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A Domino Desulfitative Coupling/Acylation/Hydration Process Cocatalyzed by Copper(I) and Palladium(II): Synthesis of Highly Substituted and Functionalized Pyrimidines

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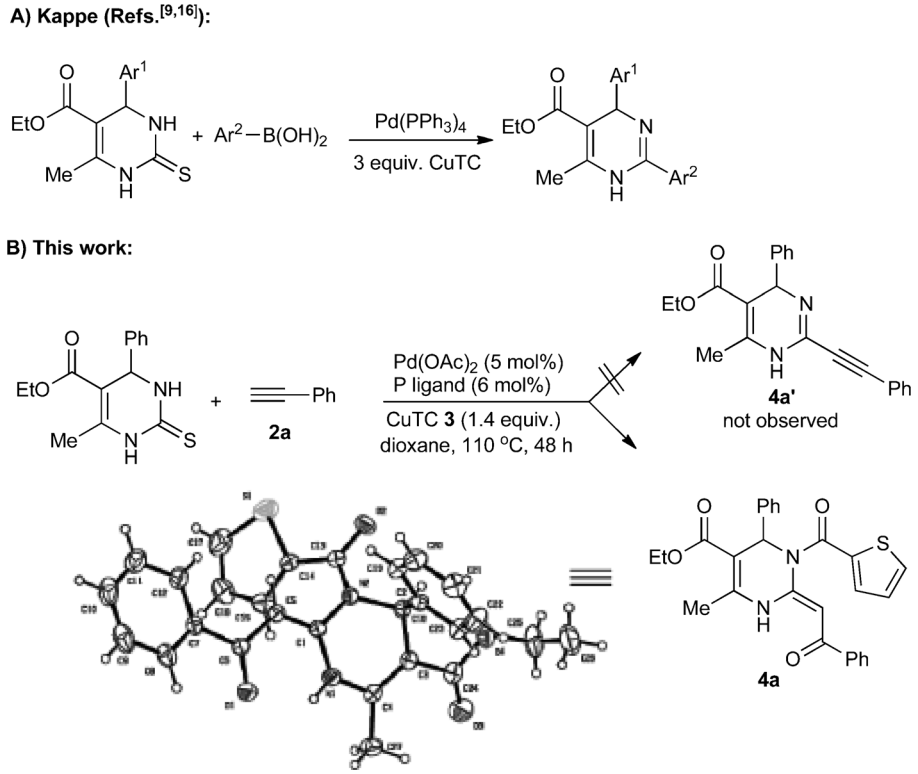
Abstract: A domino desulfitative coupling/acylation/hydration process to synthesize C-2-(2-oxo-2-phenylethylidene)- and N-3-carbonyl-substituted pyrimidines by unprecedented C–C and C–N cross-coupling reactions is described. This methodology couples 3,4-dihydropyrimidine-2-thiones and alkynes under modified Liebeskind–Srogl conditions using palladium acetate and copper(I) carboxylate. Remarkably the copper(I) carboxylates simultaneously act as desulfitative and acylation reagents in the reaction.

Keywords: C–C bond formation; C–N bond formation; copper(I) carboxylates; cross-coupling; 3,4-dihydropyrimindine-2-thiones; palladium

Transition metal-catalyzed cross-coupling reactions are versatile and powerful tools to construct new C–C and C–N bonds.[1] In a cross-coupling reaction, the electrophile species are predominantly organic halides and aryl/alkenyl triflates or sulfonates. In the past two decades, transition metal-catalyzed carbon–carbon and carbon–heteroatom bond formation *via* selective cleavage of C–S bonds has been rigorously investigated.[2] Among these methodologies, Cu(I) carboxylate-mediated, Pd-catalyzed cross-coupling reactions of boronic acids with different sulfur compounds including thioesters, alkynyl thioethers, and thioamides, have attracted extensive interest in the organic synthetic community.[3] Different nucleophilic partners such as organozinc reagents,[4] organostannanes,[5] organoindium,[6] and arylsiloxanes[7] have also been used in the C–S cleavage reaction followed by the C–C bond formation. More recently, this Pd-catalyzed reaction has been modified to allow the coupling of cyclic thionocarbamates with alkynes.[8] A key feature of these desulfitative C–C couplings are the requirement of both the Pd(0) catalyst and the stoichiometric Cu(I) carboxylate additive.[9]

Since the utility of these coupling reactions to construct a single bond has now been established, the quest to improve efficiency has driven further exploration of one-pot procedures for effecting multiple transformations, often by domino and multicomponent reaction (MCR) approaches.[10] MCRs have gained wide acceptance because they represent a highly valuable synthetic tool for the construction of novel and complex molecular structures in an economically favorable way by using processes that are reasonably simple.[11] Additionally, transition metal-catalyzed MCRs producing complex molecules from three or more simple building blocks have become an important method for C–C bond formation.[12]

Dihydropyrimidinones (DHPMs) are a class of heterocyclic compounds possessing a wide range of biological activity.[13] It has been previously established that *N*-acyl-/*N*-benzoyl- and C-2-DHPM derivatives display more interesting pharmacological properties than other derivatives.[14] For example, 2-(hetero)aryl-substituted dihydropyrimidines are highly potent non-nucleosidic inhibitors of hepatitis B virus replication that have *in vitro* and *in vivo* antiviral activity.[15] Although some synthetic approaches have now been established, the methods to synthesize this type compounds are still limited.[13] Recently, the Kappe group have developed an efficient desulfitative carbon-carbon coupling reaction between 3,4-dihydropyrimidine-2-thiones (**1**) and boronic acids under modified Liebeskind–Srogl Pd(0)-catalyzed and Cu(I)-mediated conditions (Scheme 1, A).[9,16] Other methods have been promoted by the dehydrogenation and PyBroP-



Scheme 1. Modified Liebeskind–Srogl Pd(II)-catalyzed, Cu(I)-mediated coupling of DHPM.

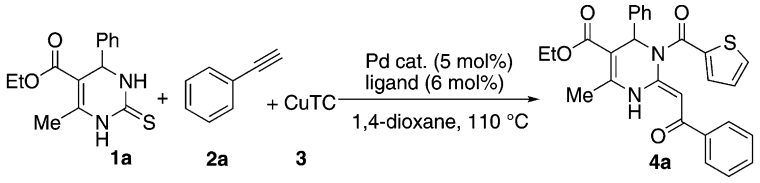
mediated coupling reaction of pyrimidin-2(1*H*)-one with boronic acids,[17] and only two examples have used alkynes.[18] To this date, there has been no report concerning the direct coupling of 3,4-dihydropyrimidine-2-thiones with alkynes to synthesize DHPM derivatives. There is also no report of the preparation of the *N*- and C-2-disubstituted pyrimidine derivatives directly from 3,4-dihydropyrimidine-2-thiones in a single step.

Due to their utilization as precursors in the synthesis of pyrimidine bases,[19] combined with our previous experience on the synthesis of DHPM derivatives,[20] we investigated a Pd(II)- and copper(I) carboxylate-catalyzed coupling reaction between 3,4-dihydropyrimidine-2-thiones and alkynes to access C-2-alkynyl DHPM derivatives (Scheme 1, B).

Herein, we report a multicomponent-domino desulfitative coupling/acylation/hydration process for the synthesis of C-2- and N-3-disubsituted pyrimidines (**4**). This method utilizes an unprecedented C–C and C–N cross-coupling reaction between a 3,4-dihydropyrimidinethione, an alkyne and a copper(I) carboxylate under the modified Liebeskind–Srogl conditions (Scheme 1). Here, copper carboxylate acts not only as a desulfitative reagent but also as an acylation reagent. Initially, the reaction between 3,4-dihydropyrimidine-2-thione (**1a**) and phenylacetylene (**2a**) in 1,4-dioxane at 110 °C was tested using copper (I) thiophenecarboxylate (CuTC) (**3a**) and $Pd(OAc)_2$ as the catalyst. To our delight, C–C and C–N cross-coupling product **4a** was isolated in 77% yield (Table 1, entry 1) with no Sonogashira cross-coupling product **4a′** detected. This novel structure was unambiguously determined by deuterium/water exchange experiments, DEPT, HSQC, HMBC and X-ray crystallographic analysis.[21] An optimization of the reaction conditions was then undertaken. Various palladium sources were tested (entries 2–4), all provided lower yields of **4a** than $Pd(OAc)_2$. Improved yields were obtained when $Pd(OAc)_2$ was screened using different ligands (entries 5–8). Generally, 5 mol% of $Pd(OAc)_2$ and 6 mol% of DPEPhos, SPhos or tBuXPhos were sufficient to achieve excellent yields within 48 h at 110 °C. Lower catalyst loadings (< 3 mol%) led to decreased reaction efficiency and lower yields. No advantageous effects were observed when 10 mol% Pd was used. When CuI and $CuBr(PPh_3)_2$, were employed no reaction was detected by TLC and ^{1}H NMR analysis. When we investigated $CuBr{\cdot}Me_2S$ mixed with CuI as copper source, a complex mixture was detected by TLC, LC-MS and ^{1}H NMR without the desired product **4a′** (entry 13). Using the sole CuTC without Pd catalyst did not result in a C–C coupling reaction (entry 14).[22]

With the optimized conditions in hand, we used DHPMs and a diverse set of alkynes to test the reaction scope. In general, good to excellent yields were obtained under the standard reaction conditions. The

Table 1. Optimization of the desulfitative cross-coupling reaction of DHPM with phenylacetylene and CuTC.[a]



Entry	Catalyst (mol%)	Ligand (mol%)	Cu	Yield [%][b]
1	$Pd(OAc)_2$ (5)	–	CuTC	77
2	$PdCl_2(PPh_3)_2$ (5)	–	CuTC	71
3	$PdCl_2$ (5)	–	CuTC	60
4	$Pd(PPh_3)_4$ (5)	–	CuTC	51
5	$Pd(OAc)_2$ (5)	PPh_3 (6)	CuTC	85
6	$Pd(OAc)_2$ (5)	DPEPhos (6)	CuTC	91
7	$Pd(OAc)_2$ (5)	SPhos (6)	CuTC	90
8	$Pd(OAc)_2$ (5)	tBuXPhos (6)	CuTC	93
9	$Pd(OAc)_2$ (3)	tBuXPhos (3)	CuTC	80
10	$Pd(OAc)_2$ (10)	tBuXPhos (6)	CuTC	94
11	$Pd(OAc)_2$ (5)	DPEPhos (6)	CuI	–[c]
12	$Pd(OAc)_2$ (5)	DPEPhos (6)	$CuBr(PPh_3)_2$	–[c]
13	$Pd(OAc)_2$ (5)	DPEPhos (6)	$CuBrMe_2S$/CuI	–[d]
14	–	–	CuTC	–[c]

[a] *Reaction conditions:* **1a** (0.25 mmol), **2a** (0.375 mmol, 1.5 equiv.), CuTC (**3**, 0.35 mmol, 1.4 equiv.), 1,4-dioxane (3 mL) at 110 °C for 48 h.
[b] Isolated yield.
[c] No reaction was detected by TLC and ^{1}H NMR.
[d] Without adding **2a** and a mixture was obtained.

reaction tolerated a variety of dihydropyrimidine-2-thiones and alkynes containing aromatic and non-aromatic substituents giving a series of pyrimidine derivatives *via* C–C and C–N cross-coupling reaction (Table 2). In terms of the effect of structural features, introducing steric hindrance *ortho* to the aromatic ring was detrimental to the reaction, with the desired products **4f–4h** being isolated in lower yields (entries 6–8).

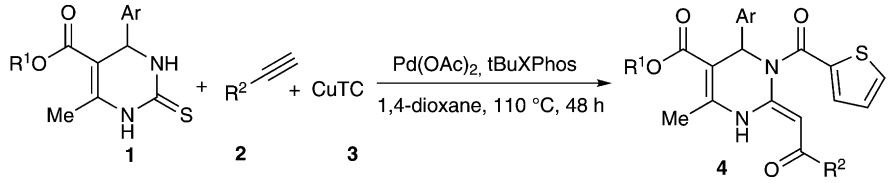
To explore the scope of differentiated Cu(I) carboxylates in the observed C–C and C–N coupling reaction, the copper(I) furan-2-carboxylate (CuFC) **5** and copper(I) benzoate (CuBC) **6** were exposed to the standard reaction conditions, resulting in the formation of C–C and C–N coupling products **7a–f** and **8a–c** (Table 3). As depicted in Table 3, successful cross-couplings were achieved with CuFC and CuBC. In general, good to excellent yields of the desired products were obtained. As in the previous case, *o*-methoxy-substituted DHPM led to lower yields (entries 3, 4 and 8). A *tert*-butyl carboxylate on DHPM was well tolerated (entries 5 and 9), as were DHPMs bearing an electron-withdrawing group (entry 5). The structures of the final product **7a** and **7c** were also characterized by X-ray crystallographic analysis (Figure 1).[21]

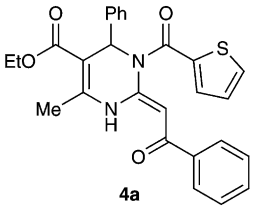
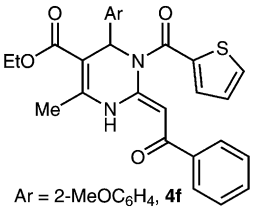
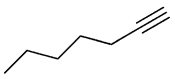
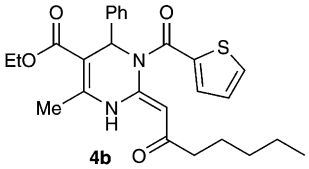
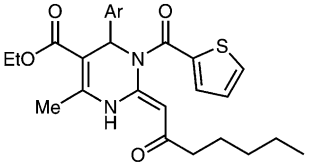
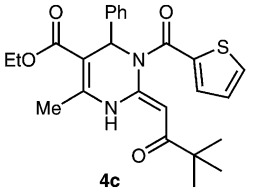
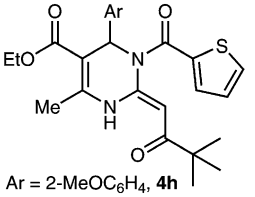
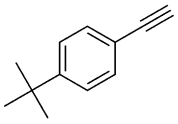
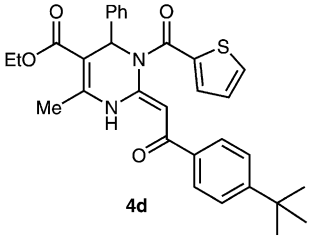
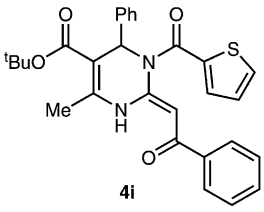
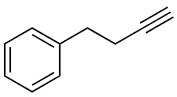
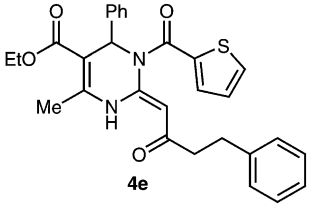
To gain additional evidence for the C–C and C–N cross-coupling reaction mechanism, 2-(phenylethynyl)-1,2-dihydropyrimidine (**11**)[23] was exposed to the optimized reaction conditions without using Pd and ligand. The desired product (**4a**) was obtained in 95% yield (Scheme 2). In order to confirm the isomerism of product **4**, 2-(phenylethynyl)-1,4-dihydropyrimidine (**10**) was directly added to the mixture of CuTC in 1,4-dioxane. The acylation/hydration giving the product **12** was clearly evident on monitoring the reaction mixture by LC-MS. The isomers **12a** and **12b** were further confirmed by ^{1}H NMR and ^{13}C NMR showing that **12b** was the major isomer (Scheme 3).

Next, 3-benzoylpyrimidine-2-thione (**13**) was used instead of 3,4-dihydropyrimidine-2-thione (**1a**) under the optimal reaction conditions (Scheme 4). There was no evidence for a cross-coupling reaction at the C-2 position; however, the desulfitative product (**14**)[24a] (detected by TLC and LC-MS) was obtained.

On the basis of both the above observations and previously reported carbon-carbon cross-couplings by Kappe,[16] we can deduce that firtsly the acylation step showed a unique selectivity to give the N-3 products, although it is the more hindered nitrogen. The selectivity may be due to the higher reactivity of the N-3 position, in comparison to the N-1, which is both in conjugation with the C=C double bond at C-6 and the

Table 2. The desulfitative cross-coupling reaction of DHPMs with alkynes and CuTC.[a]



Entry	Alkyne **2**	Product **4**	Yield [%][b]	Entry	Alkyne **2**	Product **4**	Yield [%][b]
1	 **2a**	 **4a**	93	6	**2a**	 Ar = 2-MeOC$_6$H$_4$, **4f**	44
2	 **2b**	 **4b**	86	7	**2b**	 Ar = 2-MeOC$_6$H$_4$, **4g**	67
3	 **2c**	 **4c**	63	8	**2c**	 Ar = 2-MeOC$_6$H$_4$, **4h**	66
4	 **2d**	 **4d**	83	9	**2a**	 **4i**	56
5	 **2e**	 **4e**	82				

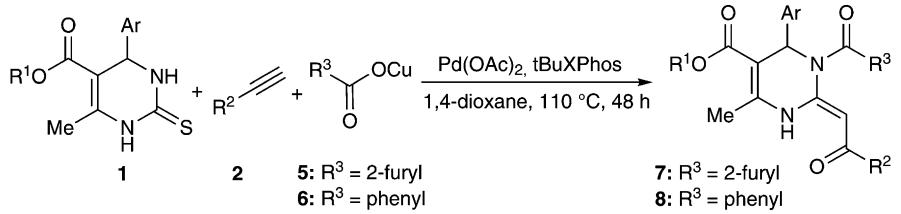
[a] *Reaction conditions:* **1** (0.5 mmol), **2** (0.75 mmol, 1.5 equiv.), **3** (0.70 mmol, 1.4 equiv.), $Pd(OAc)_2$ (0.025 mmol, 5 mol%), tBuXPhos (0.030 mmol, 6 mol%), 1,4-dioxane (3 mL) at 110 °C for 48 h.

[b] Isolated yield of pure product after column chromatography.

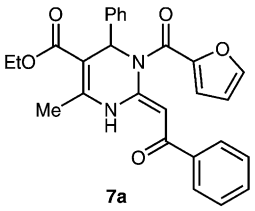
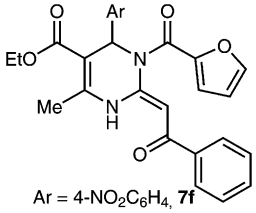
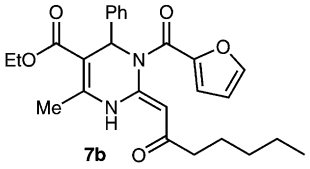
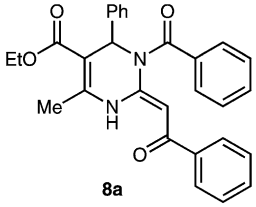
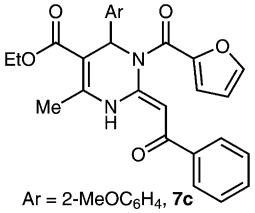
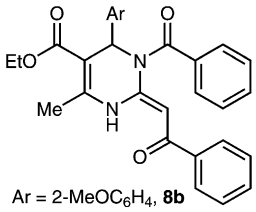
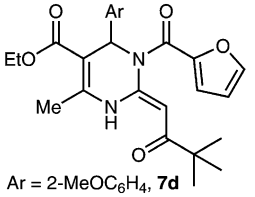
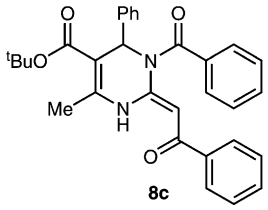
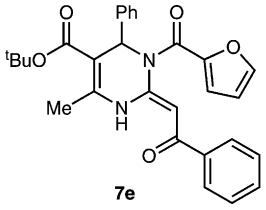
ester functionality at C-5, thereby the N-1 position is representing a weaker nucleophilic activity. The result was consistent with previously reported results.[20a,c,e,24] Secondly, the desulfitative cross-coupling reaction giving intermediate 2-phenylethynyl-1,4-dihydropyrimidines (**D**) occurred prior to the acylation. Thirdly, the formation of the product **D** played a central role in the next acylation step. This can be explained by considering possible complex **E**. Finally the acylation could be performed using CuTC without a Pd catalyst (Scheme 5).

We propose the possible mechanism of the Pd-catalyzed desulfitative coupling/acylation/hydration process that is shown in Scheme 5.[3a,8,25] The mechanism of the desulfitative cross-coupling step is related to the traditional Liebeskind–Srogl protocols,[3,4] specifi-

Table 3. The desulfitative cross-coupling reaction of DHPMs with alkynes and CuFC **5** and CuBC **6**.[a]



1 **2** **5:** R^3 = 2-furyl **6:** R^3 = phenyl **7:** R^3 = 2-furyl **8:** R^3 = phenyl

Entry	Alkyne **2**	Product	Yield [%][b]	Entry	Alkyne **2**	Product	Yield [%][b]
1	**2a**	 **7a**	70	6	**2a**	 Ar = 4-$NO_2C_6H_4$, **7f**	96
2	**2b**	 **7b**	82	7	**2a**	 **8a**	73
3	**2a**	 Ar = 2-$MeOC_6H_4$, **7c**	62	8	**2a**	 Ar = 2-$MeOC_6H_4$, **8b**	36
4	**2c**	 Ar = 2-$MeOC_6H_4$, **7d**	39	9	**2a**	 **8c**	93
5	**2a**	 **7e**	63				

[a] *Reaction conditions:* **1** (0.5 mmol), **2** (0.75 mmol, 1.5 equiv.), **5** or **6** (0.70 mmol, 1.4 equiv.), $Pd(OAc)_2$ (0.025 mmol, 5 mol%), tBuXPhos (0.030 mmol, 6 mol%), 1,4-dioxane (3 mL) at 110 °C for 48 h.

[b] Isolated yield of pure product after column chromatography.

cally to the cross-couplings of cyclic thioamides with alkynes.[8] Then coordination of a Sonogashira cross-coupling type product **D** to the copper salt would promote C=N activation (deprotonation) of **D** to give the acylation product **F**, forming CuOH *in situ*, which transformed into Cu_2O (Cu_2O may react with HTC giving the CuTC) and H_2O when heated. The acylation product may subsequently undergo hydration with water to produce the C-2-oxo-2-phenylethyl product **G**, which isomerizes to give the product **4.** Compound **4** is stablized by the conjugation of the two carbonyl C=O double bonds and the C=C double bond.

In conclusion, we have developed an efficient multicomponent domino process of desulfitative carbon-carbon cross-coupling, acylation and hydration for the

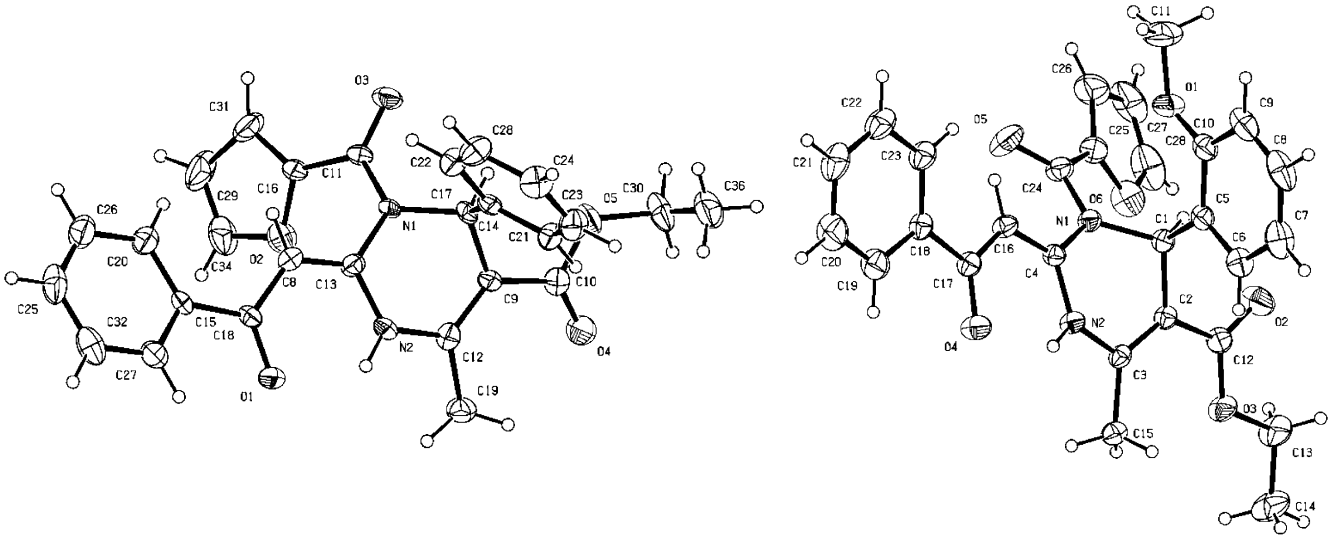
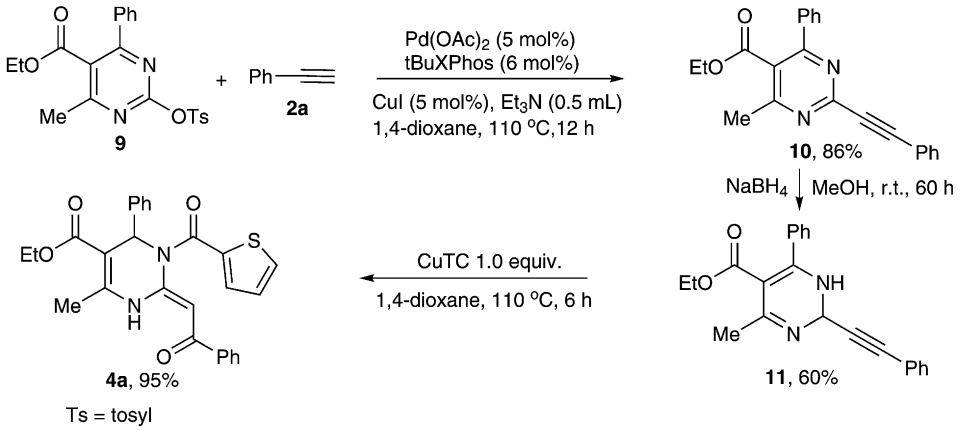
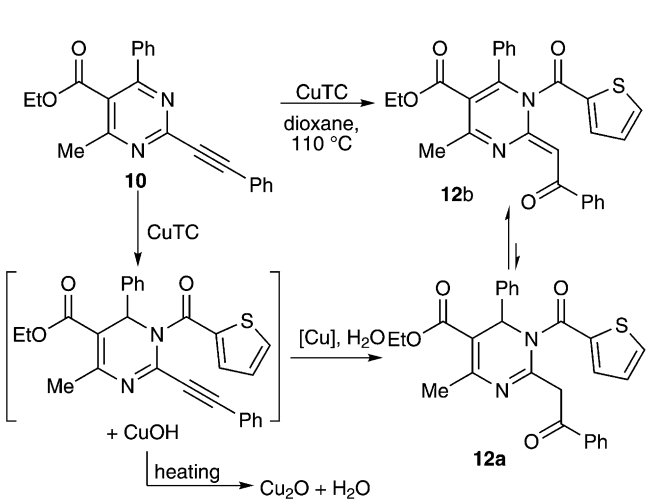


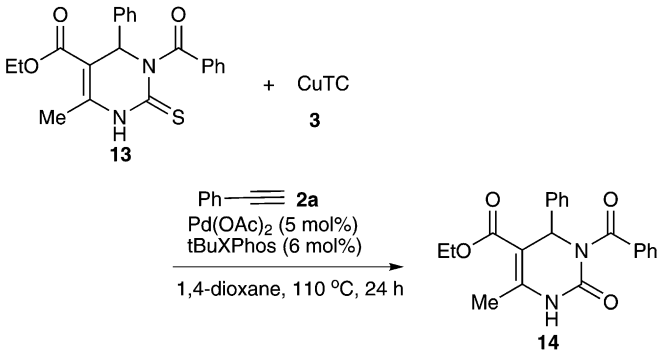
Figure 1. X-ray structures of compounds **7a** and **7c**.



Scheme 2. The C–N cross-coupling/acylation of 2-(phenylethynyl)-1,2-dihydropyrimidine with CuTC.

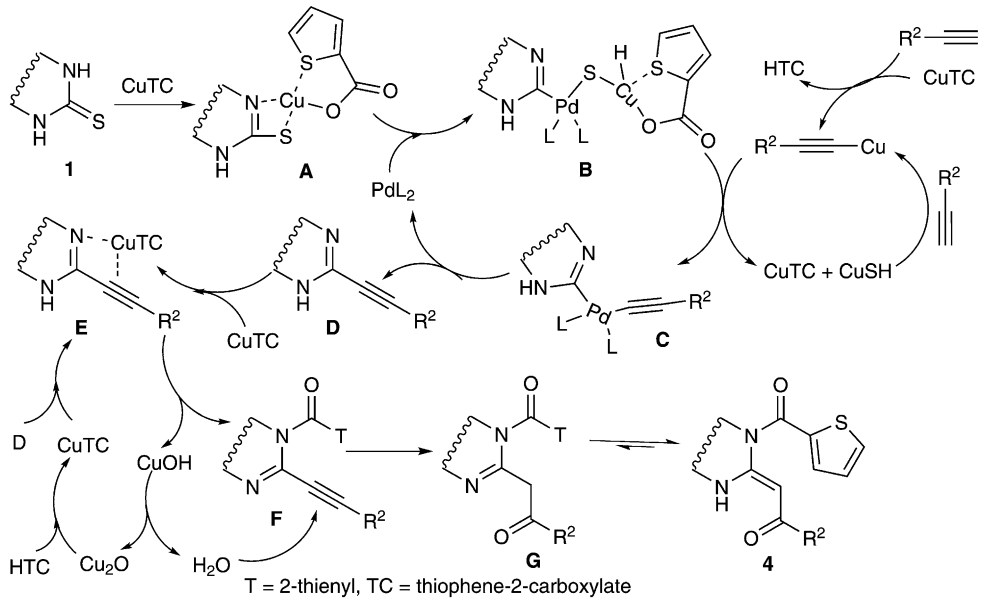


Scheme 3. The C–N cross-coupling/acylation of 2-(phenylethynyl)-1,4-dihydropyrimidine with CuTC.



Scheme 4. The desulfitative reaction catalyzed by CuTC.

synthesis of a series of C-2-(2-oxo-2-phenylethylidene)-N-3-carbonyl-substituted pyrimidines. Furthermore, this protocol possibly opens up a new pathway for direct C–C and C–N bond construction in which



Scheme 5. The possible mechanism.

the copper(I) carboxylate is involved not only as a catalyst but also as an acylation reagent and at least four different reactions (desulfitation, C–C coupling, acylation and hydration) occur in a cascade way. The extensive availability of reaction partners suggests new possibilities for the synthesis of highly functionalized compounds under these cross-coupling conditions. We are currently focusing on promoting this highly efficient transformation and further exploring its use in the construction of more variable and complex compounds. Further mechanism studies of this reaction are also underway in our laboratory.

Experimental Section

General Procedure for Cross-Coupling Reactions

The mixture of 3,4-dihydropyrimidine-2-thione (**1a**, 0.5 mmol, 138.2 mg), phenylacetylene (**2a**, 0.75 mmol, 76.6 mg, 1.5 equiv.), CuTC (**3**, 0.7 mmol, 1.4 equiv., 133.5 mg), tBuXPhos (0.03 mmol, 12.7 mg, 0.06 equiv.) and $Pd(OAc)_2$ (0.025 mmol, 5.6 mg, 0.05 equiv.) in 1,4-dioxane (3 mL) was stirred at 110 °C for 48 h under N_2. Then the reaction misture was cooled to room temperature, quenched with saturated NH_4Cl solution (2 mL) and then extracted with ethyl acetate (2×10 mL). The combined organic extracts were washed with NaOH (1 M, 2 mL), brine and dried over $MgSO_4$. The crude product was purified by flash column chromatography (silica gel; ethyl acetate/hexane = 1:4) to afford the product **4a** as a white solid; yield: 219.3 mg (0.46 mmol, 93%).

In a similar manner, compounds **4b–4i**, **7a–7f**, and **8a–8c** were prepared from the corresponding DHPMs, alkynes and Cu(I) carboxylates.

(*E*)-Ethyl 6-methyl-2-(2-oxo-2-phenylethylidene)-4-phenyl-3-(thiophene-2-carbonyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4a): white solid; yield: 219.3 mg (0.46 mmol, 93%); mp 157–158 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.72 (1H, brs, NH), 7.60–7.27 (12H, m, Ph*H* and thiophene*H*), 7.03 (1H, t, J = 4.0 Hz, thiophene*H*), 6.45 (1H, s, 4-C*H*), 5.71 (1H, s, C=C*H*), 4.21 (2H, q, J = 8.0 Hz, OCH_2), 2.65 (3H, s, CH_3), 1.27 (3H, t, J = 8.0 Hz, OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 188.75, 165.15, 163.19, 151.16, 144.40, 139.01, 138.91, 136.91, 132.43, 132.11, 131.84, 128.63, 128.36, 128.15, 128.48, 127.22, 127.08, 106.89, 92.66, 60.49, 54.81, 18.82, 14.25; HR-MS (EI$^+$): m/z = 472.1452, calcd. for $C_{27}H_{24}N_2O_4S^+$: 472.1451.

(*E*)-Ethyl 6-methyl-2-(2-oxoheptylidene)-4-phenyl-3-(thiophene-2-carbonyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4b): yellow oil; yield: 200.2 mg (0.43 mmol, 86%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.20 (1H, brs , NH), 7.56 (1H, t, J = 4.0 Hz, thiophene*H*), 7.50 (1H, t, J = 4.0 Hz, thiophene*H*), 7.40–7.29 (5H, m, Ph*H*), 7.03 (1H, t, J = 4.0 Hz, thiophene*H*), 6.38 (1H, s, 4-C*H*), 4.99 (1H, s, C=C*H*), 4.17 (2H, q, J = 8.0 Hz, OCH_2), 2.58 (3H, s, CH_3), 2.10 (2H, t, J = 8.0 Hz, heptynylCH_2), 1.25–1.23 (2H, m, heptynylCH_2), 1.22–1.11 (5H, m, heptynylCH_2 and OCH_2CH_3), 1.50–1.09 (2H, m, heptynylCH_2), 0.90 (3H, t, J = 8.0 Hz, heptynylCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 200.05, 165.19, 163.00, 149.42, 144.58, 139.12, 136.93, 132.26, 131.89, 128.56, 128.05, 127.25, 127.22, 106.13, 95.56, 60.36, 54.66, 42.96, 31.30, 25.16, 22.40, 18.77, 14.23, 13.87; HR-MS (EI$^+$): m/z = 466.1922, calcd. for $C_{26}H_{30}N_2O_4S^+$: 466.1921.

(*E*)-Ethyl 2-(3,3-dimethyl-2-oxobutylidene)-6-methyl-4-phenyl-3-(thiophene-2-carbonyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4c): white solid; yield: 142.3 mg (0.32 mmol, 63%); mp 127–128 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.16 (1H, brs, NH), 7.54 (1H, t, J = 4.0 Hz, thiophene*H*), 7.46 (1H, t, J = 4 Hz, thiophene*H*), 7.41–7.29 (5H, m, Ph*H*), 7.02 (1H, t, J = 4.0 Hz, thiophene*H*), 6.37 (1H, s, 4-C*H*), 5.10 (1H, s, C=C*H*), 4.17 (2H, q, J = 8.0 Hz,

OCH_2), 2.58 (3H, s, CH_3), 1.24 (3H, t, J=8.0 Hz, OCH$_2$CH_3), 0.87 (9H, s, *t*-butylCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ=205.18, 165.22, 163.18, 150.04, 144.48, 139.24, 137.12, 131.92, 131.51, 128.55, 128.04, 127.33, 127.21, 106.16, 92.56, 60.35, 54.70, 42.23, 26.88, 18.78, 14.23; HRMS (EI$^+$): m/z=452.1767, calcd. for $C_{25}H_{28}N_2O_4S^+$: 452.1764.

(*E*)-Ethyl 2-{2-[4-(*tert*-butyl)phenyl]-2-oxoethylidene}-6-methyl-4-phenyl-3-(thiophene-2-carbonyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4d): white solid; yield: 219.2 mg (0.42 mmol, 83%); mp 168–169 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=12.70 (1H, brs, NH), 7.80–7.58 (2H, m, Ph*H* and thiophene*H*), 7.45–7.42 (4H, m, Ph*H* and thiophene*H*), 7.36–7.29 (5H, m, Ph*H*), 7.03 (1H, t, J=4.0 Hz, thiophene*H*), 6.45 (1H, s, 4-C*H*), 5.71 (1H, s, C=C*H*), 4.21 (2H, q, J=8.0 Hz, OCH_2), 2.65 (3H, s, CH_3), 1.36–1.26 (12H, m, *i*-butylCH_3 and OCH$_2$CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ=188.53, 165.43, 162.88, 155.57, 150.83, 144.50, 139.10, 136.17, 132.41, 132.05, 128.61, 128.10, 127.47, 127.22, 127.02, 125.35, 106.68, 92.86, 60.44, 54.78, 34.95, 31.08, 18.84, 14.26; HR-MS (EI$^+$): m/z=528.2082, calcd. for $C_{31}H_{32}N_2O_4S^+$: 528.2077.

(*E*)-Ethyl 6-methyl-2-(2-oxo-4-phenylbutylidene)-4-phenyl-3-(thiophene-2-carbonyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4e): yellow oil; yield: 205.5 mg (0.41 mmol, 82%); ^{1}H NMR (400 MHz, $CDCl_3$): δ=12.21 (1H, brs, NH), 7.56 (1H, t, J=4.0 Hz, thiophene*H*), 7.51 (1H, t, J=4.0 Hz, thiophene*H*), 7.41–7.18 (8H, m, Ph*H*), 7.07 (2H, d, J=4.0 Hz, Ph*H*), 7.02 (1H, t, J=4 Hz, thiophene*H*), 6.40 (1H, s, 4-C*H*), 5.03 (1H, s, C=C*H*), 4.19 (2H, q, J=8.0 Hz, OCH_2), 2.75–2.70 (2H, m, CH_2CH$_2$), 2.60 (3H, s, CH_3), 2.47–2.42 (2H, m, CH$_2$CH_2), 1.26 (3H, t, J=8.0 Hz, OCH$_2$CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ=198.30, 165.15, 163.02, 149.75, 144.48, 140.94, 139.06, 136.83, 132.38, 132.07, 128.62, 128.42, 128.13, 127.28, 127.23, 126.04, 106.36, 95.21, 60.43, 54.72, 44.31, 31.11, 18.78, 14.25; HR-MS (EI$^+$): m/z=500.1770, calcd. for $C_{29}H_{28}N_2O_4S^+$: 500.1764.

(*E*)-Ethyl 4-(2-methoxyphenyl)-6-methyl-2-(2-oxo-2-phenylethylidene)-3-(thiophene-2-carbonyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4f): white solid; yield: 110.3 mg (0.22 mmol, 44%); mp. 130–131 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=13.11 (1H, brs, NH), 7.70 (2H, t, J=8.0 Hz, thiophene*H*), 7.59 (2H, dd, J=8.0 Hz, 4 Hz, thiophene*H*), 7.43–7.41 (1H, m, Ph*H*), 7.36 (2H, t, J=8.0 Hz, Ph*H*), 7.24 (2H, d, J=8.0 Hz, Ph*H*), 7.08 (1H, q, J=4.0 Hz, thiophene*H*), 6.91–6.40 (2H, m, Ph*H*), 6.63 (1H, s, 4-C*H*), 6.40 (1H, s, C=C*H*), 4.25–4.09 (2H, m, OCH_2), 3.73 (3H, s, CH_3), 2.66 (3H, s, CH_3), 1.25 (3H, t, J=8.0 Hz, OCH$_2$CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 189.50, 165.08, 164.27, 157.63, 151.21, 145.32, 139.34, 137.84, 131.60, 131.42, 129.76, 128.90, 128.30, 127.20, 120.31, 111.03, 104.17, 89.27, 60.20, 54.93, 53.75, 18.84, 14.28; HR-MS (EI$^+$): m/z=502.1555, calcd. for $C_{28}H_{26}N_2O_5S^+$: 502.1557.

(*E*)-Ethyl 4-(2-methoxyphenyl)-6-methyl-2-(2-oxoheptylidene)-3-(thiophene-2-carbonyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4g): white solid; yield: 166.6 mg (0.34 mmol, 67%); mp 139–140 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=12.59 (1H, brs, NH), 7.58 (1H, t, J=4.0 Hz, thiophene*H*), 7.51 (2H, t, J=4.0 Hz, thiophene*H*), 7.26–7.17 (1H, m, Ph*H*), 7.06 (1H, q, J=4.0 Hz, thiophene*H*), 6.90–6.85 (2H, m, Ph*H*), 6.57 (1H, s, 4-C*H*), 5.62 (1H, s, C=C*H*), 4.22–3.74 (2H, m, OCH_2), 3.49 (3H, s, CH_3), 2.59 (3H, s, CH_3), 2.21 (2H, q, J=4.0 Hz, heptynylCH_2), 1.46–1.34 (4H, m, heptynylCH_2), 1.25–1.19 (5H, m, heptynylCH_2 and OCH$_2$CH_3), 0.85 (3H, t, J=8.0 Hz, heptynylCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ=200.82, 165.13, 164.02, 157.57, 149.49, 145.48, 137.87, 131.53, 131.26, 129.65, 128.87, 127.05, 126.24, 120.27, 110.99, 103.59, 92.24, 60.08, 54.92, 53.39, 43.15, 31.46, 25.32, 22.44, 18.79, 14.26, 13.91; HR-MS (EI$^+$): m/z=496.2022, calcd. for $C_{27}H_{32}N_2O_5S^+$: 496.2026.

(*E*)-Ethyl 2-(3,3-dimethyl-2-oxobutylidene)-4-(2-methoxyphenyl)-6-methyl-3-(thiophene-2-carbonyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4h): yellow solid; yield: 159.5 mg (0.33 mmol, 66%); mp 120–121 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=12.49 (1H, brs, NH), 7.54 (1H, d, J=4.0 Hz, thiophene*H*), 7.46 (1H, d, J=4.0 Hz, thiophene*H*), 7.31–7.24 (2H, q, J=4.0 Hz, Ph*H*), 7.02 (1H, q, J=4.0 Hz, thiophene*H*), 6.92–6.85 (2H, m, Ph*H*), 6.48 (1H, s, 4-C*H*), 5.51 (1H, s, C=C*H*), 4.12 (2H, q, J=8.0 Hz, OCH_2), 3.71 (3H, s, CH_3), 2.56 (3H, s, CH_3), 1.22 (3H, t, J=8.0 Hz, OCH$_2$CH_3), 0.99 (9H, s, *i*-butylCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ=205.76, 165.27, 163.93, 157.65, 150.54, 144.71, 137.77, 131.22, 131.18, 129.89, 129.55, 127.07, 127.01, 120.24, 110.98, 103.93, 89.97, 60.05, 54.84, 53.73, 42.29, 27.16, 18.82, 14.22; HR-MS (EI$^+$): m/z=482.1868, calcd. for $C_{26}H_{30}N_2O_5S^+$: 482.1870.

(*E*)-*tert*-Butyl 6-methyl-2-(2-oxo-2-phenylethylidene)-4-phenyl-3-(thiophene-2-carbonyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4i): yellow oil; yield: 40.1 mg (0.28 mmol, 56%); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H=12.69 (1H, brs , NH), 7.60–7.57 (2H, m, Ph*H*), 7.50–7.47 (2H, m, Ph*H* and thiophene*H*), 7.44–7.40 (3H, m, Ph*H* and thiophene*H*), 7.35–7.27 (5H, m, Ph*H*), 7.02 (1H, q, J=4.0 Hz, thiophene*H*), 6.37 (1H, s, 4-C*H*), 5.71 (1H, s, C=C*H*), 2.62 (3H, s, CH_3), 1.46 (9H, s, *i*-butylCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ=188.62, 164.41, 163.24, 151.28, 143.33, 139.17, 138.98, 137.01, 132.38, 132.06, 131.75, 128.56, 128.34, 128.06, 127.45, 127.24, 127.06, 108.51, 92.46, 81.11, 67.09, 55.20, 28.22, 26.92, 18.68; HR-MS (EI$^+$): m/z=500.1760, calcd. for $C_{29}H_{28}N_2O_4S^+$: 500.1764.

(*E*)-Ethyl 3-(furan-2-carbonyl)-6-methyl-2-(2-oxo-2-phenylethylidene)-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (7a): white solid; yield: 160.6 mg (0.35 mmol, 70%); mp 159–160 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=12.70 (1H, brs, NH), 7.55–7.53 (2H, m, Ph*H* and furan*H*), 7.47–7.42 (4H, m, Ph*H* and furan*H*), 7.36–7.27 (6H, m, Ph*H*), 6.55 (1H, d, J=4.0 Hz, furan*H*), 6.44 (1H, s, 4-C*H*), 5.50 (1H, s, C=C*H*), 4.21 (2H, q, J=8.0 Hz, OCH_2), 2.64 (3H, s, CH_3), 1.27 (3H, t, J=8.0 Hz, OCH$_2$CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ=189.04, 165.11, 158.84, 150.55, 147.03, 145.35, 144.44, 138.98, 131.81, 128.61, 128.35, 128.12, 127.22, 127.02, 118.78, 112.25, 106.62, 90.55, 60.45, 54.31, 18.83, 14.26; HR-MS (EI$^+$): m/z=456.1678, calcd. for $C_{27}H_{24}N_2O_5^+$: 456.1680.

(*E*)-Ethyl 3-(furan-2-carbonyl)-6-methyl-2-(2-oxoheptylidene)-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (7b): yellow oil; yield: 185.3 mg (0.41 mmol, 82%); ^{1}H NMR (400 MHz, $CDCl_3$): δ=12.17 (1H, brs, NH), 7.47 (1H, d, J=4.0 Hz, furan*H*), 7.40–7.27 (5H, m, Ph*H* and furan*H*), 7.17 (1H, d, J=4.0 Hz, furan*H*), 6.52 (1H, d, J=4.0 Hz, furan*H*), 6.38 (1H, s, 4-C*H*), 4.77 (1H, s, C=C*H*), 4.17 (2H, q, J=8.0 Hz, OCH_2), 2.58 (3H, s, CH_3), 2.12 (2H, t, J=8.0 Hz, heptynylCH_2), 1.39 (2H, d, J=8.0 Hz, heptynylCH_2), 1.26–1.16 (7H, m, heptynylCH_2 and OCH$_2$CH_3), 0.86 (3H, t, J=8.0 Hz, heptynylCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ=

200.26, 165.16, 158.71, 147.02, 144.91, 144.63, 139.10, 128.54, 128.03, 127.26, 118.52, 112.15, 105.85, 93.59, 60.33, 54.15, 42.94, 31.36, 25.39, 22.42, 18.79, 14.25, 13.88; HR-MS (EI$^+$): m/z = 450.2148, calcd. for $C_{26}H_{30}N_2O_5^+$: 450.2149.

(*E*)-Ethyl 3-(furan-2-carbonyl)-4-(2-methoxyphenyl)-6-methyl-2-(2-oxo-2-phenylethylidene)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (7c): white solid; yield: 151.2 mg (0.31 mmol, 62%); mp 71–72 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 13.04 (1H, brs, NH), 7.71 (2H, t, J = 8.0 Hz, Ph*H*), 7.53 (1H, s, Ph*H*), 7.44 (1H, t, J = 4.0 Hz, furan*H*), 7.38–7.18 (7H, m, Ph*H* and furan*H*), 6.87 (2H, t, J = 8.0 Hz, Ph*H*), 6.64 (1H, s, 4-C*H*), 6.54 (1H, d, J = 4.0 Hz, furan*H*), 6.19 (1H, s, C=C*H*), 4.22–4.13 (2H, m, OCH_2), 3.73 (3H, s, CH_3), 2.63 (3H, s, CH_3), 1.26 (3H, t, J = 8.0 Hz, OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.55, 165.18, 159.76, 157.59, 150.95, 147.40, 145.22, 144.73, 139.31, 131.61, 129.70, 129.11, 128.31, 127.14, 126.39, 120.32, 117.53, 111.90, 111.01, 104.42, 88.58, 60.18, 54.95, 52.93, 18.83, 14.28; HR-MS (EI$^+$): m/z = 486.1783, calcd. for $C_{28}H_{26}N_2O_6^+$: 486.1785.

(*E*)-Ethyl 2-(3,3-dimethyl-2-oxobutylidene)-4-(2-methoxyphenyl)-6-methyl-3-(thiophene-2-carbonyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (7d): yellow oil; yield: 91.0 mg (0.19 mmol, 39%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.47 (1H, brs, NH), 7.47 (1H, s, furan*H*), 7.32–7.22 (2H, m, Ph*H*), 7.08 (1H, d, J = 4.0 Hz, furan*H*), 6.49 (1H, d, J = 4.0 Hz, furan*H*), 6.47 (1H, s, 4-C*H*), 5.33 (1H, s, C=C*H*), 4.15–4.06 (2H, m, OCH_2), 3.69 (3H, s, CH_3), 2.54 (3H, s, CH_3), 1.22 (3H, t, J = 8.0 Hz, OCH_2CH_3), 0.98 (9H, s, *i*-butylCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 206.03, 165.29, 159.53, 157.61, 150.16, 147.56, 144.68, 144.34, 129.97, 129.51, 127.25, 120.23, 117.36, 11.86, 110.97, 103.99, 88.36, 60.02, 54.85, 53.12, 42.28, 27.38, 18.82, 14.21; HR-MS (EI$^+$): m/z = 466.2095, calcd. for $C_{26}H_{30}N_2O_6^+$: 466.2098.

(*E*)-*tert*-Butyl 3-(furan-2-carbonyl)-6-methyl-2-(2-oxo-2-phenylethylidene)-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (7e): yellow oil; yield: 152.2 mg (0.31 mmol, 63%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.66 (1H, brs, NH), 7.54 (2H, d, J = 8.0 Hz, Ph*H*), 7.47–7.35 (4H, m, Ph*H*), 7.33–7.26 (6H, m, Ph*H* and thiophene*H*), 6.54 (1H, t, J = 4.0 Hz, furan*H*), 6.36 (1H, s, 4-C*H*), 5.49 (1H, s, C=C*H*), 2.60 (3H, s, CH_3), 1.46 (9H, s, *i*-butylCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 188.91, 164.39, 158.91, 150.69, 147.10, 145.32, 143.34, 139.13, 139.00, 131.75, 128.54, 128.33, 128.03, 127.24, 127.00, 118.70, 112.22, 108.25, 90.35, 81.06, 54.67, 53.89, 28.23, 22.65, 14.71; HR-MS (EI$^+$): m/z = 484.1989, calcd. for $C_{29}H_{28}N_2O_5^+$: 484.1993.

(*E*)-Ethyl 3-(furan-2-carbonyl)-6-methyl-4-(4-nitrophenyl)-2-(2-oxo-2-phenylethylidene)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (7f): yellow solid; yield: 241.8 mg (0.48 mmol, 96%); mp 115–116 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.71 (1H, brs, NH), 8.18 (2H, d, J = 8.0 Hz, Ph*H*), 7.62 (2H, d, J = 8.0 Hz, furan*H*), 7.54–7.44 (4H, m, Ph*H* and furan*H*), 7.34 (3H, t, J = 8.0 Hz, Ph*H*), 6.58 (1H, d, J = 4.0 Hz, furan*H*), 6.47 (1H, s, 4-C*H*), 5.48 (1H, s, C=C*H*), 4.22 (2H, q, J = 8.0 Hz, OCH_2), 2.66 (3H, s, CH_3), 1.28 (3H, t, J = 8.0 Hz, OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 189.20, 164.89, 158.74, 149.75, 147.66, 146.58, 146.25, 145.69, 145.32, 138.59, 132.16, 128.45, 128.37, 127.05, 123.92, 119.45, 112.48, 105.37, 103.26, 90.71, 83.10, 60.73, 53.71, 18.98, 14.28; HR-MS (EI$^+$): m/z = 501.1530, calc. for $C_{27}H_{23}N_3O_7^+$: 501.1531.

(*E*)-Ethyl 3-benzoyl-6-methyl-2-(2-oxo-2-phenylethylidene)-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (8a): white solid; yield: 170.5 mg (0.37 mmol, 73%); mp 193–194 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.63 (1H, brs, NH), 7.66 (2H, t, J = 4.0 Hz, Ph*H*), 7.51–7.23 (13H, m, Ph*H*), 6.55 (1H, s, 4-C*H*), 5.32 (1H, s, C=C*H*), 4.22 (2H, q, J = 8.0 Hz, OCH_2), 2.66 (3H, s, CH_3), 1.28 (3H, t, J = 8.0 Hz, OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 188.84, 169.82, 165.17, 150.95, 144.37, 139.18, 138.92, 135.06, 131.85, 131.73, 128.66, 128.63, 128.49, 128.20, 128.12, 127.23, 126.95, 106.84, 93.64, 60.47, 54.02, 18.83, 14.26; HR-MS (EI$^+$): m/z = 466.1885, calcd. for $C_{29}H_{26}N_2O4^+$: 466.1887.

(*E*)-Ethyl 3-benzoyl-4-(2-methoxyphenyl)-6-methyl-2-(2-oxo-2-phenylethylidene)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (8b): white solid; yield: 89.2 mg (0.18 mmol, 36%); mp 153–154 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.92 (1H, brs, NH), 7.67 (2H, t, J = 4.0 Hz, Ph*H*), 7.51–7.34 (6H, m, Ph*H*), 7.30–7.23 (4H, m, Ph*H*), 6.93–6.85 (2H, m, Ph*H*), 6.51 (1H, s, 4-C*H*), 5.86 (1H, s, C=C*H*), 4.15 (2H, q, J = 8.0 Hz, OCH_2), 3.73 (3H, s, OCH_3), 2.64 (3H, s, CH_3), 1.23 (3H, t, J = 8.0 Hz, OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.18, 170.51, 165.22, 157.67, 151.39, 144.44, 135.25, 131.60, 131.55, 129.79, 129.61, 128.47, 128.41, 128.22, 127.04, 120.30, 111.07, 104.82, 99.98, 91.31, 60.17, 54.96, 53.19, 18.81, 14.22; HR-MS (EI$^+$): m/z = 496.1992, calcd. for $C_{30}H_{28}N_2O_5^+$: 496.1993.

(*E*)-*tert*-Butyl 3-benzoyl-6-methyl-2-(2-oxo-2-phenylethylidene)-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (8c): white solid; yield: 230.4 mg (0.47 mmol, 93%); mp 187–188 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.59 (1H, brs, NH), 7.67 (2H, t, J = 4.0 Hz, Ph*H*), 7.50–7.34 (6H, m, Ph*H*), 7.32–7.23 (7H, m, Ph*H*), 6.46 (1H, s, 4-C*H*), 5.31 (1H, s, C=C*H*), 2.63 (3H, s, CH_3), 1.45 (9H, s, *i*-butylCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 188.71, 169.87, 164.43, 151.07, 143.29, 139.33, 138.99, 135.13, 131.81, 131.65, 128.63, 128.55, 128.50, 128.18, 128.03, 127.26, 126.93, 108.45, 93.44, 81.09, 67.09, 54.41, 28.22, 18.69; HR-MS (EI$^+$): m/z = 494.2198, calcd. for $C_{31}H_{30}N_2O_4^+$: 494.2200.

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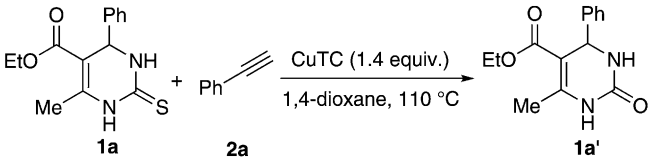
[21] CCDC 869876 (**4a**), CCDC 869878 (**7a**) and CCDC 869879 (**7c**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.
[22] **1a** was treated with **2a** and CuTC in 1,4-dioxane by heating at 110 °C for 12 h yielding the disulfitative product 3,4-dihydropyrimidinone **1a′**.



[23] 2-Phenylethynyl-1,4-dihydropyrimidine (**10**) resulted from 2-(tosyloxy)pyrimidine (**9**)[20d] cross-coupling with phenylacetylene. Then **10** was treated with $NaBH_4$ at room temperature for 60 h to give the **11** (see the Supporting Information).
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