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An Unusual Iodocyclization: An Efficient Synthesis of Pyrimidine-annelated Spiro-heterocycles

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A simple and efficient method for the synthesis of some hitherto unreported pyrimidine-annelated spiro-heterocycles via 5-*endo* mode iodocyclization has been described. The reaction is an example of iodocyclization of 1,5-enynes which proceeds in the absence of base and affords the products in excellent yields.

The synthesis of pyrimidine and its annelated-heterocycles has received much attention due to their wide spectrum of biological activities.[1,2] A number of pyrimidine and uracil-based molecules[3] such as 3′-azido-3′-deoxythiamidine (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 C-5 and C-6 positions of uracil leads to biologically interesting molecules.

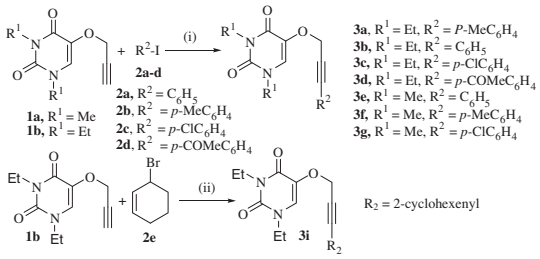
Iodocyclization of heteroatom-tethered alkynes is found to be an effective and high yielding method to prepare a large number of heterocyclic compounds,[5] for example quinolines,[6] isoquinolines,[7] benzothiophenes,[8] polycyclic aromatics,[9] indoles,[10] furopyridines,[11] isocoumarins,[12] and isochromens.[13] Iodonium-promoted heteroannulations are quite attractive because they offer an alternative protocol for the synthesis of complex molecules that are not easily available by the usually used organometallic reagents.

Earlier we have reported the synthesis of pyrimidine-annelated spiro-heterocycles using tin hydride-mediated radical cyclization,[14] however there are many drawbacks associated with such tin-based radical chemistry.[15] So there is always demand for new methodologies that provide easy access to the target compounds. In continuation of our research interest to the synthesis of potentially bioactive pyrimidine-annelated heterocycles,[16] we have undertaken a study on the reaction of 1,3-dimethyl-5-prop-2-ynyloxyuracil with molecular iodine. Herein we report our results.

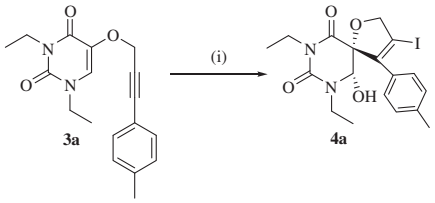
The precursors **3a**–**3g** and **3i** required for our present investigation were synthesized by the Sonogashira coupling of the substrates **1a** and **1b** with different aryl halide **2a**–**2e** using $[Pd(PPh_3)_2Cl_2]$ as catalyst, CuI as cocatalyst in anhydrous DMF containing Et_3N and stirring at the required temperature (Scheme 1).

We have initiated our investigation with the substrate **3a**. When **3a** was treated with 2 equiv of finely ground iodine powder in moist CH_3CN as solvent in the presence or absence of any base, it afforded a new compound in 87% yield (Scheme 2).

Initially the structure of the new compound **4a**[17] was characterized by the spectral and analytical data. IR spectroscopy indicated the presence of a hydroxy group at 3314 cm^{-1} which was confirmed by D_2O-exchange NMR spectroscopy. The exact structure of compound **4a** was established from its single-crystal XRD data[18] (Figure 1). From the X-ray analysis it is



Scheme 1. *Reagents and conditions*:[21] (i) $[Pd(PPh_3)_2Cl_2]$, CuI, anhydous DMF, Et_3N, rt, 1 h; (ii) $[Pd(PPh_3)_2Cl_2]$, CuI, anhydous DMF, Et_3N, 80 °C, 3 h.



Scheme 2. *Reagents and conditions*:[21] (i) I_2 (2 equiv), moist CH_3CN, 1.5 h.

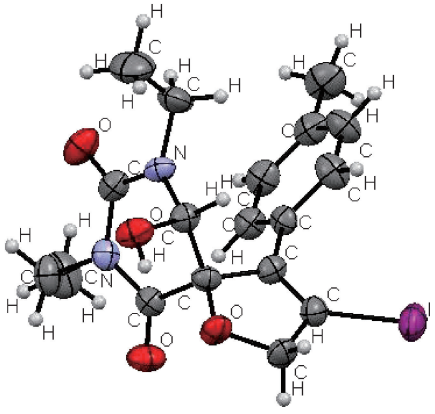


Figure 1. X-ray crystal structure of compound **4a**.

clear that compound **4a** is cis-substituted with respect to the ring substituents i.e., hydroxy (–OH) group and ether (–O–) linkage.

To achieve the optimized reaction conditions a series of experiments were conducted. Under a rigorously anhydrous solvent conditions (CH_3CN) the reaction rate was found to be quite slow and afforded poor yield of the cyclized product (35%) only after work up with water. But addition of water to the solvent i.e., a 1:1 mixture of CH_3CN–H_2O accelerated the reaction rate and completed the reaction within 40 min. So it is evident from the above experiment that water plays an important role in this reaction. Then we also performed the same reaction

Table 1. Optimization of iodine-mediated reaction[a]

Entry	I_2 /equiv	Base	Time /min	Solvent	Yield of **6a**/%[b]
1	**2**	**—**	**40**	**CH_3CN–H_2O (1:1)**	**87**
2	2	$NaHCO_3$	40	CH_3CN–H_2O (1:1)	86
3	2	—	45	DCM[c]–H_2O (1:1)	84
4	1	—	90	CH_3CN–H_2O (1:1)	80
5	2	K_2CO_3	40	CH_3CN–H_2O (1:1)	82
6	4	—	40	CH_3CN–H_2O (1:1)	85
7	2	—	120	Toluene–H_2O (1:1)	trace
8	2	—	120	THF–H_2O (1:1)	0

[a]All the reactions are carried out at room temparature. [b]Isolated yield of products. [c]Dichloromethane.

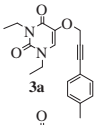
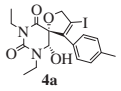
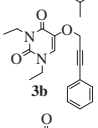
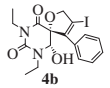
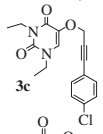
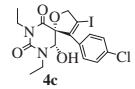
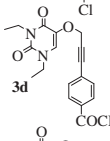
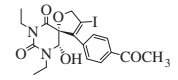
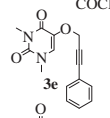
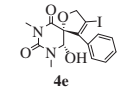
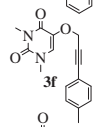
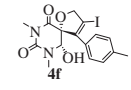
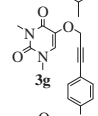
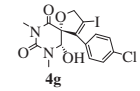
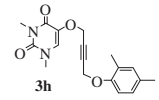
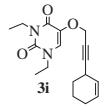
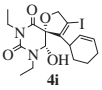
in other solvents among which only CH_2Cl_2–H_2O was found to be effective to give the product (Table 1, Entry 3). The addition of bases ($NaHCO_3$ and K_2CO_3) did not improve the yield of the product. We have also noticed the effect of the amount of molecular iodine in this reaction and interestingly we found that increasing the amount of iodine did not improve the yield of the product **4a** or accelerated the reaction rate. However, the reaction was found to be slow on decreasing the amount of iodine from 2 equiv to 1 equiv (Table 1, Entry 4). Therefore we have considered 2 equiv of iodine as the optimized amount for this reaction. Thus the optimal reaction conditions developed so far (from Table 1) include stirring of the substrate with 2 equiv of iodine in CH_3CN–H_2O (1:1) at room temperature for 40 min.

We have used this optimal reaction conditions (Table 1, Entry 1), to explore the scope and generality of the transformations with the substrates **3b**–**3i** and **1a** (Table 2). Under the above-optimized reaction conditions the substrates **3b**–**3g** afforded the desired cyclized products **4b**–**4g** in 45–86% yields. The substrate **3d** having a strong electron-withdrawing group in the *para*-position of the arene, afforded the product **4d** in relatively poor yield (45%). Moreover, the substrates **1a** and **3h**[16e] failed to give any cyclized product. But the substrate **3i** bearing an alkenyl substituent present on the alkyne terminal also gave the cyclized product **4i** in moderate yield (72%).

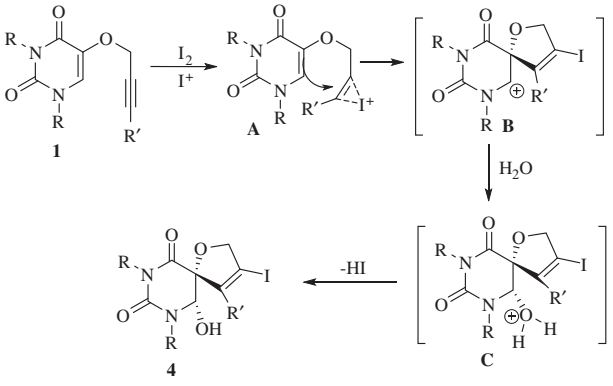
From the results shown in Table 2, it is observed that the reaction shows high diastereoselectivity to give one isomer exclusively. The reactions may proceed through the formation of iodonium intermediate (**A**). Intramolecular nucleophilic attack by the double bond of the pyrimidine ring to the activated triple bond by a 5-*endo dig* mode of cyclization leads to the formation of the intermediate **B**. Then H_2O may attack the carbocation from the opposite side of the substituent –R′ to avoid the steric crowding to form the intermediate **C**. The intermediate **C** finally affords the spiro-product. Thus diastereoselectivity of the reaction is controlled by steric factors. The failure of the substrates **1a** and **3h** to give spiro-heterocyclic products may be rationalized by the instability of the initially formed iodonium intermediate (**A**) by the coordination of the triple bond[6] of the acetylenic moiety with the iodine (Scheme 3). The yields of the spiro-proudct may also be rationalized by the nature of the group present on the alkyne terminal; a more electron-donating group which stabilized the iodonium intermediate (**A**) gave better yield than that of the electron-withdrawing substituent (–$COCH_3$).

Larock et al. reported[19] the synthesis of spiro[4,5]trienones by intramolecular *ipso*-halocyclization of 4-(*p*-methoxyaryl)-1-alkynes. Li et al. have also reported[20a] the synthesis of spiro-[4,5]trienyl acetates via an intramolecular electrophilic *ipso*-iodocyclization. Our findings are significant not only for the

Table 2. Summarized results of iodocyclization[21]

Entry	Substrate	Time/min	Product	Yield/%[a]
1	 **3a**	40	 **4a**	87
2	 **3b**	40	 **4b**	84
3	 **3c**	40	 **4c**	85
4	 **3d**	60	 **4d**	45
5	 **3e**	40	 **4e**	86
6	 **3f**	40	 **4f**	85
7	 **3g**	40	 **4g**	80
8	 **1a**	60	—	0
9	 **3h**	60	—	0
10	 **3i**	40	 **4i**	72

[a]Isolated yields.



Scheme 3. Plaussible mechanism for the synthesis of the spiro-heterocycles.

novel pyrimidine derivatives obtained, but more general as an example of an iodocyclization of hetero-1,5-enynes which are currently a topic of general interest. The 5-*endo* cyclizations of 1,5-enynes have been reported in some cases.[20] Although Larock et al. also reported the formation of the spiro-heterocyclic products, the substrates are limited by the presence of 4-methoxy substitutent without which the suggested mechanism would not operate. Moreover the products are spiroquinones with a five-membered heterocyclic ring.

In summary we have achieved the regioselective synthesis of some potentially bioactive pyrimidine-annelated spiro-heterocycles by the implementation of iodocyclization. The reaction conditions are very simple, cyclization proceeds under mild conditions in the presence of water without any base according to 5-*endo dig* cyclization and affords the products in good to excellent yields. It is also evident that water plays an important role in the reaction. Moreover, during the cyclization iodine atom is incorporated in the final compounds, which are attractive for further transformation to other substituted heterocyclic compounds. Further application of this methodology to the synthesis of other spiro-heterocyclic compounds is currently underway and will be reported in due course.

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17 ***General procedure for the synthesis of the compound 4a***: To a solution of the compound **3a** (200 mg, 0.64 mmol) in CH_3CN–H_2O (1:1) (5 mL), I_2 (325 mg, 1.28 mmol) was added. The reaction mixture was stirred at room temperature for 40 min. After completion of the reaction (monitored by TLC), the reaction mixture was diluted with CH_2Cl_2 (40 mL) and washed with 20 mL of satd. $Na_2S_2O_3$ (aq). The organic layer was separated and the aqueous layer was extracted with additional CH_2Cl_2 (25 mL). The combined organic layer was dried (Na_2SO_4) and filtered. The filtrate was concentrated and the crude product mass was purified by column chromatography over silica gel (60–120 mesh) using petroleum ether and ethyl acetate (4:1) as eluent to give the white solid product **4a**. Compound **4a**: Yield: 87%, solid; mp 120–122 °C; IR(KBr) ν_{max}: 1656, 1720, 3314 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ_H 7.14 (d, 2H, $J = 7.9$ Hz), 6.85 (d, 2H, $J = 8.0$ Hz), 5.1 (d, 1H, $J = 12.6$ Hz), 4.84 (d, 1H, $J = 12.6$ Hz), 4.77 (s, 1H), 3.87–3.75 (m, 2H), 3.24–3.18 (m, 1H), 3.05 (s, 1H), 3.04–2.98 (m, 1H), 2.34 (s, 3H), 1.15 (t, 3H, $J = 7.1$ Hz), 0.93 (t, 3H, $J = 7.2$ Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 12.3, 20.3, 28.6, 35.8, 42.3, 80.9, 81.5, 88.5, 93.7, 126.7, 128.1, 128.4, 138.1, 141.4, 149.7, 166.5. MS m/z: 457 [$M^+ + H$]. Anal. Calcd for $C_{18}H_{21}IN_2O_4$: C, 47.38; H, 4.64; N, 6.14%. Found: C, 47.64; H, 4.69; N, 6.42%.

18 CCDC reference No. for the CIF file of the compound **4a**: CCDC-798741. Copies of the data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif.

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