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Regioselective synthesis of pyrano[3,2-*c*]pyrimidine derivatives via a palladium-catalyzed unusual [1,3] aryloxy shift and cycloisomerization: first report of a [1,3] shift of an aryloxy group

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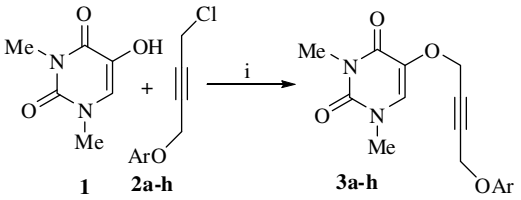
ABSTRACT

Uracil-annulated pyrano heterocycles are regioselectively synthesized in excellent yields (92–100%) via a palladium-catalyzed unusual [1,3] aryloxy shift followed by 6-*endo* dig cyclization and [1,3] prototropic shift.

The importance of pyrimidine and its derivatives are well-known[1,2] due to their high biological activities. A number of pyrimidine and uracil-based molecules,[3] such as 3′-azido-3′-deoxythymidine (AZT), 2,3-dideoxycytidine (DDC) and (*E*)-5-[2-(bromovinyl)-2′-deoxyuridine (BVDU) active against cancer and AIDS viruses,[4] have already been synthesized. The introduction of functionality at the C5- and C6-positions of uracils leads to biologically interesting molecules. The Claisen rearrangement is an important and powerful method[5] for constructing carbon–carbon bonds. On the other hand, [1,3] O-migration is rare and whilst thermal [1,3] sigmatropic shifts that relay stereochemical information have been reported, there is a dearth of examples and the transformation lacks generality. Recently, Rovis et al. reported[6] in their review article that the [1,3] O-migration to C is very rare in the literature. So far, to our knowledge, there is no report of the [1,3] aryloxy migration to C via palladium-catalyzed (or even any transition metal-catalyzed) rearrangement. In 1979, Ferrier reported[7] a [1,3] rearrangement of hexose to cyclohexanone using $HgCl_2$ as a catalyst. Subsequently, Adam[8] independently, and Trost et al. reported[9] a similar transformation by electrophilic-Pd activation of a vinyl ether. Therefore, the above findings prompted us to undertake a study of the palladium-catalyzed transformation[10] of 1,3-dimethyl-5-(4′-aryloxybut-2′-ynyloxy)uracils, and herein we report the results of our investigation.

The requisite starting materials 1,3-dimethyl-5-(1-aryloxybut-2-ynyloxy)uracils **3a–j** were prepared in 80–96% yields by the



1 **2a-h** **3a-h**

3a, Ar = Ph, 88%
3b, Ar = 4-OMeC$_6$H$_4$, 95%
3c, Ar = 4-MeC$_6$H$_4$, 91%
3d, Ar = 2,6-Me$_2$C$_6$H$_3$, 90%
3e, Ar = 3,5-Me$_2$C$_6$H$_3$, 94%
3f, Ar = 4-Bu^{t}C$_6$H$_4$, 80%
3g, Ar = 2,4-Cl$_2$C$_6$H$_3$, 84%
3h, Ar = 1-naphthyl, 83%
3i, Ar = 2-naphthyl, 82%
3j, Ar = 2-ClC$_6$H$_4$

Scheme 1. Reagents and conditions: (i) acetone, K_2CO_3, reflux, 6–8 h.

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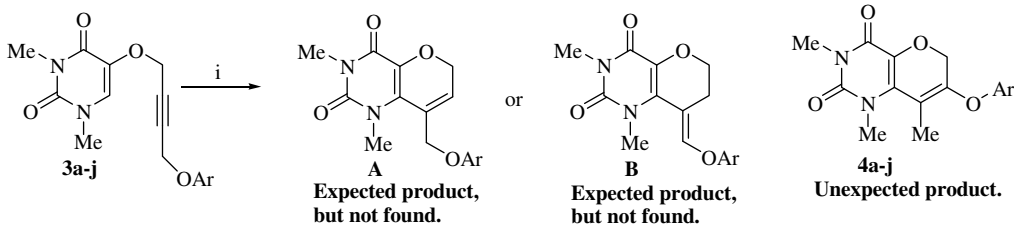
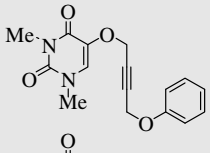
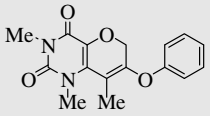
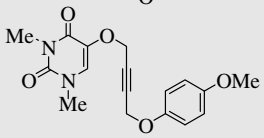
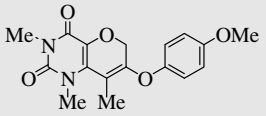
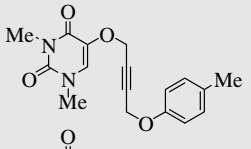
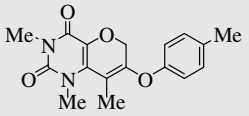
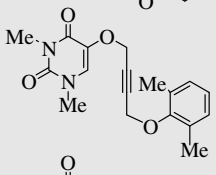
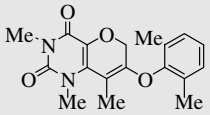
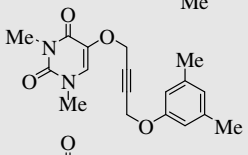
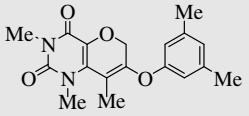
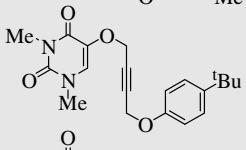
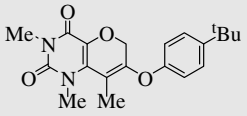
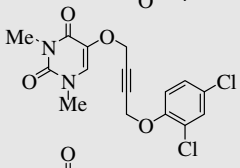
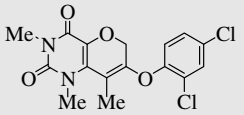
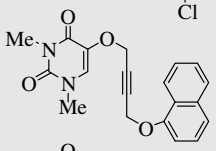
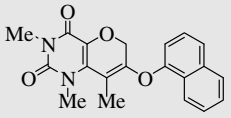
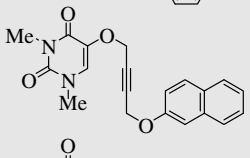
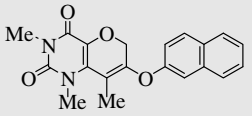
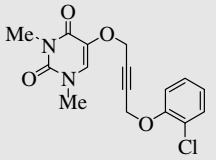
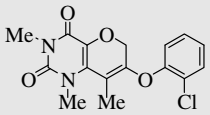
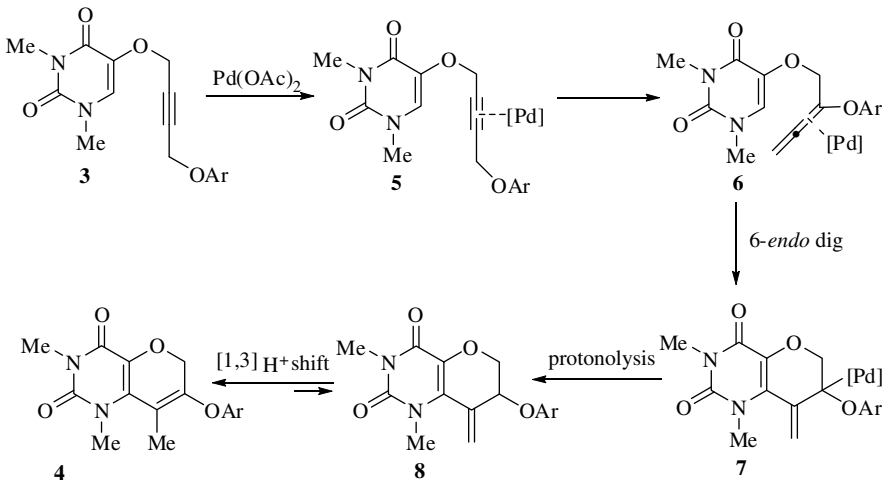


Scheme 2. Reagents and conditions: (i) $Pd(OAc)_2$, DMF, Et_3N, N_2-atmosphere.

Table 1
Summarized results of the Claisen rearrangements[a]

Entry	Substrates **3**	Time (min)	Product **4**	Yield[b] (%)
1		45		100
2		35		100
3		40		100
4		45		99
5		45		99
6		60		98
7		70		92
8		80		100
9		80		100
10		65		97

[a] All reactions were performed at 80 °C.
[b] Isolated yields.



Scheme 3. Proposed mechanistic pathway of the reaction.

alkylation of 1,3-dimethyluracil[11] **1** with different 1-aryloxy-4-chlorobut-2-ynes **2a–j**[12] in refluxing acetone in the presence of anhydrous potassium carbonate for 6–8 h (Scheme 1).

When the reaction of **3a** was performed in the presence of $Pd(OAc)_2$ (2 mol %) as catalyst, Et_3N as the base in dry DMF under a nitrogen atmosphere for 45 min, the cyclized product **4a** was obtained in almost quantitative (~100%) as a white solid by an unusual pathway. From our previous research,[13] the expected products should have been either **A** or **B**. However, we did not obtain even a trace of either **A** or **B**. The structure of the cyclized product **4a** was established from its elemental analysis and spectroscopic data. The ^1H NMR spectrum showed three, three-proton singlets due to the three methyl groups in the compound; a two-proton singlets due to one OCH_2 and five protons in the aromatic region due to the phenyl ring. The DEPT (135) experiment revealed one OCH_2 moiety present in the compound, and finally the structure was further supported by its HRMS spectrum. Therefore, to test the generality of the process we conducted the reaction with substrates **3b–j** under the same reaction conditions to give the corresponding cyclized products **4b–j** in 92–100% yields (Scheme 2 and Table 1).

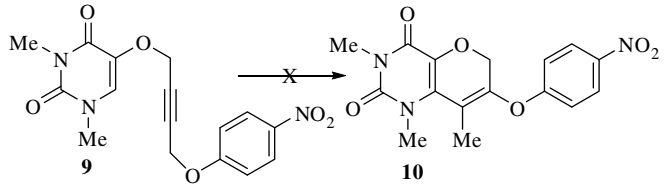
The reaction may occur either via, (i) a thermal [3,3] Claisen rearrangement followed by a [1,3] migration of the aryloxy group, or (ii) by a palladium-catalyzed [1,3] migration of the aryloxy group. To the best of our knowledge, the thermal [1,3] shift is known, but the palladium-catalyzed [1,3] aryloxy shift is unknown. In our present case, the reaction involves a palladium-catalyzed rearrangement as corroborated by the following reactions.

When the substrates were subjected to Claisen rearrangement either in dry DMF or in dry Et_3N at 80 °C, the cyclization did not occur or all the starting materials remained unreacted. There was no reaction when the reaction was carried out in DMF in the presence of Et_3N at 80 °C. Therefore, the reaction was performed separately either in DMF or Et_3N in the presence of $Pd(OAc)_2$ at 80 °C. However, the reaction did not proceed at all as evidenced by TLC monitoring of the reaction. Therefore, the thermal Claisen rearrangement pathway was ruled out. It is therefore reasonable to assume that the reaction followed a palladium-catalyzed unusual [1,3] aryloxy migration pathway followed by 6-*endo* dig cyclization and [1,3] prototropic shift.

The mechanistic pathway of the palladium-catalyzed rearrangement is depicted in Scheme 3. Initially, $Pd(OAc)_2$ may be reduced by the organic base[14] (Et_3N) to give the active species Pd(0), which may then coordinate to the triple bond of substrate **3** lowering the energy of activation of the substrates and giving the intermediate complexes **5**. The intermediate complexes **5** may undergo an unusual [1,3] aryloxy migration to give allenyl ethers **6**. These allenyl ethers **6** may then undergo a 6-*endo* dig cyclization [15] to give intermediates **7**. Protonolysis[16] of intermediates **7** gives intermediates **8**. The desired product **4** may be formed from the exocyclic product **8** by a simple [1,3] prototropic shift.

The following experiment supported the involvement of an unusual [1,3] migration of the aryloxy group in the reaction. When the palladium-catalyzed reaction was performed with substrate **9** containing a 4-nitro group on the aryloxy moiety, the reaction did not occur at all and this is perhaps due to the unavailability of the lone pair of electrons of the oxygen atom of the 4-nitrophenol moiety. Due to the strong electron-withdrawing tendency of the nitro group, the lone pair of the oxygen atom is engaged in extended conjugation with the nitro group, and consequently the lone pair becomes unavailable resulting in no reaction (Scheme 4). The results are summarized in Table 1. The reaction pathway from **3** to **4** follows a concerted mechanism which is evidenced from the following cross-over type experiment. A different phenol was added to the reaction mixture and no cross-product was obtained, suggesting the 'concerted' nature of the reaction.

In summary, we have developed an efficient high yielding protocol for the regioselective synthesis of pyrano[3,2-*c*]pyrimidines. The protocol involves a palladium-catalyzed unusual [1,3] aryloxy group migration followed by a 6-*endo* dig cyclization, protonolysis and a [1,3] prototropic shift, perhaps in a concerted manner. Our literature search did not reveal any earlier reports of catalyzed [1,3] aryloxy shift.



Scheme 4.

1. General procedure for the preparation of the compounds 3a–j

A mixture of 1,3-dimethyl-5-hydroxyuracil **1** (500 mg, 3.8 mmol), 1-aryloxy-4-chlorobut-2-yne **2a** (688 mg, 3.8 mmol) and dry K_2CO_3 (4.0 g) in dry acetone (75 ml) was refluxed for a period of 6 h. After cooling, the reaction mixture was filtered and the

solvent was removed. The residual mass was extracted with dichloromethane, washed with water and brine and then dried (Na_2SO_4). Removal of dichloromethane afforded a crude product which was chromatographed over silica gel (60–120 mesh). Elution of the column with 30% petroleum ether–ethyl acetate gave compound **3a** in 88% yield. Substrates **3b–j** were prepared according to this procedure.

2. General procedure for the synthesis of the compounds 4a–j

A mixture of compound **3a** (100 mg, 0.33 mmol) and $Pd(OAc)_2$ (1.48 mg, 2 mol %) was heated in dry DMF (3 ml) in the presence of a catalytic amount of dry Et_3N under a nitrogen atmosphere at 80 °C for 35–80 min with continuous stirring. After completion of the reaction (monitored by TLC), the reaction mixture was cooled and water (3 ml) was added. It was extracted with dichloromethane (3 × 25 ml) and washed with water (3 × 15 ml) followed by brine (20 ml). The organic layer was dried (Na_2SO_4). Evaporation of dichloromethane furnished a crude mass, which was purified by column chromatography over silica gel. Elution of the column with 30% petroleum ether–ethyl acetate afforded the product **4a**. Similarly, compounds **4b–j** were prepared from substrates **3b–j**.

2.1. Compound 4a

Yield: 100%, white solid, mp 158–160 °C, IR (KBr): ν_{max} = 1668, 1718 cm^{-1}, ^1H NMR ($CDCl_3$, 400 MHz): δ_H = 2.45 (s, 3H, CH_3), 3.42 (s, 3H, N–CH_3), 3.61 (s, 3H, N–CH_3), 4.94 (s, 2H, OCH_2), 6.94–7.33 (m, 5H, ArH). HRMS calcd [M^+] for $C_{16}H_{16}N_2O_4$: 300.1101. Found: [M^+]: 300.1100. DEPT (135): δ_C = 13.1; 28.8; 32.2; 60.1 (OCH_2), 115.2; 122.5; 130.2. Anal. Calcd for $C_{16}H_{16}N_2O_4$: C, 63.99; H, 5.37; N, 9.33. Found: C, 63.89; H, 5.41; N, 9.53.

3.2. Compound 4b

Yield: 100%, white solid, mp 148–150 °C, IR (KBr): ν_{max} = 1672, 1708 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ_H = 2.42 (s, 3H, CH_3), 3.42 (s, 3H, N–CH_3), 3.63 (s, 3H, N–CH_3), 3.78 (s, 3H, OCH_3), 4.89 (s, 2H, OCH_2), 6.86–6.87 (m, 4H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz), δ_C = 12.6; 28.3; 29.7; 31.8; 55.7; 60.6; 76.7; 107.8; 114.9; 116.1; 129.7; 137.7; 151.4; 152.0; 153.3; 154.8; 159.5. HRMS calcd [M+Na] for $C_{17}H_{18}N_2O_5$ Na: 353.1113. Found: [M+Na]: 353.1113. Anal. Calcd for $C_{17}H_{18}N_2O_5$: C, 61.81; H, 5.49; N, 8.48. Found: C, 62.01; H, 5.37; N, 8.29.

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