mmol, 5 mol %), IPr (16 mg, 0.040 mmol, 10 mol %), and 4.1 mL of toluene. After stirring at 80 °C overnight, the solvent was removed.

In a glove box, to a Schlenk flask equipped with a stir bar, $Pd(PPh_3)_4$ (47 mg, 0.041 mmol, 10 mol %), phenyl iodide (166 mg, 0.082 mmol, 200 mol %), *N*,*N*-dimethyl formamide (4.1 mL), and copper iodide (78 mg, 0.41 mmol, 100 mol %) were successively added. After stirring for 1 min, the residue from the cycloaddition mixture was added. The flask was then taken out of the glove box and stirred under N_2 at 60 °C for 3 h. The reaction mixture was cooled down, diluted with Et_2O, and washed with water. The aqueous layer was further extracted with Et_2O. The combined organic layers were dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography on silica gel (10% ethyl acetate/hexane then 3% methanol/methylene chloride) to afford **5** as a white solid (79 mg, 75%).

4.2.13.1. Analytical data for 5.

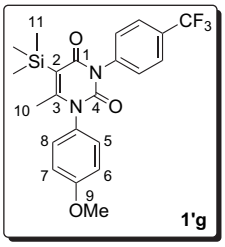


^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 7.42–7.33 (m, 3H), 7.22–7.20 (m, 2H), 4.08–3.99 (m, 4H), 2.17 (s, 3H), 1.35 (t, 7.1 Hz, 3H), 1.26 (t, 7.1 Hz, 3H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$, ppm): δ 162.0, 151.4, 147.9, 134.5, 131.0, 128.5, 127.8, 114.6, 40.8, 37.0, 17.5, 14.3, 13.0. HMBC cross-peaks: H5 and C1, C4; H6 and C5; H7 and C3, C4, C8; H9 and C2, C3; and other cross-peaks of aromatic protons and aromatic carbons. IR ($CHCl_3$, cm^{-1}): 1696, 1644. Anal. Calcd for $C_{15}H_{18}N_2O_2$: C, 69.74; H, 7.02; N, 10.84, found: C, 69.44; H, 6.83; N, 10.76.

4.2.14. 3-(4-(Trifluoromethyl)phenyl)-1-(4-methoxyphenyl)-6-methyl-5-(trimethylsilyl)pyrimidine-2,4(1*H*,3*H*)-dione (1g), 1,3-bis(4-(trifluoromethyl)phenyl)-6-methyl-5-(trimethylsilyl)pyrimidine-2,4(1*H*,3*H*)-dione (1′g), and 1-(4-(trifluoromethyl)phenyl)-4,6-dimethyl-3,5-bis(trimethylsilyl)pyridin-2(1*H*)-one (2g). The general procedure was used with 1-trimethylsilyl-1-propyne (32 mg,

0.29 mmol, 0.1 M), α,α,α-trifluoro-*p*-tolyl isocyanate (107 mg, 0.58 mmol, 0.2 M), 4-methoxyphenyl isocyanate (85 mg, 0.58 mmol, 0.2 M), $Ni(COD)_2$ (3.9 mg, 0.014 mmol, 5 mol %), IPr (11 mg, 0.028 mmol, 10 mol %), and 2.9 mL of toluene. The reaction mixture was purified by column chromatography on silica gel (4:6 hexane/methylene chloride then 10% ethyl acetate/hexane) to give **1g** (15 mg, 11%), **1′g** (18 mg, 14%), and **2g** (26 mg, 44%) as white solids.

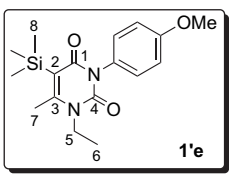
4.2.14.1. Analytical data for 1′g.



^{1}H NMR (500 MHz, acetone, ppm): δ 7.80 (d, 8.8 Hz, 2H), 7.52 (d, 8.8 Hz, 2H), 7.34 (d, 8.8 Hz, 2H), 7.05 (d, 8.8 Hz, 2H), 3.85 (s, 3H), 2.05 (s, 3H), 0.30 (s, 9H). ^{13}C {^{1}H} NMR (125 MHz, acetone, ppm): δ 164.9, 160.1, 158.4, 151.8, 140.4, 130.9, 130.2, 129.6 (q, 33 Hz), 125.9, 124.6 (q, 271 Hz), 114.7, 106.7, 55.2, 21.2, 1.2. HMBC cross-peaks: H5 and C2, C3; H6 and C2; and other cross-peaks of aromatic protons and aromatic carbons. NOE was observed for H5/H8 and H6, H7, H10; H6/H7 and H9. IR (CH_2Cl_2, cm^{-1}): 1710, 1654. HRMS (*m/z*): calcd for $C_{22}H_{23}N_2O_3SiF_3$ (M^+) 448.1430, found 448.1426.

4.2.15. 1,3-Bis(4-methoxyphenyl)-6-methyl-5-(trimethylsilyl)pyrimidine-2,4(1*H*,3*H*)-dione (1e), 1-(4-methoxyphenyl)-4,6-dimethyl-3,5-bis(trimethylsilyl)pyridin-2(1*H*)-one (2e), and 1-ethyl-3-(4-methoxyphenyl)-6-methyl-5-(trimethylsilyl)pyrimidine-2,4(1*H*,3*H*)-dione (1′e). The general procedure was used with 1-trimethylsilyl-1-propyne (33 mg, 0.29 mmol, 0.1 M), 4-methoxyphenyl isocyanate (88 mg, 0.58 mmol, 0.2 M), ethyl isocyanate (42 mg, 0.58 mmol, 0.2 M), $Ni(COD)_2$ (3.9 mg, 0.014 mmol, 5 mol %), IPr (11 mg, 0.028 mmol, 10 mol %), and 2.9 mL of toluene. The reaction mixture was purified by column chromatography on silica gel with 10–25% ethyl acetate/hexane to obtain **2e** (10 mg, 18%), then with 10% acetone/hexane to obtain **1′e** (28 mg, 29%), and then with 5% acetone/methylene chloride to obtain **1e** (34 mg, 28%).

4.2.15.1. Analytical data for 1′e.



^{1}H NMR (300 MHz, CD_2Cl_2, ppm): δ 7.09 (d, 9.0 Hz, 2H), 6.98 (d, 9.0 Hz, 2H), 3.97 (q, 7.1 Hz, 2H), 3.84 (s, 3H), 2.39 (s, 3H), 1.29 (t, 7.1 Hz, 3H), 0.30 (s, 9H). ^{13}C {^{1}H} NMR (125 MHz, CD_2Cl_2, ppm): δ 165.6, 159.8, 157.1, 152.7, 130.0, 129.4, 114.8, 108.3, 56.0, 40.9, 20.1, 14.4, 2.1. HMBC cross-peaks: H5 and C3, C4, C6; H7 and C2, C3; H8 and C2. IR (CH_2Cl_2, cm^{-1}): 1700, 1642, 1580. Anal. Calcd for $C_{17}H_{24}N_2O_3Si$: C, 61.41; H, 7.28; N, 8.43, found: C, 61.46; H, 7.23; N, 8.34.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.03.119.

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