Electrophilic Iodo-Mediated Cyclization in PEG under Microwave Irradiation: Easy Access to Highly Functionalized Furans and Pyrroles

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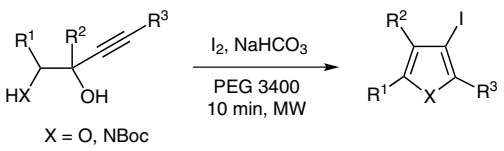
Abstract: The rapid and facile synthesis of highly substituted β-iodofurans and β-iodopyrroles is reported using a mixture of molecular iodine and a base in solid PEG 3400 as alternative, eco-friendly and nontoxic solvent under microwave irradiation, in a very short time. The heterocycles are efficiently recovered in good yields by a simple workup procedure, avoiding chromatographic purification.

Key words: iodocyclization, microwave, poly(ethylene glycol), furans, pyrroles

The insertion of iodine in a heterocyclic ring represents an important starting point for the construction of more functionalized systems. The utility of iodocyclization was demonstrated by several research groups and the large potential of this synthetic approach has been illustrated in the synthesis of carbocycles[1,2] or different halo-heterocyclic systems[3,4] such as furan derivatives,[5–10] isochroman-3-ones[11] and isochromenes,[12,13] prolines,[14] pyrroles,[15,16] isoxazoles,[17] indolizinones[18] and benzo[*b*]thiophene.[19]

The iodocyclization reaction of a series of 3-alkyne-1,2-diols and 3-hydroxy-2-sulfonylamino-4-alkynes leading to iodofurans or iodopyrroles, respectively, has been already described[20] using the non-eco-friendly acetonitrile as the reaction solvent.

For many years, our research group has been involved in the development of green methodologies in organic synthesis, devoted to eliminate the use of hazardous organic solvents. In this context, we have widely demonstrated that PEGs are effective as solvent for organic reactions.[21–25] In this report, we present the unprecedented use of solid PEG 3400 in the electrophilic iodo-mediated cyclization reaction of diols or N-protected 1,2-amino alcohols under microwave irradiation (Scheme 1).



Scheme 1 Iodocyclization in solid PEG 3400

In the course of this reaction, the carbon–carbon triple bond of the substrate is activated by the electrophilic halogenating reagent (I^+), then undergoes a *5-endo-dig* intramolecular cyclization triggered by the O- or N-nucleophile present in the molecule to afford β-iodofurans or β-iodopyrroles, respectively, in basic medium.

In order to compare our procedure with those previously reported,[10] we tested the iodocyclization of 1,2-amino alcohol derivative **1a** in the presence of an equimolar mixture of molecular iodine I_2 and $NaHCO_3$ (1:1, 3 equiv), replacing acetonitrile by 300 mg of PEG 3400.[26] The mixture was heated to 50 °C under microwave activation for 15 minutes. At this point, the analysis of the crude reaction mixture showed the complete conversion of the starting material. The crude was diluted in a small amount of CH_2Cl_2, precipitated in Et_2O and filtered, leading to an organic phase which was washed with a saturated solution of sodium thiosulfate ($Na_2S_2O_3$) to neutralize the excess of iodine. The corresponding highly substituted pyrrole **2a** was obtained in 44% yield as a pure compound, by simple evaporation (Table 1, entry 1), confirming our initial hypothesis. In the search for more effective conditions, the reaction time was reduced to ten minutes. However the yield was not improved (42%, Table 1, entry 2). We tried to perform the reaction in ten minutes in more diluted conditions by increasing the quantity of PEG 3400 (350 mg) and reducing the amount of I_2 and $NaHCO_3$ to two equivalents (Table 1, entry 3). Those conditions were the best ones and the expected product was obtained in 81% yield.[26] However, if the reaction was stopped after five minutes (Table 1, entry 4), the yield decreased to 69%. The reaction outcome was also studied using one equivalent of 1:1 molar ratio of I_2/base, but the conversion of the substrate was not complete and the yield of **2a** was low (Table 1, entry 5). The conversion was also incomplete when the reaction was carried out, unoptimized, on a larger scale.

In all cases, only the formation of the expected product **2a** was detected. Encouraged by these results, the method was extended to other substrates such as β-amino alcohol **1b** and 1,2-diols **1c**–**f** (Table 2) bearing aromatic or aliphatic substituents on the triple bond. In all cases, the conversion of the substrate was complete leading to original tri- or tetrasubstituted iodinated pyrroles or furans **2b**–**f** in

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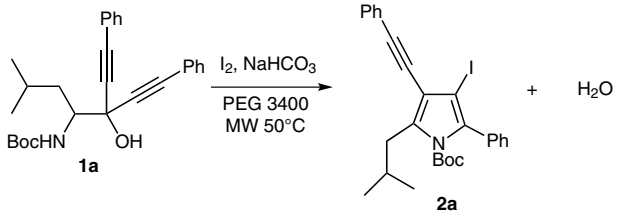
Table 1 Screening of the Parameters for Iodocyclization in PEG



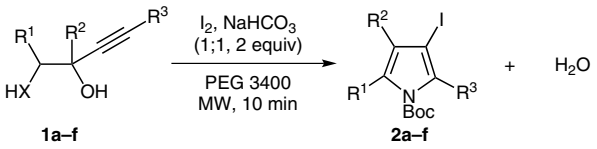
Entry	I_2 (equiv)	$NaHCO_3$ (equiv)	Time (min)	Yield (%)[a]
1	3	3	15	44
2	3	3	10	42
3	2	2	10	81
4	2	2	5	69
5	1	1	10	36 (73)[b]

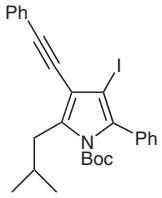
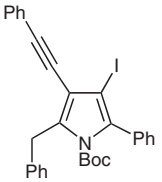
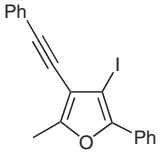
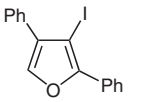
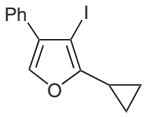
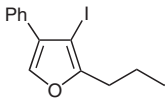
[a] Yields and conversions were calculated by ^{1}H NMR using CH_2Br_2 as an internal standard;
[b] In parenthesis residual quantity of substrate **1a** is given, determined by HPLC.

good to satisfying yields in only ten minutes (Table 2). β-Iodopyrroles[16] were previously synthesized using a related reaction in conventional solvents (acetonitrile or dichloromethane) but this approach required a two-step procedure, involving the formation of an hydroxydihydropyrrole intermediate and requiring the use of MsCl in the presence of Et_3N to promote the final dehydration reaction. These reactions were performed at room temperature requiring long reaction time (2–16 h) while the reactions were shorter for β-iodofurans (3 h).[10,11] Moreover, a chromatographic purification was always necessary. In comparison with the literature data, our method is powerful not only because of the use of an eco-friendly solvent such as PEG, but also for the shorter reaction times (only ten minutes) under microwave irradiation and in the case of pyrrole, for a more straightforward route.

On one hand, the nitrogen reactivity for the formation of the tetrasubstituted β-iodopyrroles is probably modulated by the nature of the α-substitution (Table 2, entries 1 and 2); on the other hand the *5-endo-dig* cyclization leading to the formation of β-iodofurans seems to be mostly influenced by the nature of the substituent on the triple bond undergoing the nucleophilic attack. Probably, the steric hindrance and/or the electronic effects are responsible for the different yields obtained in the series of trisubstituted β-iodofurans (entries 4–6, Table 2). These experimental observations were confirmed by an unexpected result during the iodocyclization of N-protected amino alcohol **1g**, bearing a butyl chain on the triple bond (Table 3). To our surprise, the *5-endo-dig* iodocyclization afforded a mixture of two different products identified respectively as the expected iodocyclized tetrasubstituted β-iodopyrrole **2g** and one of its derivative **3g**, in which the second triple bond was diiodinated. This result can be explained by the presence of the electron-donating butyl group on the triple

Table 2 Synthesis of Iodinated Furans and Pyrroles in PEG 3400 under MW Irradiation



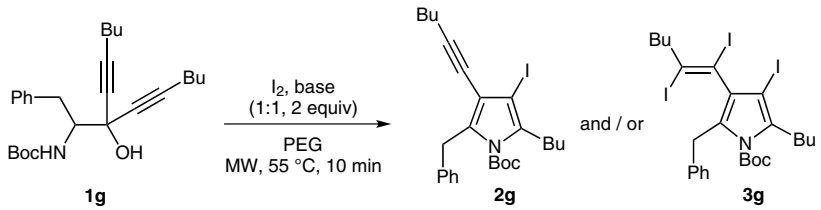
Entry	Product		Temp (°C)	Yield (%)[a]
1	**2a**		50	81
2	**2b**		55	67
3	**2c**		50	66
4	**2d**		55	63
5	**2e**		55	37
6	**2f**		50	42

[a] Yields were calculated by ^{1}H NMR using CH_2Br_2 as an internal standard.

bond which is not involved in the *5-endo-dig* cyclization, bringing an increased nucleophilicity of the alkyne moiety. In this perspective, the excess of electrophilic iodine would favor this side reaction, not observed in the case of the other substrates tested during this study, bearing a conjugated phenyl group on the triple bond. Similar observations were described in previous reports, showing that both halogen atoms generated from electrophiles could be effectively used.[27–29] Double addition of iodine has been observed in the presence of molecular iodine, while iodohalogenation was observed with iodine monochloride or monobromide.[27]

Then we explored the possibility to direct the course of the reaction towards the formation of only one of the two

Table 3 Iodocyclization of **1g**



1g **2g** **3g**

Entry	PEG	Base	Temp (°C)	Yield (%)[a] of **2g**	Yield (%)[a] of **3g**
1	PEG 3400	$NaHCO_3$	50	50	39
2	PEG 2000-$(OMe)_2$	$NaHCO_3$	55	18	42
3	PEG 3400	K_2CO_3	55	45	0
4	PEG 3400	–	55	0	71

[a] Yields were calculated by ^1H NMR using CH_2Br_2 as an internal standard. All the reactions were carried out using 350 mg of PEG 3400.

products **2g** and **3g**, by modulating the reaction conditions. Selected data are reported in Table 3.

The reaction was carried out using always two equivalents of molecular iodine, with or without a base, in different PEGs, under microwave activation with an initial power of 400 W. When an equimolar quantity of $I_2/NaHCO_3$ was used, the selectivity of the reaction was governed by the nature of PEG. In PEG 3400, the global yield of **2g**/**3g** was 89%, with a preference for the monoiodinated pyrrole **2g** (Table 3, entry 1), while in PEG 2000-$(OMe)_2$, even if the global yield was slightly lower (70%), the reaction proceeded preferentially towards the formation of triiodinated pyrrole **3g** (Table 3, entry 2). However, in PEG 3400 the nature of the base played an important role: monoiodinated **2g** was formed as the only product when I_2/K_2CO_3 (1:1, 2 equiv) was used and no traces of **3g** could be detected (Table 3, entry 3). The selectivity was completely reversed when the reaction was carried out in PEG 3400 in the absence of base, affording **3g** in good yield as the only product (71%, Table 3, entry 4). This represents the first example of iodocyclization in which a triiodinated pyrrole was obtained efficiently.[30]

In conclusion, the results reported herein demonstrate again the importance of PEG as a practical, alternative, cheap and eco-friendly solvent for organic synthesis. We are also delighted to present the first examples of iodocyclization reaction of alkynyl diols or *N*-Boc alkynyl amino alcohols using PEG as solvent under microwave irradiation.

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(26) **Typical Experimental Procedure**: A mixture of I_2 (25 mg, 0.1 mmol), $NaHCO_3$ (0.1 mmol), PEG 3400 (350 mg) and substrate **1a** (0.05 mmol) was reacted under microwave irradiation at 50 °C (initial power 400 W) for 10 min. The reaction mixture was diluted with CH_2Cl_2 (2.0 mL),

precipitated in Et_2O (250 mL), cooled for 3 h at –18 °C to improve PEG precipitation and filtered. The organic phase was washed with a saturated solution of sodium thiosulfate ($Na_2S_2O_3$) to neutralize the excess of iodine. Compound **2a** was recovered as a yellow oil in 81% yield. Spectral data for **2a**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.55–7.58 (m, 2 H), 7.31–7.43 (m, 8 H), 3.00 (d, *J* = 7.1 Hz, 2 H), 2.03 (m, 1 H), 1.18 (s, 9 H), 1.04 (d, *J* = 6.6 Hz, 3 H), 1.02 (d, *J* = 6.6 Hz, 3 H). ^{13}C NMR (300 MHz, $CDCl_3$): δ = 148.6, 140.3, 134.8, 134.3, 128.26, 127.8, 123.8, 112.7, 93.6, 84.5, 84.4, 75.1, 36.3, 29.7, 27.0, 22.6. HMRS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{27}H_{29}NO_2I$: 526.1243; found: 526.1245.

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(30) Spectral data for **2g**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.93 (t, *J* = 7.2 Hz, 3 H), 0.94 (t, *J* = 7.2 Hz, 3 H), 1.33 (s, 9 H), 1.38–1.61 (m, 8 H), 2.43 (t, *J* = 7.2 Hz, 2 H), 2.87 (dd, 2 H), 4.37 (s, 2 H), 7.07–7.14 (m, 2 H), 7.16–7.25 (m, 3 H). ^{13}C NMR (300 MHz, $CDCl_3$): δ = 148.6, 139.8, 136.3, 136.0, 128.2, 128.0, 125.9, 113.6, 94.5, 84.6, 74.6, 74.5, 33.7, 31.2, 31.0, 29.3, 27.4, 22.5, 22.0, 19.3, 14.0, 13.6. ESI–MS (+): *m*/*z* = 520.1 $[M + H]^+$, 464.0 $[M + H - t\text{-Bu}]^+$, 419.9 $[M + 2 H - Boc]^+$.
Spectral data for **3g**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.95 (t, *J* = 7.2 Hz, 3 H), 0.98 (t, *J* = 7.3 Hz, 3 H), 1.26 (s, 9 H), 1.40–1.51 (m, 8 H), 2.69–2.76 (m, 1 H), 2.82–2.92 (m, 3 H), 4.14 (s, 2 H), 7.10–7.17 (m, 3 H), 7.22–7.26 (m, 2 H). ^{13}C NMR (300 MHz, $CDCl_3$): δ = 148.7, 138.7, 136.8, 134.1, 129.4, 128.3, 128.2, 125.9, 111.1, 89.5, 84.7, 71.3, 49.7, 33.5, 32.0, 30.6, 29.1, 27.2, 22.5, 21.7, 14.1.

