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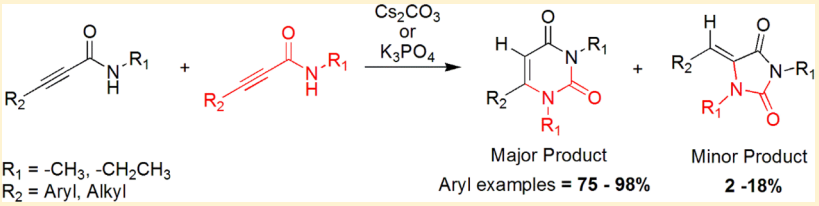
A Regioselective Synthesis of 6-Alkyl- and 6-Aryluracils by Cs_2CO_3- or K_3PO_4-Promoted Dimerization of 3-Alkyl- and 3-Aryl-2-Propynamides

Suranga M. Rajapaksha, Todd E. Mlsna,* and Charles U. Pittman, Jr.*

Department of Chemistry, Mississippi State University, Mississippi State, Mississippi 39762, United States

Supporting Information



ABSTRACT: A regioselective synthesis of 6-alkyl- and 6-aryluracils was developed by the dimerization of 3-alkyl- and 3-aryl-2-propynamides promoted by either Cs_2CO_3 or K_3PO_4. A range of 3-aryl-2-propynamides, with both electron-deficient and electron-rich 3-aryl substituents, were successfully reacted in high yields. Cs^+ acts as a soft Lewis acid to polarize the carbon−carbon triple bond, and solid K_3PO_4 interacts with carbonyl oxygen, promoting intermolecular nucleophilic attack by the only weakly nucleophilic amide nitrogen. Experiments were conducted to support the proposed mechanism.

1. INTRODUCTION

Nitrogen heterocycles with the pyrimidinone motif have long been known as important scaffolds in drug discovery, exhibiting a wide range of biological activities.[1−3] C-Aryl-substituted uracils, a class of pyrimidinones, have gained significant attention.[4−20] Recently, 6-aryluracils have been widely studied as hepatitis C viral NS5B inhibitors,[14] GnRH antagonists,[5,6] sirtuin inhibitors,[7] dipeptidyl peptidase IV inhibitors,[8] Epstein−Barr virus early-antigen inhibitors,[21] HIV-1 reverse-transcriptase inhibitors,[9] and also as antimicrobial and anticancer agents.[10] Herein, we report a new and unexpected route to 6-alkyl- and 6-aryluracils from readily prepared secondary propynylamide.

The C5- and C6-aryl-substituted uracils are usually prepared by palladium-promoted cross-coupling reactions from the corresponding C-halouracils.[2,19,20,22−28] However, the syntheses of C-halouracils are challenging because of limitations such as harsh conditions and lower yields.[28−30] Direct C−H[31−36] and C−O[37] bond activation have also been reported to prepare 6-aryluracils. Cross-coupling and many direct arylation reactions use transition-metal catalysis. The Stille cross-coupling[20,22,25] uses arylstannanes with C-halouracils. Trace amounts of these toxic stannane and palladium impurities should be avoided in biological and pharmacological applications. Photochemical[38] and heterocyclization reactions (HCRs)[39−47] have also been reported as tools to construct C-substituted uracils. Classic heterocyclization condensation reactions by Davidson et al.[39] and Schwartz et al.[40] have long been used to construct certain uracil skeletons.

C-Alkyl-substituted uracil syntheses have continually been pursued for potential biological and pharmacological applications.[48−52] The following methods have been used to synthesize 6-alkyl-substituted uracils: (1) lithiation followed by reaction with an electrophile,[30,52,53] (2) heterocyclization reactions,[41,43,46,47,49] and (3) direct nucleophilic substitution with alkyl Grignard reagents[54] on 6-cyanouracil, derived from 6-halouracil.[55] However, 6-alkyluracil syntheses are often limited by low yields and harsh reaction conditions. Thus, our new synthetic approach should be of interest.

In this paper, a simple and efficient method for the regioselective synthesis of 6-alkyl- and 6-aryluracil derivatives was discovered, employing the Cs_2CO_3- or K_3PO_4-promoted dimerization of secondary 3-alkyl- and 3-aryl-2-propyanamides. The "Cesium Effect" is known to produce advantageous yields and improved reaction conditions compared to analogous routes without the cesium ion.[56,57] Various cesium bases have previously been reported to catalyze syntheses with alkynes.[58−62] On the other hand, successful use of the less expensive K_3PO_4 in place of Cs_2CO_3 in Buchwald's amination and amidation reactions[63] inspired us to also test the scope of the regioselective dimerization of 3-substituted-2-propynamides using K_3PO_4 as a dimerization catalyst. To the best of our knowledge, the first dimerization reactions of 3-alkyl- and 3-aryl-2-propynamides to 6-alkyl- and 6-aryluracils are demonstrated herein. This reaction is promoted by either Cs_2CO_3 or K_3PO_4.

2. RESULTS AND DISCUSSION

While attempting to construct the oxindole skeleton using sequential reactions in a one-pot process that employed a $[Pd(allyl)Cl]_2$ and JackiePhos catalyst for *N*-arylation,[64] followed by $Pd(OAc)_2$ and bis-1,1′-diphenylphosphinoferrocene (DPPF) to catalyze ring closure,[65] the dimerization of **1a** was observed. Although this oxindole synthesis failed, further investigation of this palladium-catalyzed dimerization of **1a**

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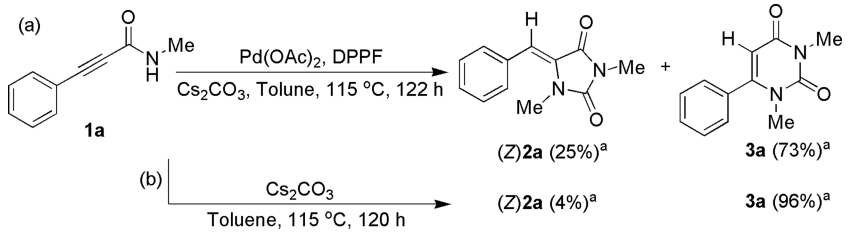
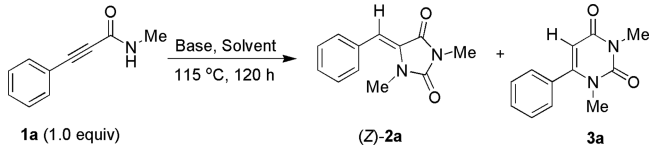
Scheme 1. (a) Palladium-Catalyzed, (b) Cs_2CO_3-Promoted Dimerization of 1a



[a]GC yield.

Table 1. Optimization of Reaction Conditions for the Dimerization of *N*-Methyl-3-phenyl-2-propynamide to *N*, *N*-Dimethyl-6-phenyluracil[a]



entry	base (1.0 equiv)	solvent	conversion of **1a** (%)[b]	yield (%)[b]	
				(*Z*)-**2a**	**3a**
1	no base	toluene	0	0	0
2	no base	THF	0	0	0
3	K_2CO_3	toluene	7	2	5
4	$CaCO_3$	toluene	3	1	2
5	KOH	toluene	97	1	70
6	K^{t}OBu	toluene	98	1	80
7	Cs_2CO_3 (0.1 equiv)	toluene	100	10	89
8	Cs_2CO_3 (0.5 equiv)	toluene	100	9	90
9	Cs_2CO_3 (1.0 equiv)	toluene	100	4	96
10	Cs_2CO_3 (2.0 equiv)	toluene	100	6	94
11	Cs_2CO_3	benzene	100	6	94
12	Cs_2CO_3	1,4-dioxane	100	6	94
13	Cs_2CO_3	THF	100	4	96
14	Cs_2CO_3	EtOH	100	0	14[c]
15	$CsNO_3$	toluene	0	0	0
16	CsOAc	toluene	38	4	34
17	CsF	toluene	73	6	67
18	CsOH	toluene	100	0	56
19	K_3PO_4	toluene	100	4	96

[a]Reaction conditions: **1a** (0.4 mmol, 1.0 equiv), base (0.4 mmol, 1.0 equiv), solvent (2.5 mL), at 115 °C for 120 h. [b]GC yield. [c]Reaction time: 6 h.

surprisingly found that a 73% yield of **3a** and a 25% yield of (*Z*)-**2a** were produced (Scheme 1). While we were extending these findings to a novel synthetic route to arylidenehydantoins by the palladium-catalyzed dimerization of *N*-alkyl-3-aryl-2-propynamides,[66] we serendipitously discovered the dimerization of **1a**, using only Cs_2CO_3 with no palladium and no DPPF ligand present. It gave a 96% yield of **3a** and only a 4% yield of (*Z*)-**2a** (Scheme 1 and Table 1, entry 9). Here, we describe development of a new synthetic route to construct 6-substituted uracils by the dimerization of *N*-alkyl-3-subtituted-2-proynamides.

A variety of bases, cesium salts, and solvents were then tested with **1a** to prepare uracil **3a** (Table 1). Neither (*Z*)-**2a** nor **3a** formed without any added base present in both polar and nonpolar solvents (Table 1, entries 1 and 2). A small amount of **3a** was formed when either K_2CO_3 or $CaCO_3$ was used in toluene (Table 1, entries 3 and 4). Employing either KOH or K^{t}OBu as the base gave conversions of **1a** of over 97%. However, KOH gave only 70% of **3a** while K^{t}OBu gave 80% of **3a** (Table 1, entries 5 and 6). In both entries, a large number of other byproducts were also observed by GC−MS. Apparently, strong bases like KOH and K^{t}OBu can also induce side reactions along the path to uracils. In sharp contrast to the other bases, Cs_2CO_3 provided very high yields and high selectivity to uracil derivative **3a** (Table 1, entries 7−13). Varying the amount of Cs_2CO_3 from 0.1 to 1.0 equiv increased the yields of **3a** from 89% to 96% (Table 1, entries 7−9). In contrast, when the amounts of Cs_2CO_3 used were increased from 1.0 to 2.0 equiv, no further increase in **3a** formation occurred (Table 1, entry 9 vs 10). Hence, 1.0 equiv of Cs_2CO_3 was used as the standard amount.

Reactions employing Cs_2CO_3 always proceeded smoothly and in high yields in both nonpolar (Table 1, entries 7−11) and polar aprotic (Table 1, entries 12−13) organic solvents. After 100% conversion of **1a** within 6 h in the polar protic solvent, ethanol, only a 14% yield of **3a** was achieved (Table 1, entry 14). A variety of cesium salts were also tested for the **1a** dimerizations in toluene (Table 1, entries 15−18). No **3a** was formed with $CsNO_3$. CsOAc gave poor yields of **3a**, while CsF gave a fair yield (67%) (Table 1, entries 16 and 17). When

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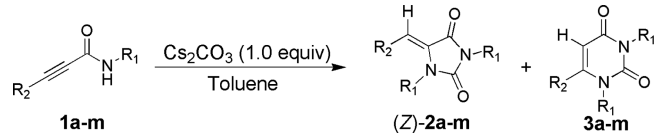
Table 2. Cs_2CO_3-Promoted Dimerizations of 1a−m under Optimized Conditions[a]



Entry	Amide 1	Hydantoin 2 (Yield%)[b] [%][c]	Uracil 3 (Yield%)[b] [%][c]
1.	1a	(Z)-2a (2) [4]	3a (93) [96]
2.	1b	(Z)-2b (4)	3b (94)
3.	1c	(Z)-2c (2) [4]	3c (93) [96]
4.	1d	(Z)-2d (-)[d] [3]	3d (94) [97]
5.	1e	(Z)-2e (-)[d] [2]	3e (94) [98]
6.[e]	1f	(Z)-2f (-)[d]	3f (96)
7.[e]	1g	(Z)-2g (-)[d] [14]	3g (80) [84]
8.[e]	1h	(Z)-2h (15) [18]	3h (73) [75]
9.	1i	(Z)-2i (-)[f]	3i (-)[f]
10.	1j	(Z)-2j (-)[f]	3j (-)[f]
11.	1k	(Z)-2k (-)[f]	3k (-)[f]
12.	1l	(Z)-2l (-)[f]	3l (-)[f]
13.	1m	(Z)-2m (-)[f]	3m (32) [40]

[a]Reaction conditions: Amide **1** (1.0 equiv), Cs_2CO_3 (1.0 equiv), dry toluene, at 115 °C for 96 h. **1a** was also converted to **3a** in 96% GC yield and (Z)-**2a** in 4% GC yield when refluxed at 110.6 °C at 1 atm with exposure to air. [b]Isolated yield. [c]GC yield. [d]Product was not isolated. [e]Reaction time 120 h. [f]Product was not observed by GC−MS.

CsOH was used (Table 1, entry 18), complete conversion of **1a** generated only a 56% yield of **3a** because hydroxide also attacked uracil **3a**. Hydroxide opened the **3a** ring by nucleophilic attack on the C-2 carbonyl carbon, followed by decarboxylation to produce (*Z*)-*N*-methyl-3-(methylamino)-3-phenylacrylamide.[66] High yields of **3a** were given by Cs_2CO_3 because both cesium and carbonate ions play crucial acid and base roles. Likewise, acetate, fluoride, and hydroxide act as bases in entries 16, 17, and 18. Surprisingly, when K_3PO_4 was used as a base, complete consumption of **1a** gave a 96% yield of **3a** (Table 1, entry 19) and the reaction composition was similar to that of the Cs_2CO_3-promoted reaction (Table 1, entry 19 vs 9). Therefore, to further examine the reaction scope, both K_3PO_4 and Cs_2CO_3 were selected to test with a variety of substrates (Tables 2 and 3).

Although there was no difference in **3a** yields in either THF and toluene after complete consumption of **1a** (Table 1, entries 9 and 13), the reaction rates were different (Figure 1). About 90% conversion of **1a** was observed within 12 h, and **1a** was totally consumed after 50 h in THF at 115 °C. This is compared

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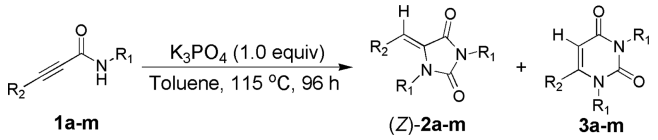
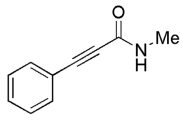
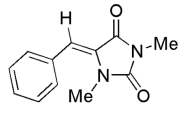
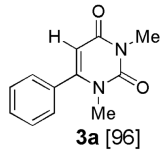
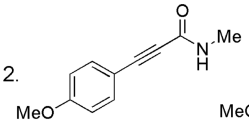
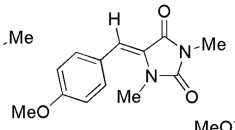
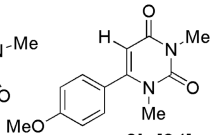
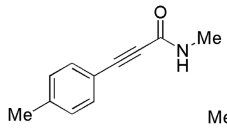
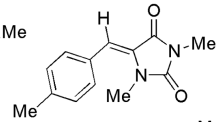
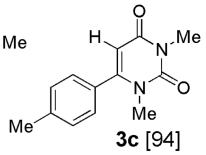
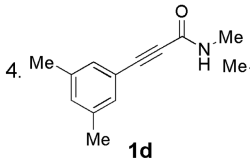
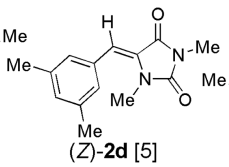
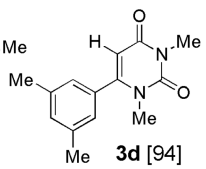
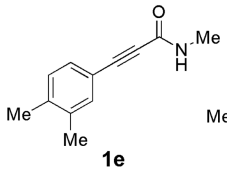
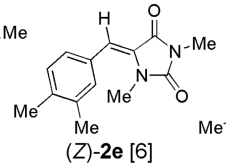
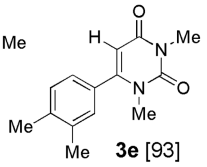
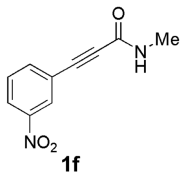
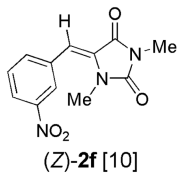
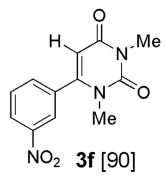
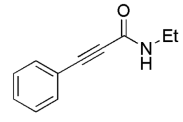
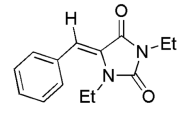
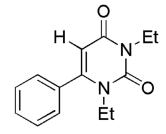
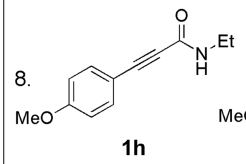
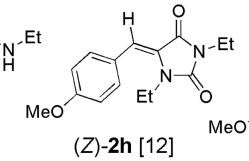
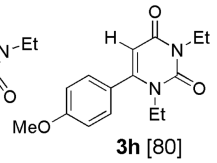
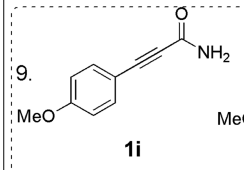
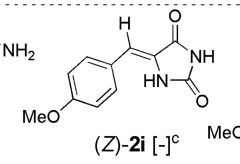
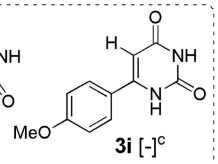
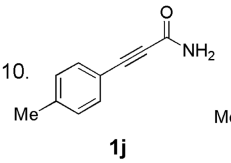
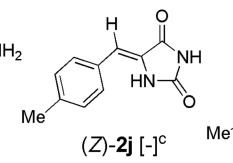
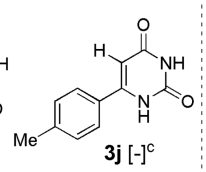
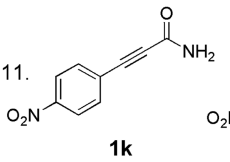
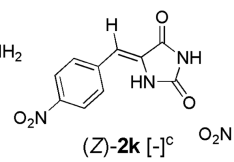
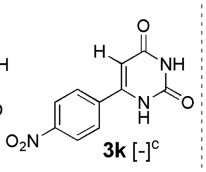
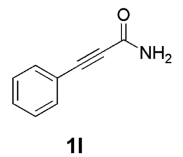
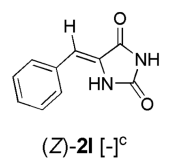
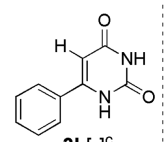
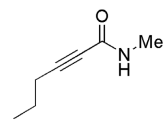
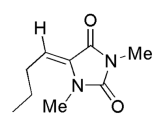
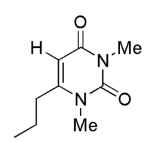
Table 3. K_3PO_4-Promoted Dimerizations of 1a−m under Optimized Conditions[a]



Entry	Amide 1	Hydantoin 2 [%][b]	Uracil 3 [%][b]
1.[d]	 1a	 (Z)-2a [4]	 3a [96]
2.	 1b	 (Z)-2b [6]	 3b [94]
3.	 1c	 (Z)-2c [5]	 3c [94]
4.	 1d	 (Z)-2d [5]	 3d [94]
5.	 1e	 (Z)-2e [6]	 3e [93]
6.	 1f	 (Z)-2f [10]	 3f [90]
7.	 1g	 (Z)-2g [11]	 3g [88]
8.	 1h	 (Z)-2h [12]	 3h [80]
9.	 1i	 (Z)-2i [-][c]	 3i [-][c]
10.	 1j	 (Z)-2j [-][c]	 3j [-][c]
11.	 1k	 (Z)-2k [-][c]	 3k [-][c]
12.	 1l	 (Z)-2l [-][c]	 3l [-][c]
13.	 1m	 (Z)-2m [-][c]	 3m [2]

[a]Reaction conditions: Amide **1** (1.0 equiv), K_3PO_4 (1.0 equiv), dry toluene, at 115 °C for 96 h. [b]GC yield. [c]Product was not observed by GC−MS. [d]Reaction was also performed in refluxing toluene (110.6 °C) in a 25 mL round-bottomed flask, connected to a water-cooling condenser for 120 h.

to 80% conversion within 12 h and complete conversion within 96 h in toluene.

A variety of *N*-R_1-3-R_2-2-propynamides, **1a−m,** were used to explore this reaction's scope with both Cs_2CO_3 and K_3PO_4. Substituents R_2 included both electron-rich and electron-deficient 3-aryl substrates and an alkyl example (R_2 = propyl). In addition, the *N*-methyl, ethyl, and hydrogen substituents were selected as R_1. Each substrate **1a−m** was reacted under the selected conditions mentioned above to prepare 6-aryl or 6-propyluracil derivatives (Table 2). Excellent yields were achieved using both electron-rich and electron-deficient aryl substrates when R_1 was $-CH_3$ (Table 2, entries 1−6). The *N*-ethyl examples again favored the 6-aryluracil over the benzylidene-hydantoin, but in lower selectivity than the corresponding *N*-methyl analogues (Table 2, entries 7 and 8 vs 1 and 2, respectively). Unfortunately, the reaction failed to give either the corresponding uracil or hydantoin derivatives when R_1 was -H. Instead, a large number of byproducts were observed by GC−MS after complete consumption of the starting amide (Table 2, entries 9−12). These complex product mixtures were not further characterized. The use of a primary amide allows side reactions, limiting the scope of this

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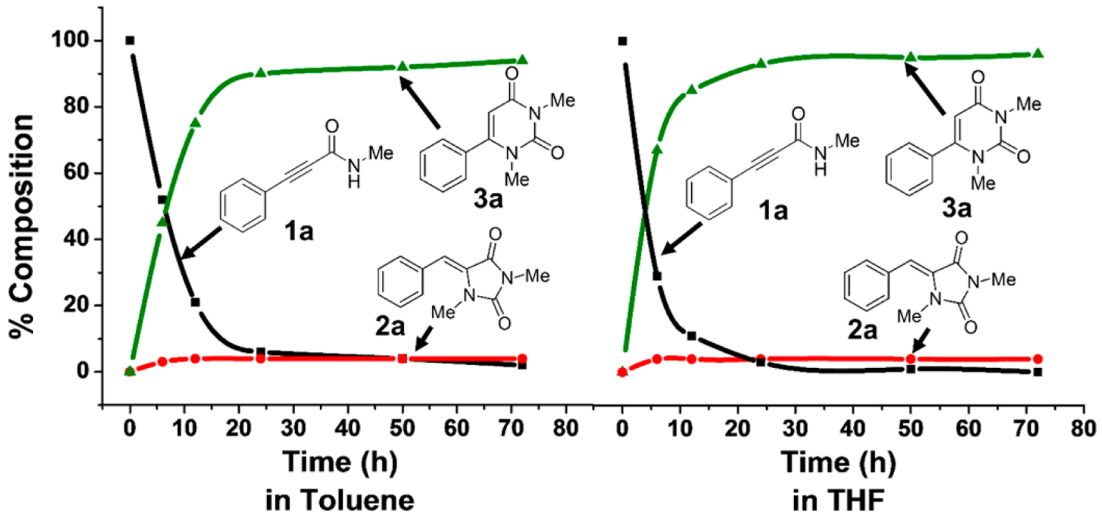
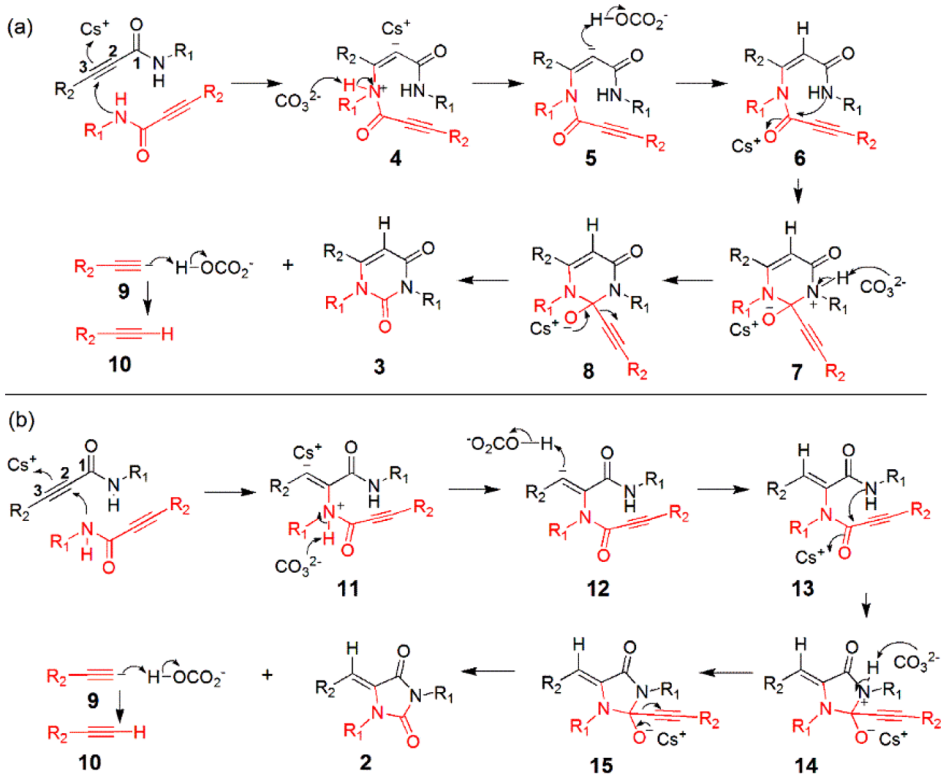


Figure 1. Reaction composition vs time in THF and toluene. Reaction conditions: *N*-methyl-3-phenyl-2-propynamide (1.0 equiv), Cs_2CO_3 (1.0 equiv), 115 °C, solvent (2.0 mL), time (h).

Scheme 2. Proposed Mechanism for the Regioselective Synthesis of (a) 6-Alkyl and 6-Aryluracils and (b) (*Z*)-5-Benzylidene-Hydantoins Promoted by Cs_2CO_3



dimerization/cyclization reaction of secondary 3-substituted-2-propynamides. Surprisingly, when R_2 was the alkyl group, n-propyl, all of the starting amide was consumed, generating the 6-propyluracil derivative **3m** in only 40% yield, whereas substituted hydantoin (*Z*)-**2m** was not observed by GC−MS (Table 2, entry 13).

Surprisingly, substrates **1a−h** were successfully dimerized to their corresponding uracil analogues, similar to Cs_2CO_3-promoted dimerization, when K_3PO_4 was used as the catalyst. Similarly, no uracil products were observed with substrates in which R_1 is -H (Table 3). Dimerization of **1m** with K_3PO_4 was not successful as it was with Cs_2CO_3. The dimerization of **1a** was also performed in a round-bottom flask equipped with a condenser under toluene reflux and exposure to air. No change in reaction composition was observed compared to performing the reaction in airtight culture tubes at 115 °C.

Insights into the Dimerization Mechanism. Two mechanisms were proposed on the basis of the dimerization results (Scheme 2a, b). Intermolecular nucleophilic attack by the secondary amide nitrogen should occur on (β)-carbon (C-3), followed by an intramolecular ring-closing nucleophilic attack on the carbonyl carbon to generate the six-membered uracil ring (Scheme 2a). Similarly, if nucleophilic amide-nitrogen attack took place on the (α)-carbon (C-2) and was followed by ring-

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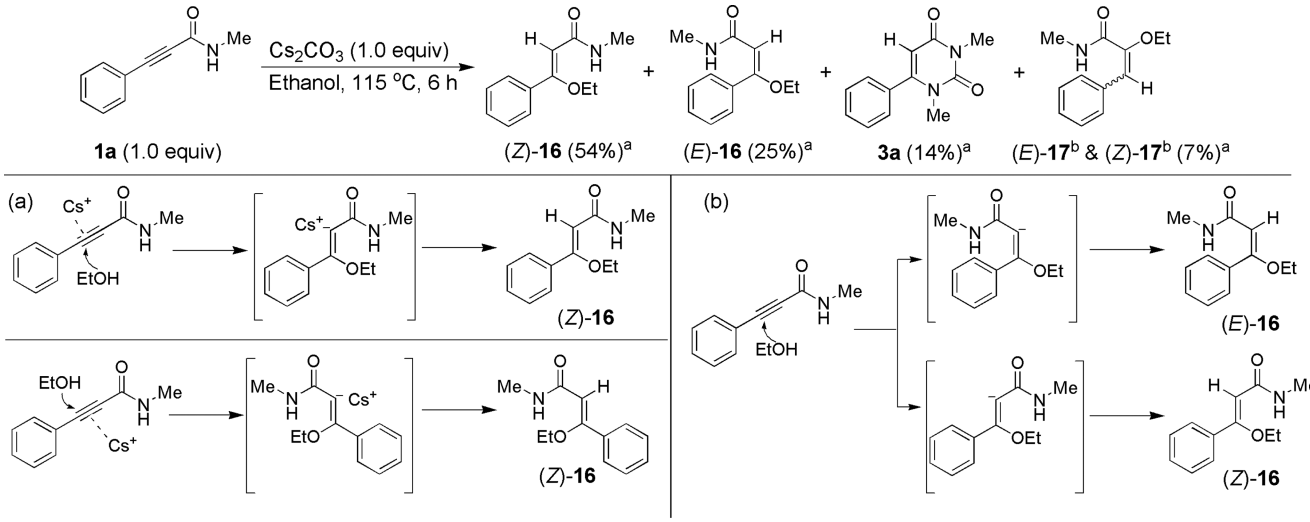
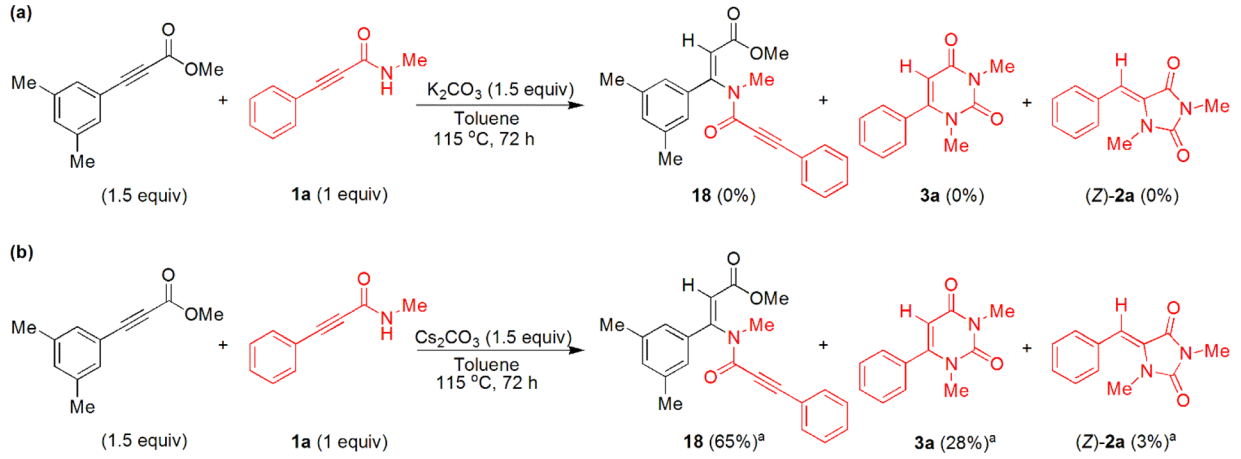
Scheme 3. Conversion of 1a to (*Z*)-16 and (*E*)-16 in Ethanol



[a]GC yield. [b]Neither (*E*)-**17** nor (*Z*)-**17** was isolated and fully characterized by ^{1}H NMR and ^{13}C NMR. However, **17** were identified by their mass spectra obtained using GC−MS.

Scheme 4. Synthesis of Intermediate 18



[a]Isolated yield.

closing intramolecular nucleophilic attack on the carbonyl carbon, this would produce the five-membered hydantoin ring (Scheme 2b). Cyclization of the R_1-substituted amide nitrogen at alkynyl amide carbonyl, as shown in **6** (Scheme 2a), is also represented here as promoted by Cs^+. Displacement of the relatively good aryl acetylene leaving group **10** must occur from **8**, and this corresponding terminal acetylene was detected during each GC−MS analysis of the products. This route is further suggested on the basis of related literature reports.[56,60,62,67]

Scheme 2a and 2b illustrate the conjugate addition of the neutral amide to the Cs^+-activated alkyne carbon on the alkynylamide function. An alternate possibility is that Cs_2CO_3 deprotonates the secondary amide to generate the amide's Cs^+ salt. The nitrogen-centered anion would be a far better nucleophile than the amide itself. However, it is uncertain that Cs_2CO_3 is a sufficiently strong base to remove the proton of neutral amide to convert it to the anionic amide. The pK_a of the secondary alkynyl amides **1a**−**1h** are unknown, but can be estimated to be about 23, based on the known pK_a of $CH_3CONHCH_3$ (25.90),[68] $PhCONH_2$ (23.35),[69] CH_3CONH_2 (25.50),[70] and other models in DMSO. Thus, the question becomes whether or not the carbonate anion in toluene can generate a kinetically relevant amount of the alkynyl amide's Cs^+ salt in toluene at 115 °C. We cannot rule this out, but we note that the equilibrium between the alkynyl amide, **1a**−**1h**, and their Cs^+ salts in toluene should be significantly less favorable than that same equilibria in highly polar DMSO.

Evidence To Support the Proposed Reaction Mechanism (Scheme 2a). Important clues regarding the reaction mechanism were collected when the dimerization of **1a** was performed using ethanol as a solvent. Two ethanol adducts were collected, including a 54% yield of (*Z*)-**16** and a 25% yield of (*E*)-**16** (Scheme 3). Because ethanol is a competing nucleophile, major products of the reaction were (*Z*)-**16** and (*E*)-**16**. Self-dimerization of **1a** gave **3a**, but only as a minor product, because amide **1a** is a weaker nucleophile than ethanol. A 93% overall predominance C-3 addition was observed with nucleophilic attack on amide **1a** when comparing the sum of products (*Z*)-**16**, (*E*)-**16**, and **3a** versus (*E*)-**17** and (*Z*)-**17** (Scheme 3).

The crucial role of the Cs_2CO_3 was investigated while trying to construct intermediate **18** (Scheme 4). No intermolecular

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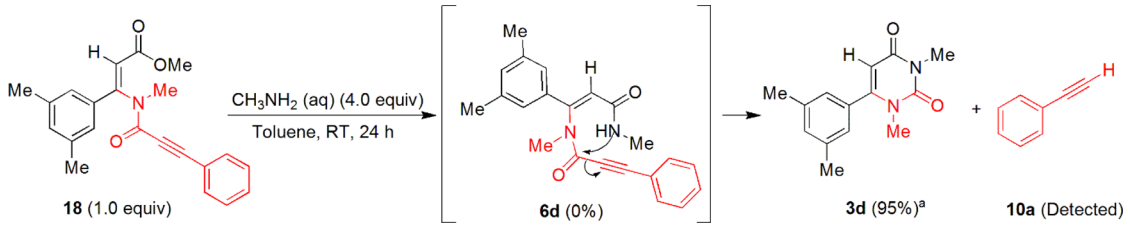
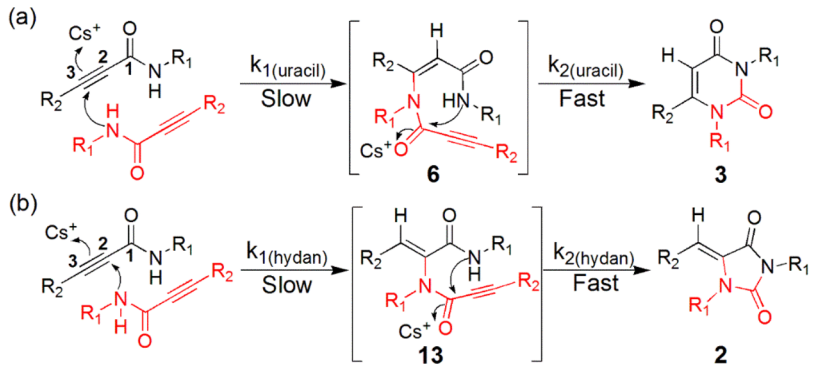
Scheme 5. Attempted Synthesis of 6d

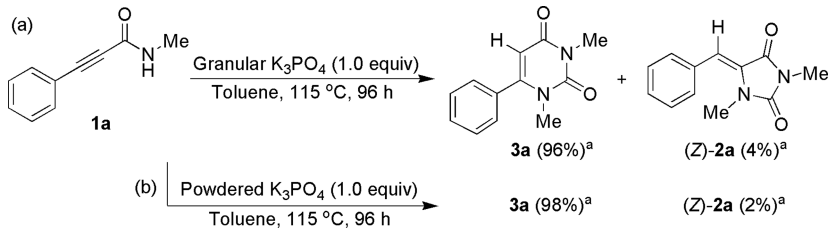


[a]Isolated yield.

Scheme 6. Possible Rate-Determining Steps for Dimerization of Secondary 3-Alkyl- And 3-Aryl-2-Propynamides, (a) To 3, and (B) To (Z)-2



Scheme 7. Dimerization of 1a with, (a) Granular K_3PO_4, (b) Powdered K_3PO_4



[a]GC yield.

nucleophilic addition was observed when the reaction was performed with K_2CO_3 (Scheme 4a). However, when using Cs_2CO_3, the reaction proceeded to the expected intermediate **18** in a 65% yield, to **3a** in 32% yield, and to (*Z*)-**2a** in 3% yield (Scheme 4b). These results support coordination of the "soft" Lewis acid Cs^+ to the triple bond, activating it to nucleophilic attack by the amide nitrogen of a second molecule of **1a**. During the dimerization to **3a–h**, **m** and to (*Z*)-**2a–h**, this same Cs^+ coordination also activates the triple bond to undergo intermolecular nucleophilic attack by the amide nitrogen of a second secondary amide. However, because secondary amide nitrogens are such weak nucleophiles, Cs^+ activation of the triple bond must occur (Scheme 4a vs 4b). The carbonyl group of the amide also polarizes the triple bond, leaving C-3 (*β*-carbon) as the most electrophilic carbon.

Synthesis of **6d** from intermediate **18** was attempted by reacting intermediate **18** with aqueous methyl amine solution at room temperature. Surprisingly, 100% conversion of intermediate **18** within 24 h was observed by GC–MS analysis, but no **6d** was detected. Instead, uracil **3d** was isolated in 95% yield, and 1-ethynylbenzene **10a** was formed (Scheme 5). Formation of **3d** at room temperature supports the rapid facile cyclization of **6d** as proposed in Scheme 2. This cyclization could be catalyzed by Cs^+ (see **13** in Scheme 2). The formation of **18** (Scheme 4) supports Cs^+ activation of the triple bond to undergo nucleophilic attack by the amide nitrogen of a second secondary amide, as proposed in Scheme 2. The intramolecular cyclization step of the **6d** secondary amide nitrogen at the amide-carbonyl carbon (Scheme 5) occurred without any Cs^+ present. Because Cs^+ polarization of the carbonyl oxygen is not required for the cyclization, its role in cyclization of **6** in Scheme 2 and 5 may not be required. Alternatively, carbonate deprotonation of the amide function of **6** and **13** may occur instead to facilitate the cyclization.

Intermediates **6** and **13** were never observed in samples taken during the course of these reactions, so step one (bimolecular nucleophilic attack at C-2 or C-3) should be rate determining (Scheme 6).

Significant amounts of Cs_2CO_3 dissolve in toluene at 115 °C, so Cs^+ is available as a soft Lewis acid in the solution to promote the dimerization reactions. However, K_3PO_4 solubility was very low (940 ppm) in toluene at ~115 °C. The behavior of K_3PO_4 vs Cs_2CO_3 catalysis was investigated during Buchwald's CuI-promoted amidation of aryl halides.[71] The particle size of K_3PO_4 was found to be a critical factor. These amidations proceeded best when granular K_3PO_4 was used, but they were inhibited

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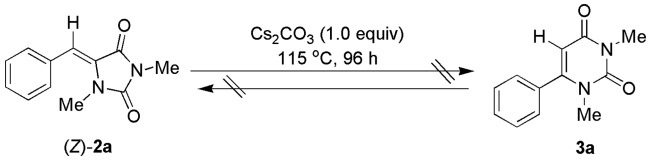
when powdered-form K_3PO_4 was used. These results were explained in the following words "We believe that these observations are best explained by variable kinetic basicity of different K_3PO_4 samples, which should be heavily influenced by the particle size of this heterogeneous base".[71]

In our study, the role of K_3PO_4 does not simply act as a base, but it plays the critical role of determining the regioselectivity. We suggest that K_3PO_4 might serve as a solid-phase heterogeneous catalyst, where K^+ ions are influenced by PO_4^{3-} ions in the solid's lattice structure. If dissolved K_3PO_4 is the actual catalyst, PO_4^{3-} ions in the toluene solution might be expected to be closely associated with K^+, thereby weakening its hard Lewis acid character. Therefore, no change of reaction product composition would be expected upon switching from granular K_3PO_4 to powder K_3PO_4. To test this hypothesis, because the granular form K_3PO_4 was also used in our experiments, granular K_3PO_4 was ground to a fine powder with a mortar and pestle. Then, this powdered K_3PO_4 was used in the **1a** dimerization, and the product composition was determined (Scheme 7). Granular K_3PO_4 gave 96% of **3a** with 4% of (*Z*)-**2a** (Scheme 7a), whereas powdered K_3PO_4 gave 98% of **3a** and 2% of (*Z*)-**2a** (Scheme 7b). Neither reaction inhibition nor lower product yields were observed while using powdered K_3PO_4. In fact, the **3a** yield was slightly increased from 96% to 98% when powdered K_3PO_4 was used. These observations are consistent with similar reactivity displayed by such bifunctional solids such as $CePO_4$, which acts both as a base and also as a heterogeneous catalyst.[72]

The possible interconversion of (*Z*)-**2a** into **3a** or, alternatively **3a** into (*Z*)-**2a**, was investigated at 115 °C in the presence of Cs_2CO_3 to determine whether the proposed mechanisms (Scheme 2a,b) might involve the ring-opening of 6-substituted uracils **3** or (*Z*)-5-arylidenehydantoins like **6** or **13** (Scheme 2). If this occurred, the reaction could be under thermodynamic control. However, absolutely no conversion of (*Z*)-**2a** to **3a** or **3a** to (*Z*)-**2a** occurred, ruling out any equilibrium occurring between **2** and **3**. These results confirm the formation of (Z)-**2a** and **3a** are kinetically controlled under these reaction conditions (Scheme 8).

Scheme 8. Attempted Interconversion of (*Z*)-2a to 3a and 3a to (*Z*)-2a



3. CONCLUSIONS

This paper reports a novel one-pot synthesis of 6-substituted uracil derivatives from readily available N-substituted-3-alkyl- and 3-aryl-2-propynamides. Both Cs_2CO_3 and K_3PO_4 successfully promoted the regioselective syntheis of 6-aryl- and 6-alkyl-substituted uracils. The starting substituted 2-propynamide is easily constructed with a wide structural diversity. The scope of reactions can be further extended to obtain many uracil analogues. The atom efficiency is reduced by the displacement of one aryl (or alkyl) acetylide function from one of the two dimerizing *N*-substituted-3-substituted-2-propynamides. The observation that Cs_2CO_3 can catalyze the addition of alcohols to C-2 or C-3 of 2-propynamides, in addition to secondary amide nitrogens, suggests a host of other such additions might be successful. Thus, additions of alcohols, phenols, thiols, amines, hydroxyl amines, and so on to electron-deficient alkynes should be explored. The facile syntheses herein of **16** and **18** suggest other useful synthetic procedures could result from extensions of this work.

4. EXPERIMENTAL SECTION

General Information. All commercial materials and solvents were used directly without further purification. Melting points were determined in open-glass capillaries and were uncorrected (heating rates: 5 °C min^{-1} from RT to 80 °C and 1−2 °C min^{-1} above 80 °C). ^1H NMR chemical shifts (in ppm) were referenced to tetramethylsilane (δ = 0 ppm) in $CDCl_3$ as an internal standard at room temperature. ^{13}C NMR spectra were calibrated with $CDCl_3$ (δ = 77.16 ppm). The IR spectra were recorded with a FT-IR spectrophotometer, and only major peaks were reported in cm^{-1}. A high-resolution mass spectrometer equipped with an ESI source (positive mode) and a TOF detector was used to obtain spectra (HRMS). Column chromatography was performed on silica gel (70−230 mesh ASTM) using the reported eluents. Thin layer chromatography (TLC) was carried out on plates with a layer thickness of 250 μm (silica gel 60 F254). Gas chromatography coupled with a mass detector was used to performed GC−MS analysis, employing a 60 m × 320 μm × 1 μm, 100% dimethylpolysiloxane capillary column. Unless otherwise noted, reactions were carried out with constant stirring in oven-dried glassware.

Methyl 3-aryl-2-propynoates were prepared according to the method reported by Negishi et al.[73] A procedure reported by Strübing et al.[74] was modified to prepare *N*-substituted-3-alkyl and 3-aryl-2-propynamides **1a−m**. A methyl or ethyl amine solution (4.0 equiv) was added to a methyl arylpropiolate solution (1.0 equiv in THF) at room temperature. The reaction mixture was stirred for 15−90 min at room temperature. Then, the reaction mixture was concentrated under reduced pressure to remove remaining volatile amines. The product was collected by the flash column chromatography using a silica gel column with ethyl acetate and hexane as eluting solvents. It should be noted that these syntheses went smoothly except in the case of the desired reagent, *N*-methyl-3-(4-nitrophenyl)-2-propynamide. Repeated attempts were unsuccessful because of a side reaction in which hydroxide nucleophilic addition occurred across the triple bond of the desired *N*-methyl-3-(4-nitrophenyl)-2-propynamide. Hydroxyl addition was followed by keto−enol tautomerization, which generated 90% isolated yields of *N*-methyl-3-(4-nitrophenyl)-3-oxopropanamide as the only observed product.[66]

General Procedure for the Cs_2CO_3-Promoted Dimerizations of 1a−h, m to 6-Substituted-Uracils. All reactions were performed under air in an airtight screw-head reaction tubes with constant stirring on a Cole-Parmer Aluminum metal block on a hot plate at 115 °C for 96−120 h. *N*-R_1-3-R_2-2-propynamides **1a−h, m** (0.4 mmol, 1.0 equiv), Cs_2CO_3 (0.4 mmol, 1.0 equiv), and anhydrous toluene (2.5 mL) were placed in the reaction tube. After the reaction, the contents were cooled to room temperature, and the solvent was removed under reduced pressure. This crude product was then purified by flash column chromatography using a silica gel column with ethyl acetate and hexane as eluting solvents (Note: flash column chromatography was performed according to TLC R_f values).

Uracils **3a**,[28,31,32,35,75] **3b**,[31,32] **3c**,[31,32] **3d**,[32,75] **3e**,[32,75] and **3g**[35] are known, and their characterization data (^1H NMR, ^{13}C NMR, HRMS, IR and mp) matched those reported in the literature. Complete analytical characterization data for the uracil analogues **3a−h** and **3m** are reported below.

*1,3-Dimethyl-6-phenylpyrimidine-2,4(1H,3H)-dione (**3a**).*[28,31,32,35,75] Purification was carried out by flash column chromatography to obtain **3a** as a white solid (40 mg, 93% isolated yield): mp 98−100 °C; R_f = 0.40 (EtOAc/hexane, 1:1); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.51−7.47 (m, 3H), 7.35−7.32 (m, 2H), 5.70 (s, 1H), 3.41 (s, 3H), 2.23 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 162.5, 154.7, 152.7, 133.4, 130.2, 129.0, 127.8, 102.5, 34.6, 28.1; FT-IR was

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recorded using the solid: 3103, 3057, 2930, 1689, 1637, 1602, 1447, 1429 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{12}H_{12}N_2NaO_2$ $[M + Na]^+$ 239.0791, found 239.0792.

*6-(4-Methoxyphenyl)-1,3-dimethylpyrimidine-2,4(1H,3H)-dione (**3b**).*[31,32] Purification was carried out by flash column chromatography to obtain **3b** as a white solid (46 mg, 94% isolated yield): mp 105−107 °C; R_f = 0.34 (EtOAc/hexane, 1:1); ^1H NMR ($CDCl_3$, 600 MHz) δ 7.27−2.26 (m, 2H), 6.99 (d, 2H, *J* = 9.0 Hz), 5.68 (s, 1H), 3.87 (s, 3H), 3.40 (s, 3H), 3.25 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 162.7, 161.1, 154.7, 153.0, 129.4, 125.7, 114.5, 102.5, 55.6, 34.8, 28.2; FT-IR was recorded using the solid: 3074, 3010, 2942, 2840, 1688, 1643, 1603, 1430, 1251, 1027 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{13}H_{14}N_2NaO_3$ $[M + Na]^+$ 269.0897, found 269.0898

*6-(4-Methylphenyl)-1,3-dimethylpyrimidine-2,4(1H,3H)-dione (**3c**).*[31,32] Purification was carried out by flash column chromatography to obtain **3c** as a white solid (43 mg, 93% isolated yield): mp 108−110 °C; R_f = 0.46 (EtOAc/hexane, 1:1); ^1H NMR ($CDCl_3$, 600 MHz) δ 7.28 (d, 2H, *J* = 7.2 Hz), 7.21 (d, 2H, *J* = 7.2 Hz), 5.68 (s, 1H), 3.41 (s, 3H), 3.23 (s, 3H), 1.54 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 162.7, 154.9, 152.9, 140.6, 130.7, 129.8, 127.8, 102.5, 34.7, 28.2, 21.5; FT-IR was recorded using the solid: 3094, 2947, 2923, 1697, 1648, 1618, 1430 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{13}H_{14}N_2NaO_2$ $[M + Na]^+$ 253.0947, found 253.0948.

*6-(3,5-Dimethylphenyl)-1,3-dimethylpyrimidine-2,4(1H,3H)-dione (**3d**).*[32,75] Purification was carried out by flash column chromatography to obtain **3d** as a white solid (46 mg, 94% isolated yield): mp 174−176 °C; R_f = 0.63 (EtOAc/hexane, 2:1); ^1H NMR ($CDCl_3$, 600 MHz) δ 7.12 (s, 1H), 6.93 (s, 2H), 5.67 (s, 1H), 3.40 (s, 3H), 3.22 (s, 3H), 2.37 (s, 6H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 162.6, 155.1, 152.8, 138.8, 133.4, 131.8, 125.4, 102.2, 34.6, 28.0, 21.3; FT-IR was recorded using the solid: 2956, 2919, 1698, 1647, 1614, 1433 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{14}H_{16}N_2NaO_2$ $[M + Na]^+$ 267.1104, found 267.1106.

*6-(3,4-Dimethylphenyl)-1,3-dimethylpyrimidine-2,4(1H,3H)-dione (**3e**).*[32,75] Purification was carried out by flash column chromatography to obtain **3e** as a white solid (46 mg, 94% isolated yield): mp 112−114 °C; R_f = 0.55 (EtOAc/hexane, 2:1); ^1H NMR ($CDCl_3$, 600 MHz) δ 7.23 (d, 1H, *J* = 7.2 Hz), 7.09 (s, 1H), 7.05 (d, 1H, *J* = 7.2 Hz), 5.67 (s, 1H), 3.40 (s, 3H), 3.23 (s, 3H), 2.32 (s, 6H, broad singlet overlap of two CH_3 signals); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 162.6, 155.0, 152.8, 139.1, 137.5, 131.0, 130.1, 128.8, 125.2, 102.3, 34.6, 28.0, 19.9, 19.7; FT-IR was recorded using the solid: 3053, 2944, 1698, 1644, 1617, 1478, 1433 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{14}H_{16}N_2NaO_2$ $[M + Na]^+$ 267.1104, found 267.1105.

*1,3-Dimethyl-6-(3-nitrophenyl)pyrimidine-2,4(1H,3H)-dione (**3f**).* Purification was carried out by flash column chromatography to obtained **3f** as a yellow solid (50 mg, 96% isolated yield): mp 161−162 °C; R_f = 0.24 (EtOAc/hexane, 1:1); ^1H NMR ($CDCl_3$, 600 MHz) δ 8.39 (d, 1H, *J* = 7.8 Hz), 8.26 (s, 1H), 7.76−7.70 (m, 2H), 5.74 (s, 1H), 3.42 (s, 3H), 3.24 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 162.0, 152.4, 151.9, 148.5, 134.9, 133.8, 130.6, 125.2, 123.1, 103.5, 34.7, 28.3; FT-IR was recorded using the solid: 3069, 2959, 1693, 1651, 1623, 1525, 1430, 1349 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{12}H_{11}N_3NaO_4$ $[M + Na]^+$ 284.0642, found 284.0643.

*1,3-Diethyl-6-phenylpyrimidine-2,4(1H,3H)-dione (**3g**).*[35] Purification was carried out by flash column chromatography to obtain **3g** as a white solid (39 mg, 80% isolated yield): mp 119−121 °C; R_f = 0.61 (EtOAc/hexane, 1:1); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.51−7.46 (m, 3H), 7.36−7.32 (m, 2H), 5.62 (s, 1H), 4.07 (q, 2H, *J* = 6.9 Hz), 3.73 (q, 2H, *J* = 7.2 Hz), 1.29 (t, 3H, *J* = 7.2 Hz), 1.11 (t, 3H, *J* = 6.9 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 162.1, 154.5, 151.7, 133.6, 130.0, 128.9, 127.8, 103.2, 41.7, 36.6, 14.3, 12.9; FT-IR was recorded using the solid: 3094, 3077, 2973, 2931, 2871, 1695, 1646, 1619, 1447, 1423 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{14}H_{16}N_2NaO_2$ $[M + Na]^+$ 267.1104, found 267.1106.

*1,3-Diethyl-6-(4-methoxyphenyl)pyrimidine-2,4(1H,3H)-dione (**3h**).* Purification was carried out by flash column chromatography to obtain **3h** as a white solid (40 mg, 73% isolated yield): mp 135−136 °C; R_f = 0.51 (EtOAc/hexane, 1:1); ^1H NMR ($CDCl_3$, 600 MHz) δ 7.27−7.26 (m, 2H), 6.98 (d, 2H, *J* = 8.4 Hz), 5.60 (s, 1H), 4.06 (q, 2H, *J* = 7.2 Hz), 3.87 (s, 3H), 3.75 (q, 2H, *J* = 7.2 Hz), 1.28 (t, 3H, *J* = 7.2 Hz), 1.11 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 162.2, 160.8, 154.5, 151.9, 129.3, 125.8, 114.3, 103.3, 55.5, 41.7, 36.6, 14.3, 13.0; FT-IR was recorded using the solid: 3095, 3008, 2982, 2938, 1696, 1647, 1618, 1604,1432, 1250, 1027 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{15}H_{18}N_2NaO_3$ $[M + Na]^+$ 297.1210, found 297.1211.

*1,3-Dimethyl-6-propylpyrimidine-2,4(1H,3H)-dione (**3m**).* Purification was carried out by flash column chromatography to obtain **3m** as a white solid (12 mg, 32% isolated yield): mp (heating rate: 1−2 °C min^{-1}) 52−53 °C; R_f = 0.23 (EtOAc/hexane, 1:1); ^1H NMR ($CDCl_3$, 600 MHz) δ 5.61 (s, 1H), 3.41 (s, 3H), 3.34 (s, 3H), 2.45 (t, 2H, *J* = 7.8 Hz), 1.65 (sextet, 2H, *J* = 7.8 Hz), 1.05 (t, 3H, *J* = 7.8 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 162.7, 154.9, 152.9, 100.3, 34.6, 31.4, 28.0, 20.5, 13.7; FT-IR was recorded using solid: 3117, 2967, 2938, 2880,1692, 1651, 1626, 1435 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_9H_{14}N_2NaO_2$ $[M + Na]^+$ 205.0947, found 205.0950.

General Procedure for the K_3PO_4-Promoted Dimerizations of 1a−m to 6-Substituted-Uracils. All reactions were performed under air in an airtight screw-head reaction tubes with constant stirring on a Cole-Parmer Aluminum metal block on a hot plate at 115 °C for 96 h. *N*-R_1-3-R_2-2-Propynamides **1a−m** (0.1 mmol, 1.0 equiv), K_3PO_4 (0.1 mmol, 1.0 equiv), and anhydrous toluene (2.0 mL) were placed in the reaction tube. Also, entry 1 of Table 3 was performed under reflux in a 25 mL round-bottomed flask connected to a water-cooling condenser. **1a** (0.6 mmol, 1.0 equiv), K_3PO_4 (0.6 mmol, 1.0 equiv), and anhydrous toluene (10.0 mL) at 115 °C for 120 h were used.

The K_3PO_4-promoted dimerizations of *N*-R_1-3-aryl-2-propynamides were scaled up to 0.8 mmol to isolate hydantoin analogues (*Z*)-**2a−h** (Table 3). All hydantoins, (*Z*)-**2a−h** were characterized by ^1H NMR, ^{13}C NMR, HRMS, and NOESY. NOESY was performed to establish the geometry of (*Z*)-**2a−h**.

*(Z)-5-Benzylidene-1,3-dimethylimidazolidine-2,4-dione [(Z)-**2a**].* Purification was carried out by flash column chromatography to obtain **2a** as a pale yellow, amorphous solid (3.8 mg, 5% isolated yield): R_f = 0.66 (EtOAc/hexane, 1:1); ^1H NMR ($CDCl_3$, 600 MHz) δ 7.39−7.29 (m, 5H), 6.95 (s, 1H), 3.14 (s, 3H), 2.95 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 163.9, 156.1, 132.8, 129.9, 129.6, 128.5, 128.4, 112.5, 30.5, 25.2; HRMS (ESI) *m/z* calcd for $C_{12}H_{12}N_2NaO_2$ $[M + Na]^+$ 239.0791, found 239.0794.

*(Z)-5-(4-Methoxybenzylidene)-1,3-dimethylimidazolidine-2,4-dione [(Z)-**2b**].*[76] Purification was carried out by flash column chromatography to obtain **2b** as a pale yellow, amorphous solid (3.2 mg, 3% isolated yield): R_f = 0.57 (EtOAc/hexane, 1:1); ^1H NMR ($CDCl_3$, 600 MHz) δ 7.24 (d, 2H, *J* = 8.4 Hz), 6.92 (d, 2H, *J* = 8.4 Hz), 6.90 (s, 1H), 3.84 (s, 3H), 3.14 (s, 3H), 3.00 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 164.0, 159.8, 156.2, 131.1, 128.8, 124.8, 113.8, 112.8, 55.4, 30.7, 25.2; HRMS (ESI) *m/z* calcd for $C_{13}H_{14}N_2NaO_3$ $[M + Na]^+$ 269.0897, found 269.0895.

*(Z)-5-(4-Methylbenzylidene)-1,3-dimethylimidazolidine-2,4-dione [(Z)-**2c**].* Purification was carried out by flash column chromatography to obtain **2c** as a pale yellow, amorphous solid (5.6 mg, 6% isolated yield): R_f = 0.71 (EtOAc/hexane, 1:1); 1H NMR ($CDCl_3$, 600 MHz) δ 7.21−7.19 (m, 4H), 6.92 (s, 1H), 3.13 (s, 3H), 2.97 (s, 3H), 2.38 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 164.0, 156.1, 138.6, 129.8, 129.6, 129.5, 129.1, 112.8, 30.6, 25.2, 21.5; HRMS (ESI) *m/z* calcd for $C_{13}H_{14}N_2NaO_2$ $[M + Na]^+$ 253.0947, found 253.0946.

*(Z)-5-(3,5-Dimethylbenzylidene)-1,3-dimethylimidazolidine-2,4-dione [(Z)-**2d**].* Purification was carried out by flash column chromatography to obtain **2d** as a pale yellow, amorphous solid (3.6 mg, 3% isolated yield): R_f = 0.81 (EtOAc/hexane, 2:1); 1H NMR ($CDCl_3$, 600 MHz) δ 6.97 (s, 1H), 6.90 (m, 3H), 3.14 (s, 3H), 2.96 (s, 3H), 2.33 (s, 6H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 164.0, 156.1, 137.9, 132.6, 130.2, 129.6, 127.4, 113.0, 30.6, 25.2, 21.4; MS (EI) *m/z*; 244.2, 229.1, 159.1, 144.1, 129.1, 115.1, 91.0, 77.1; HRMS (ESI) *m/z* calcd for $C_{14}H_{16}N_2NaO_2$ $[M + Na]^+$ 267.1104, found 267.1103.

*(Z)-5-(3,4-Dimethylbenzylidene)-1,3-dimethylimidazolidine-2,4-dione [(Z)-**2e**].* Purification was carried out by flash column chromatography to obtain **2e** as a pale yellow, amorphous solid (4.4 mg, 4% isolated yield): R_f = 0.80 (EtOAc/hexane, 2:1); 1H NMR ($CDCl_3$, 600 MHz) δ 7.14 (d, 1H, *J* = 7.2 Hz), 7.06−7.02 (m, 2H), 6.91

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(s, 1H), 3.13 (s, 3H), 2.98 (s, 3H), 2.28 (s, 6H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 164.1, 156.2, 137.4, 136.6, 130.8, 130.2, 129.6, 129.3, 127.1, 113.1, 30.6, 25.2, 19.9, 19.8; MS (EI) m/z 244.2, 229.1, 159.1, 144.1, 129.1, 115.1; HRMS (ESI) m/z calcd for $C_{14}H_{16}N_2NaO_2$ $[M + Na]^+$ 267.1104, found 267.1102.

*(Z)-5-(3-Nitrophenyl)-1,3-dimethylimidazolidine-2,4-dione [(Z)-**2f**].* Purification was carried out by flash column chromatography to obtain **2f** as a pale yellow, amorphous solid (6.3 mg, 6% isolated yield): R_f = 0.54 (EtOAc/hexane, 1:1); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.20 (d, 1H, J = 9 Hz), 8.16 (s, 1H), 7.63−7.57 (m, 2H), 6.88 (s, 1H), 3.16 (s, 3H), 2.96 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 163.4, 155.8, 148.3, 135.3, 134.8, 131.6, 129.5, 124.3, 123.2, 108.5, 30.6, 25.4; MS (EI) m/z 261, 215, 176, 130, 103, 89; HRMS (ESI) m/z; calcd for $C_{12}H_{11}N_3NaO_4$ $[M + Na]^+$ 284.0642, found 284.0641.

*(Z)-5-Benzylidene-1,3-diethylimidazolidine-2,4-dione [(Z)-**2g**].* Purification was carried out by flash column chromatography to obtain **2g** as a pale yellow, amorphous solid (7.3 mg, 7% isolated yield): R_f = 0.79 (EtOAc/hexane, 1:1); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.40−7.30 (m, 5H), 6.94 (s, 1H), 3.68 (q, 2H, J = 7.2 Hz), 3.58 (q, 2H, J = 7.2 Hz), 1.28 (t, 3H, J = 7.2 Hz), 0.77 (t, 3H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 164.0, 155.4, 133.2, 129.2, 128.5, 128.4, 128.4, 112.1, 36.8, 34.3, 13.7, 13.0; MS (EI) m/z 244, 215, 158, 130, 177; HRMS (ESI) m/z calcd for $C_{14}H_{16}N_2NaO_2$ $[M + Na]^+$ 267.1104, found 267.1102.

*(Z)-5-(4-Methoxybenzylidene)-1,3-diethylimidazolidine-2,4-dione [(Z)-**2h**].* Purification was carried out by flash column chromatography to obtain **2h** as a pale yellow, amorphous solid (8.2 mg, 7% isolated yield): R_f = 0.69 (EtOAc/hexane, 1:1); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.24 (d, 2H, J = 8.4 Hz), 6.92−6.89 (m, 3H), 3.84 (s,3H), 3.69−3.61 (m, 4H), 1.27 (t, 3H, J = 7.2 Hz), 0.80 (t, 3H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 164.1, 159.8, 155.6, 130.7, 127.6, 125.4, 113.9, 112.5, 55.5, 36.9, 34.2, 13.7, 13.0; HRMS (ESI) m/z calcd for $C_{15}H_{18}N_2NaO_3$ $[M + Na]^+$ 297.1210, found 297.1208.

General Procedure for the Dimerization of 1a In Ethanol. This reaction was conducted under air in an airtight screw-head reaction tube with constant stirring on a Cole-Parmer aluminum metal block on a hot plate at 115 °c for 6 h. **1a** (0.4 mmol, 1.0 equiv) and Cs_2CO_3 (0.4 mmol, 1.0 equiv) in ethanol (2.5 mL) were placed in the reaction tube. After 6 h, the reaction mixture was cooled to room temperature, and the solvent was removed under reduced pressure to give a crude mixture. This crude reaction mixture could not be successfully separated by column chromatography after several tries, so the products were purified by TLC separation and removing silica from the TLC plates. Analytical characterization data for the uracil analogues (*Z*)-**16** and (*E*)-**16** are reported below.

*(Z)-3-Ethoxy-N-methyl-3-phenyl-2-propenamide [(Z)-**16**].* The compound was isolated by removing silica from TLC plates after development to obtain (*Z*)-**16** as a colorless liquid (33 mg, 40% isolated yield): R_f = 0.63 (EtOAc/hexane, 99:1); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.54 (s, 1H, N−H), 7.45−7.40 (m, 5H), 5.52 (s, 1H), 3.89 (q, 2H, J = 7.2 Hz), 2.93 (d, 3H), 1.31 (t, 3H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 166.8, 161.8, 134.4, 130.0, 128.8, 127.5, 108.8, 67.2, 26.1, 15.4; FT-IR recorded in DCM: 3419, 3056, 2982, 1653, 1611, 1265, 1054 cm^{-1}; HRMS (ESI) m/z calcd for $C_{12}H_{15}N_1NaO_2$ $[M + Na]^+$ 228.0995, found 228.0996.

*(E)-3-Ethoxy-N-methyl-3-phenyl-2-propenamide [(E)-**16**].* The compound was isolated by removing silica from TLC plates after development to obtain (*E*)-**16** as a colorless liquid (15 mg, 18% isolated yield): R_f = 0.54 (EtOAc/hexane, 99:1); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.46−7.38 (m, 5H), 5.23 (s, 1H), 5.03 (s, 1H, N−H), 3.93 (q, 2H, J = 7.2 Hz), 2.63 (d, 3H), 1.40 (t, 3H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 168.0, 164.1, 135.3, 129.9, 128.8, 128.4, 97.6, 64.4, 26.4, 14.5; FT-IR recorded in DCM: 3457, 3056, 2984, 1645, 1619, 1264, 1076 cm^{-1}; HRMS (ESI) m/z calcd for $C_{12}H_{15}N_1NaO_2$ $[M + Na]^+$ 228.0995, found 228.0993.

General Procedure for the Synthesis of Intermediate 18. Reaction was conducted under air in an airtight screw-head reaction tube with constant stirring on a Cole-Parmer Aluminum metal block on a hot plate at 115 °C for 72 h. Methyl 3-(3,5-dimethylphenyl)-2-propynate (0.75 mmol, 1.5 equiv), *N*-methyl-3-phenyl-2-proynamide **1a** (0.5 mmol, 1.0 equiv), Cs_2CO_3 (0.75 mmol, 1.5 equiv), and 5 mL of toluene were placed in the reaction tube. The crude mixture was purified using a silica gel column, using hexane and ethyl acetate (1:1) as the eluting solvent mixture. Analytical characterization data are given below.

(*Z*)-Methyl 3-(3,5-dimethylphenyl)-3-(*N*-methyl-3-phenyl-2-propynamido)acrylate, **18**. Purification was carried out by flash column chromatography to obtain **18** as a pale, yellow liquid (108 mg, 65% isolated yield). R_f = 0.75 (EtOAc/hexane, 1:1); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.35−7.27 (m, 5H), 7.13−7.10 (m, 3H), 6.35 (s, 1H), 3.77 (s, 3H), 3.14 (s, 3H), 2.35 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 165.1, 154.4, 152.8, 140.0, 135.2, 132.9, 132.6, 130.1, 128.5, 125.3, 120.6, 115.8, 88.9, 82.0, 52.0, 34.5, 21.4; HRMS (ESI) m/z calcd for $C_{22}H_{21}NNaO_3$ $[M + Na]^+$ 370.1414, found 370.1410.

Determination of Concentration of the K_3PO_4 in Toluene at 115 °C. K_3PO_4 (0.5198 g) was added to 5 mL of toluene in a screw-head culture tube. It was stirred for 1 h at 115 °C. After 1 h, the solution was immediately filtered while still hot, and the K_3PO_4 solid on the filter was dried before recording the mass (0.5151 g). The concentration of K_3PO_4 in toluene at 115 °C was back-calculated to be 940 ppm.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b00508.

^{1}H NMR, ^{13}C NMR, 2D NOESY, and GC-yield caculations are included in Supporting Information section (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: tmlsna@chemistry.msstate.edu

*E-mail: CPittman@chemistry.msstate.edu

ORCID

Todd E. Mlsna: 0000-0002-4858-1372

Notes

The authors declare no competing financial interest.

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