Facile Regioselective Synthesis of Functionalized Heterocycle-Tethered Spiro Compounds via an Intramolecular Electrophilic Ipso-Iodocyclization Process

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Abstract: A general, regioselective, and efficient intramolecular electrophilic ipso-iodocyclization of a series of *N*-alkyl-*N*-aryl phenylpropiolamides in the presence of I_2 (molecular iodine) and $NaHCO_3$ via 5-*endo*-dig mode of cyclization has been developed for the synthesis of hitherto unreported coumarin, quinolone, and pyrimidine-annelated heterocyclic compounds in excellent yields (84–92%). The development of this methodology provides efficient and mild reaction conditions that allow for easy isolation of products. The synthesized spiro derivatives offer an attractive and useful scope for further functionalization and to synthesize new bioactive heterocycles.

Key words: azaspiro heterocycle, electrophilic ipso-iodocyclization, coumarin, quinolone, uracil

Many natural and biologically active compounds contain ring systems connected with each other by a spiro carbon atom. Spirocyclic systems are of immense importance owing to their ubiquitous presence in several natural products. For example, all the alkaloids depicted in Figure 1 share an azaspirocyclic framework. Pinnaic acid, isolated from the Okinawan bivalic *Pinna muricata*, exhibits inhibitory activity against phospholipase A2.[1] Halichlorine, produced by the marine sponge *Halichondria okadai*, was found to inhibit the vascular cell adhesion molecule-1 (VCAM-1).[1,2] Cephalotaxine, the major alkaloid of *Cephalotaxus harringtonia* var. *drupacea*, and its esters (harringtonines) show high antileukaemic activity.[3]The selective construction of the spiro fragment presents a challenge for these unique alkaloids and various related products.[4]

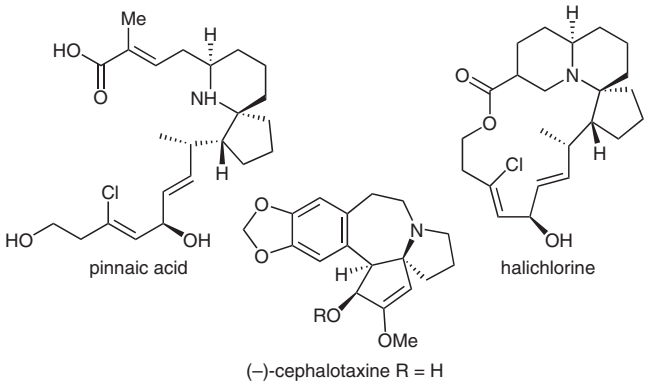

Figure 1

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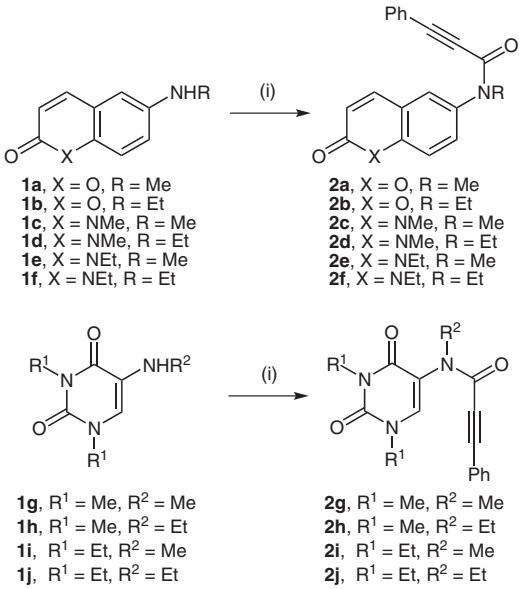
Intramolecular electrophilic iodocyclization of the aryl alkynes has recently emerged as an important area of interest in synthetic organic chemistry due to its widespread utility in the synthesis of carbocycles as well as heterocycles, natural and biologically active compounds.[5,6] Iodonium-promoted heteroannulations have drawn much attention because they offer an alternative protocol for the synthesis of complex molecules that are not easily accessible by the usual organometallic reagents. Currently, many such electrophilic cyclization strategies are carried out between alkyne and *o*-arene substitutions to construct several highly functionalized heterocycles as well as carbocycles.[5] Recently, another pathway involving an alkyne and an ipso-arene substitution to construct spirocycles[7] has been reported. However, the latter pathway has not yet been extensively investigated, only few reports appeared in the literature.[7] Literature search revealed that only few attempts have been made to synthesize spirocycles fused with potentially biologically active coumarin, quinolone, and pyrimidine systems. Applications of these substituted heterocycles are profound and spread in a wide range from pharmaceuticals and agrochemicals to electronics. Consequently, synthetic organic chemists are engaged in developing new strategies to meet the requirements of variously substituted heterocycles. Spirocyclic compounds are of considerable importance due to their ubiquitous presence in many natural products and pharmacologically active compounds.[8,9] Recent literature reveals renewed interest in terms of the synthesis of differently functionalized spirocyclic molecules implementing diverse approaches.[10] However, there are only few methods known to date that describe the synthesis of spiro-fused quinoline core.[11] Pyrimidine-annelated heterocycles have received much attention due to their wide spectrum of biological activities.[12,13] A number of pyrimidine- and uracil-based molecules,[14] such as 3′-azido-3′-deoxythiamidine (AZT), 2,3-dideoxycytidine (DDC), and (*E*)-5-[2-(bromovinyl)-2′-deoxyuridine (BVDU), are active against cancer and AIDS viruses[15] and have already been synthesized. The introduction of functionality at the C-5 and C-6 positions of uracil leads to biologically interesting molecules. Earlier we have reported the synthesis of pyrimidine-annelated spiro heterocycles using tinhydride-mediated radical cyclization,[16] however, there are many drawbacks associated with such tin-based radical chemistry.[17] Naturally, there is always a demand for new synthetic methodology that provides easy access to the target molecules. In continuation of our interest in the de-

velopment of general methods for the synthesis of pharmacologically important and potentially bioactive heterocyclic systems,[18] we have explored the feasibility of synthesizing the spiro-fused coumarins, quinolones, and pyrimidines via 5-*endo*-dig mode of electrophilic iodocyclization. Herein we report our results.

For the construction of practical building blocks for the synthesis of spiro compounds and for further development of our iodocyclization project, we have carried out the ipso-iodocyclization of aryl propiolamides **2**.[19] The precursors **2a–j** for the iodocyclization reaction were accessed from the corresponding amines **1a–j** by amidification reaction with phenylpropiolyl chloride (which was in turn prepared by refluxing phenylpropiolic acid with thionyl chloride) in the presence of a phase-transfer catalyst (TBAHS) and aqueous K_2CO_3 (Scheme 1).

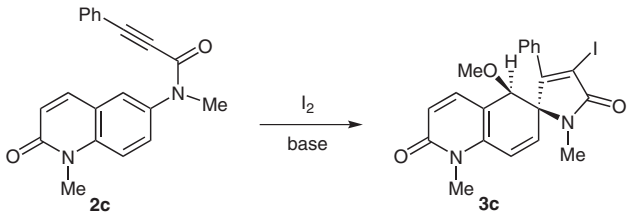


Scheme 1 *Reagents and conditions*: (i) phenylpropiolyl chloride (1.0 equiv), TBAHS, K_2CO_3, $CHCl_3$–H_2O, r.t., 12 h.

To standardize the reaction conditions for the synthesis of spiro heterocycles a series of experiments were performed with or without a base ($NaHCO_3$, K_2CO_3) and by varying the amounts of molecular iodine in different solvents such as MeCN, MeOH, and CH_2Cl_2. *N*-Methyl-*N*-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yl)-3-phenylpropiolamide (**2c**) was used as a model substrate for this purpose, and the results are summarized in Table 1.

To our delight, the reaction of the amide **2c** with I_2 (3 equiv) and $NaHCO_3$ (3 equiv) in MeCN–MeOH at room temperature for four hours proceeded selectively to afford the corresponding 4-iodo-5′-methoxy-1,1′-dimethyl-3-phenyl-1′*H*-spiro[pyrrole-2,6′-quinoline]-2′,5(1*H*,5′*H*)-dione (**3c**) in 92% yield (Table 1, entry 4). Solvents like CH_2Cl_2 and MeOH resulted in lower yield of the product. Reducing the amount of I_2 from three to 1.5 equivalents and one equivalent afforded the compound **3c** in 46% and 42% yields (Table 1, entries 1 and 2), respectively. In-

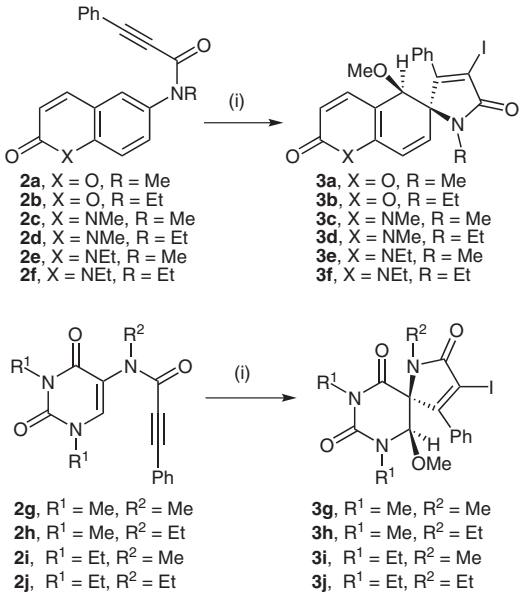
Table 1 Screening of Optimal Reaction Conditions



Entry	Solvent[a]	Base (equiv)	Iodinating agent (equiv)	Temp (°C)	Time (h)	Yield (%)[b]
1	MeCN	$NaHCO_3$ (3)	I_2 (1)	r.t.	4	42
2	MeCN	$NaHCO_3$ (3)	I_2 (1.5)	r.t.	4	46
3	MeCN	$NaHCO_3$ (3)	I_2 (3)	r.t.	8	88
4[c]	MeCN	$NaHCO_3$ (3)	I_2 (3)	r.t.	4	92
5	MeCN	$NaHCO_3$ (3)	I_2 (5)	r.t.	4	86
6	MeCN	$NaHCO_3$ (3)	I_2 (3)	60	3	80
7	MeCN	$NaHCO_3$ (3)	NIS (3)	r.t.	6	76
8	MeCN	–	I_2 (3)	r.t.	4	n.r.[d]
9	MeCN	K_2CO_3 (3)	I_2 (3)	r.t.	4	34
10	CH_2Cl_2	$NaHCO_3$ (3)	I_2 (3)	r.t.	4	39
11	MeOH	$NaHCO_3$ (3)	I_2 (3)	r.t.	4	42

[a] 1.5 equiv of MeOH was used in each case (entries 1–10).
[b] Isolated yield.
[c] Optimized reaction conditions.
[d] n.r. = no reaction.

creasing the amount of iodine from three equivalents to five equivalents did not improve the yield of the product. Increasing the reaction time from four hours to eight hours also did not improve the yield of the cyclized product. Subsequently, the temperature effect was investigated, and it turned out that the reactions at room temperature gave better results. Although the reaction rate was enhanced at 60 °C, the yield of the product decreased. We also used *N*-iodosuccinimide (NIS) as an iodinating agent in place of molecular iodine (Table 1, entry 7). However, the reaction required a longer reaction time (6 h), and also the yield of the reaction was relatively lower, 76% of the cyclized product **3c** was obtained from **2c**. The presence of a base proved to be important for the reaction, because the reaction does not occur without a base. The effect of K_2CO_3 as a base was also investigated. However, K_2CO_3 provided a much lower yield of the cyclized product **3c** than that when $NaHCO_3$ was used as base. Methanol plays a key role in the reaction. When the reaction was carried out under dry conditions, that is, using dry MeCN, without MeOH, we did not get the desired product. In the presence of a few drops of MeOH, the reaction occurs to afford the spiro product. Thus the optimized conditions for the reaction are three equivalents of I_2, three equivalents of $NaHCO_3$, MeCN–MeOH at room temperature. These conditions worked well for the synthesis of different spiro



Scheme 2 *Reagents and conditions*: (i) I_2 (3.0 equiv), $NaHCO_3$ (3.0 equiv), MeCN, MeOH (1.5 equiv).

heterocycles from the other substrates **2a**,**b**,**d**–**j** also (Scheme 2).

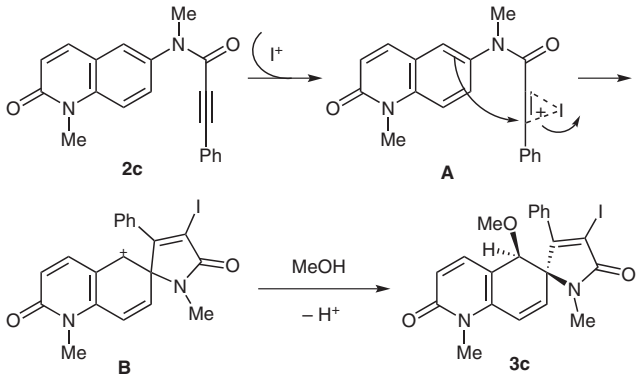
A variety of substrates were allowed to react with molecular iodine and sodium bicarbonate under the optimized reaction conditions to examine the scope of this intramolecular electrophilic ipso-iodocyclization process. The results are summarized in Table 2. Substrates having a quinolone moiety provided the best yields of the products in a reasonable reaction time than that of the corresponding coumarin-/uracil-containing substrates.

Table 2 Ipso-Iodocyclization of Amides **2a**–**j**[a]

Entry	Amide	Time (h)	Product	Yield (%)[b]
1	**2a**	4.8	**3a**	86
2	**2b**	5	**3b**	84
3	**2c**	4	**3c**	92
4	**2d**	4.6	**3d**	90
5	**2e**	4.2	**3e**	90
6	**2f**	4.4	**3f**	87
7	**2g**	4.8	**3g**	85
8	**2h**	5	**3h**	84
9	**2i**	5	**3i**	88
10	**2j**	5.1	**3j**	84

[a] Reaction conditions: I_2 (3 equiv), $NaHCO_3$ (3 equiv), MeCN, MeOH (1.5 equiv).
[b] Isolated yield.

On the basis of previous reports[5,6] a probable mechanism is outlined in Scheme 3. The formation of the spiro heterocycles **3**[20] from the substrates **2** may be explained by an initial interaction of electrophilic iodine with the alkyne residue **2** to give the iodonium intermediate **A**. This may undergo a nucleophilic attack of the aromatic π-electrons on the activated triple bond by a 5-*endo*-dig mode of cyclization triggering an intramolecular electrophilic ipso-cyclization of intermediate **A** to form the spirocyclic intermediate **B**. Finally, reaction of nucleophilic MeOH with the intermediate **B** may lead to the desired spiro compound **3**.



Scheme 3 A plausible reaction mechanism

The spectral and analytical data of the compound showed the formation of the product **3c**. We were able to obtain good-quality crystals by concentration of a dichloromethane–hexane solution with compound **3c**, and its structure has been assigned unambiguously by analysis of its single-crystal XRD data[21] (Figure 2). The X-ray crystal structure analysis of product **3c** shows clearly that the OMe group of the aromatic ring attached to the heterocycle and the amide nitrogen (–N–) are *cis* in nature with respect to each other.

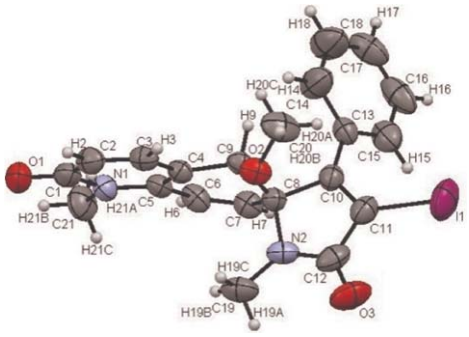


Figure 2 ORTEP diagram of compound **3c**

In the recent past Li et al.[22a,b] have published some results on the electrophilic ipso-iodocyclization of aryl alkynes. They have reported that the intramolecular ipso-iodocyclization of 4-(4-alkylaryl)alk-1-ynes with iodine monochloride or iodine proceeded smoothly, providing the corresponding 8-methylene-1-azaspiro[4.5]trienes. They applied[22c] the same electrophilic cyclization strategy for the synthesis of spiro[4.5]trienyl acetates from *para*-unactivated arylalkynes, including *N*-arylpropiolamides

and phenyl 3-phenylpropiolate in the presence of NIS and AcOH. An electrophilic ipso-cyclization involving an electrophile exchange process has also been developed[22d] in which a variety of *N*-(*p*-methoxyaryl)propiolamides and 4-methoxyphenyl 3-phenylpropiolate were cyclized in the presence of CuX (X = I, Br, SCN) and electrophilic fluoride reagents to selectively afford the corresponding spiro[4.5]decenones. In all of their reports they have only been able to isolate the product in moderate to good yields. Wada et al. reported[23] an efficient approach to the synthesis of azaspiro compounds having dissymmetric dienone cores by ipso-iodocyclization of ethoxyethyl ether to alkynes. They have constructed 1-aza-3-iodospiro[4.5]deca-3,7,9-trien-6-ones through the ipso-iodocyclization of ethoxyethyl ether to alkynes. Batra et al. have disclosed[24] a straightforward and general approach for the diastereoselective synthesis of spiro-fused (C-5)isoxazolino- or (C-3)pyrazolino-(C-3)quinolin-2-ones from the Baylis–Hillman adducts of 2-nitobenzaldehyde by sequential 1,3-dipolar cycloaddition and reductive cyclization. Larock et al. reported[25] the synthesis of spiro[4.5]trienones by intramolecular ipso-halocyclization reaction of 4-(*p*-methoxyaryl)-1-alkynes. We have been successful in designing our strategy in such a way that spiro[chromene-6,2′-pyrrole]-2,5′(1′*H*,5*H*)-dione, spiro[pyrrole-2,6′-quinoline]-2′,5(1*H*,5′*H*)-dione, and triazaspiro[4.5]dec-3-ene-2,6,8-trione derivatives were synthesized in excellent yields and within a reasonable time. Importantly, these spirocyclic compounds {specially spiro[4,5]decane skeleton} are a prevalent motif in many pharmacologically important compounds that widely occur in nature as well as they are often utilized as intermediates in organic synthesis.[26] Our findings are significant not only due to the novel heterocyclic 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 observed 5-*endo*-dig cyclization mode is rare[27] for such reactions where the 6-*endo*-dig mode seems to be more common.[28]

In summary, we have developed a general, mild, and efficient protocol for the intramolecular electrophilic ipso-iodocyclization of different *N*-aryl phenylpropiolamides to selectively synthesize spiro[chromene-6,2′-pyrrole], spiro[pyrrole-2,6′-quinoline], and triazaspiro[4.5]decene in excellent yields. As coumarin, quinolone, and uracil moieties are known to be of biological relevance, the synthesized azaspiro compounds tethered with those motifs are expected to be of biological relevance too. Moreover, an iodine atom present in the synthesized spiro derivatives offers an attractive and useful scope for further functionalization and, therefore, may be used for diversity-oriented synthesis of new bioactive heterocycles.

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(19) **General Procedure for the Synthesis of Phenyl Propiolamides 2a–j**

***N*-(1-Ethyl-2-oxo-1,2-dihydroquinolin-6-yl)-*N*-methyl-3-phenylpropiolamide (2e)**

A mixture of phenylpropiolic acid (500 mg, 3.42 mmol) and $SOCl_2$ was stirred at 100 °C for 1.5 h. After evaporation of the solvent, the residue was dissolved in CH_2Cl_2 (20 mL). A solution of amine **1e** (691 mg, 3.42 mmol) in CH_2Cl_2 (20 mL) and TBAHS (cat. amount) was added to the stirred solution of acid chloride. To this reaction mixture an aq solution of K_2CO_3 (930 mg, 6.84 mmol) was added slowly. After stirring for 6 h at r.t., the solution was washed with 5% HCl (2 × 20 mL) and then with 5% aq NaOH (2 × 20 mL). The organic layer was dried (Na_2SO_4), and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography over silica gel using EtOAc–PE (3:7) as an eluent to afford amide **2e**. Other compounds **2a–d**,**f–j** were also prepared accordingly.

White solid; mp 116–118 °C; yield 87%. IR (KBr): 2216, 1643, 1591 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.39 (t, 3 H, *J* = 7.2 Hz), 3.43 (s, 3 H), 4.36–4.43 (m, 2 H), 6.77 (d, 1 H, *J* = 9.2 Hz), 7.09 (d, 2 H, *J* = 7.2 Hz), 7.21 (t, 2 H, *J* = 7.6 Hz), 7.32 (t, 1 H, *J* = 7.2 Hz), 7.45 (d, 2 H, *J* = 8.4 Hz), 7.59 (s, 1 H), 7.68 (d, 1 H, *J* = 9.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.7, 154.3, 138.3, 138.2, 137.2, 132.3, 130.2,

129.7, 128.6, 128.4, 127.3, 123.0, 121.2, 120.1, 114.8, 91.4, 82.5, 37.6, 36.5, 12.7. HRMS (ESI$^+$): *m/z* [M + H$^+$] calcd for $C_{21}H_{18}N_2O_2$: 331.1441; found: 331.1440.

(20) **General Procedure for the Synthesis of Spiro Compounds 3a–j**
Procedure for the Synthesis of 1′-Ethyl-4-iodo-5′-methoxy-1-methyl-3-phenyl-1′*H*-spiro[pyrrole-2,6′-quinoline]-2′,5 (1*H*,5′*H*)-dione (3e)
Using the general procedure, compound **2e** (150 mg, 0.45 mmol), $NaHCO_3$ (115 mg, 1.36 mmol), and molecular I_2 (346 mg, 1.36 mmol) were added in MeCN (5 mL) containing MeOH (1.5 equiv) and stirred at r.t. for 4.2 h. Then the reaction mixture was quenched similarly with 10% $Na_2S_2O_3$ solution, extracted with CH_2Cl_2 (3 × 15 mL), washed with H_2O (2 × 10 mL) followed by brine (10 mL), and dried over anhyd Na_2SO_4. The solvent was removed to give a crude mass which was purified by column chromatography over silica gel (230–400 mesh) using EtOAc–PE (1:1) as eluent to furnish the desired product **3e**. Other compounds **3a–d**,**f–j** were also prepared accordingly. Yellow solid; mp 184–186 °C; yield: 90%. IR (KBr): 1695, 1652, 1621 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.28 (t, 3 H, *J* = 7.2 Hz), 2.91 (s, 3 H), 3.34 (s, 3 H), 4.13–4.19 (m, 2 H), 4.28 (s, 1 H), 6.01 (d, 1 H, *J* = 10.0 Hz), 6.45 (d, 1 H, *J* = 9.2 Hz), 6.92 (d, 1 H, *J* = 10.4 Hz), 7.22 (d, 1 H, *J* = 9.6 Hz), 7.37–7.42 (m, 5 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.0, 161.6, 161.4, 137.2, 136.6, 132.9, 130.4, 129.7, 128.7, 128.7, 123.5, 119.7, 114.0, 78.5, 72.4, 59.9, 38.3, 28.5, 14.5. HRMS (ESI$^+$): *m/z* [M + Na$^+$] calcd for $C_{22}H_{21}IN_2O_3$: 511.0489; found: 511.0441.

(21) CCDC-826706 contains the supplementary crystallographic data (for compound **3c**) 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.

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