Reevaluation of Benzyltrimethylammonium Dichloroiodide, Previously Reported to be a Selective Iodinating Agent

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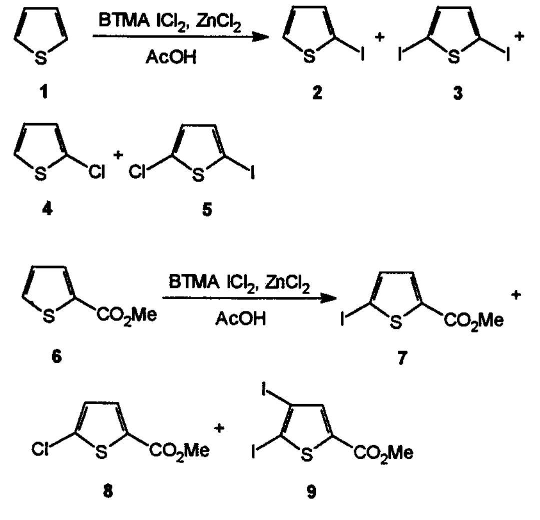
Benzyltrimethylammonium dichloroiodate, previously reported as an iodinating agent of thiophenes, appears to be a selective chlorinating agent of both thienyl and furyl derivatives containing a carbonyl group.

Benzyltrimethylammonium dichloroiodate (BTMA ICl_2) has been reported as an efficient iodinating agent of thiophene derivatives in the presence of zinc chloride.[1] In the past we have used iodothiophene and iodofuran derivatives as starting materials in various photochemical reactions.[2] We are interested in the development of new synthetic strategies for the synthesis of these starting materials, e.g. 5-iodofuran-2-carbaldehyde or 5-iodothiophene-2-carbaldehyde, since their preparations are very tedious.[3-8]

In the aforementioned paper[1] the effective iodinating agent was $[PhCH_2(CH_3)_3N]^+[ZnCl_4]^{2-}\ I^+$, formed by complexation between BTMA ICl_2 and zinc chloride.

In this paper we want to report our results obtained using BTMA ICl_2 as an iodinating agent for thiophene-2-carbaldehyde, 2-acetylthiophene, methyl 2-thiophenecarboxylate, furan 2-carbaldehyde, and 2-acetylfuran.

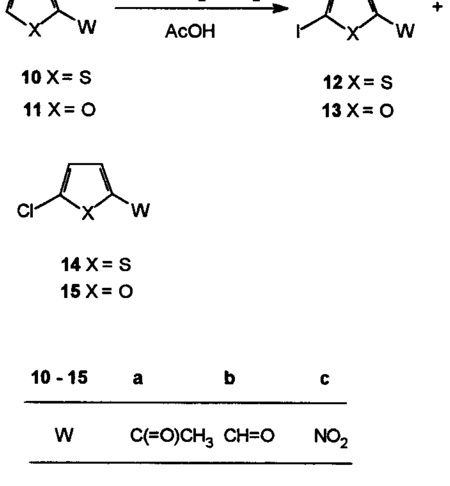
Initially, attempts were made to reproduce reported reactions. The reaction of thiophene with BTMA $ICl_2/ZnCl_2$ reagent was repeated as described in reference 1. The authors reported that 2,5-diiodothiophene (**3**) was obtained in 41 % yield as the sole product when excess (3 equivalents) reagent was used at 70 °C for 24 hours. In our hands, the reagent worked as an iodinating agent, but a complex mixture of products were obtained (GC–MS) (Scheme 1).



Scheme 1

We obtained a mixture of 2-iodothiophene (**2**), 2,5-diiodothiophene (**3**), 2-chlorothiophene (**4**), and 2-chloro-5-iodothiophene (**5**) in a 5.3 : 3.5 : 1.1 : 1 ratio. Methyl 2-thiophenecarboxylate (**6**) gave a mixture of three products in 80 % yield, the methyl 5-iodo-2-thiophenecarboxylate (**7**) being obtained in 40 % yield, the corresponding 5-chloro derivative **8** in 27 % yield and the expected 4,5-diiodo derivative **9** (the main product as reported in reference 1) in only 13 % yield. In conclusion we were unable to reproduce the previously reported results.[1]

We then used this reagent on other substrates in order to test its halogenation properties. 2-Nitrothiophene (**10c**) as starting material (Scheme 2, Table), surprisingly, gave no reaction and compound **10c** was recovered at the end of the reaction. Using 2-acetylthiophene (**10a**) as starting material, and carrying out the reaction using 1 equivalent of BTMA ICl_2 to the substrate (Table, entry 2), we obtained a 2:1 mixture of two products which were 5-chloro-2-acetylthiophene (**14a**) and the corresponding 5-iodo derivative **12a**, respectively.



Scheme 2

In an attempt to increase the formation of the iodothienyl derivative we increased the number of equivalents of BTMA $ICl_2/ZnCl_2$ to 3 (Table, entry 3). A 10 : 1 mixture of **14a** and **12a** was obtained; this method therefore represents a useful synthetic method for the preparation of 5-chloro-2-acetylthiophene. When thiophene-2-carbaldehyde (**10b**) was used as a starting material the reaction showed different behaviour compared with that shown by **10a**. Using a three-fold excess of the BTMA $ICl_2/ZnCl_2$ reagent gave a 1.4 : 1 mixture of 5-iodo- (**12b**) and 5-chlorothiophene-2-carbaldehyde (**14b**) (Table, entry 4). In this case, the reaction did not show the same behaviour as reported for **10a**: with 2-acetylthiophene the reagent was shown to be a selective chlorinating agent,

Table.

Entry	Starting material	Reaction conditions[a]	Product	Yield (%)[b]	Mp (°C) or bp (°C)/Torr Found	Reported	MS [*m/z* (%)]
1	**10c**	A	–	–	–		
2	**10a**	A	**14a**	47	49–51	52[10]	160 (159.97)
			12a	22	128–129	129[7]	252 (251.91)
3	**10a**	B	**14a**	69			
			12a	7			
4	**10b**	B	**12b**	44	47–49	49[11]	238 (237.89)
			14b	31	51–53/0.5	52–53/0.5[12]	146 (145.96)
5	**10b**	C	**12b**	50			
			14b	25			
6	**10b**	D	**12b**	40			
			14b	30			
7	**6**	B	**7**	40	88–89	88–89[13]	268 (267.91)
			8	27	116–117/30	145–147/95[14]	176 (175.97)
			9	13	100–102		394 (393.80)
8	**6**	C	**7**	65			
			9	22			
9	**11a**	C	**15a**	50	78–79	79[8]	144 (144.00)
			13a	1	85–86	85–86[8]	236 (235.93)
10	**11b**	C	**15b**	34	33–34	34–35[15]	130 (129.98)
			13b	10	127–128	127.5–128[4]	222 (221.92)

[a] A: BTMA $ICl_2/ZnCl_2$/substrate 1 : 1 : 1, 70 °C, 24 h; B: BTMA $ICl_2/ZnCl_2$/substrate 3 : 3 : 1, 70 °C, 24 h; C: BTMA $ICl_2/ZnCl_2$/substrate 3 : 3 : 1, prereaction between BTMA ICl_2 and $ZnCl_2$ (r.t., 1 h), 70 °C, 24 h; D: BTMA $ICl_2/ZnCl_2$/substrate 3 : 3 : 1, prereaction between BTMA ICl_2 and $ZnCl_2$ (r.t., 6 h), 70 °C, 24 h.

[b] All the yields refer to isolated products.

while with thiophene-2-carbaldehyde no selectivity was shown. We observed only a low preference towards the formation of the iodothienyl derivative. It is noteworthy that it is an inverse prefence to that shown using **10a**.

In an attempt to increase selectivity the experimental procedure was modified. As reported above, the iodinating agent was formed by complexation of BTMA ICl_2 and zinc chloride. In order to favour this reaction, the substrate was introduced to the reaction mixture after one hour, and during this period BTMA ICl_2 and zinc chloride were stirred in acetic acid at room temperature. An increased selectivity was found (Table, entry 5), giving a 2 : 1 mixture of **12b** : **14b**. To test this behaviour, stirring of BTMA ICl_2 and zinc chloride in acetic acid was maintained for six hours before the addition of **10b**. In this case (Table, entry 6), the same result was obtained as for entry 4, where no prereaction of the reagents was carried out.

We have shown that methyl 2-thiophenecarboxylate, in the presence of excess BTMA $ICl_2/ZnCl_2$, gave a mixture of **7**, **8**, and **9**. The use of this substrate with prereacted BTMA ICl_2 and zinc chloride confirmed the iodinating character of this reagent (Table, entry 8). In this case, we obtained methyl 5-iodo-2-thiophenecarboxylate (65 %) and the 4,5-diiodothienyl derivative (22 %).

We then tested the usefulness of this type of reagent as a halogenating agent for furans (Scheme 2). The reaction using 2-acetylfuran (**11a**) (Table, entry 9) was performed using three times excess of BTMA ICl_2 with prereaction of the reagents for one hour. Under these conditions we obtained primarily 5-chloro-2-acetylfuran (**15a**) and 1 % of the 5-iodo derivative. The use of furan-2-carbaldehyde as starting material showed the same characteristics found with the corresponding thiophene derivative. In this case, we also observed a lower selectivity in the halogenation reaction than with 2-acetylfuran (Table, entry 10), the chloro-substituted derivative **15b** being the main product of the reaction.

In conclusion, the BTMA $ICl_2/ZnCl_2$ complex obtained from BTMA ICl_2 and zinc chloride was shown to be a good chlorinating agent with thienyl ketones and furan derivatives bearing a carbonyl group, and an iodinating agent with methyl 2-thiophenecarboxylate and with thiophene-2-carbaldehyde; this was not the selectivity reported in previous work in this field.[1] These results are, therefore, in sharp contrast with previous reported results, in particular with the formation of the $[PhCH_2(CH_3)_3N]^+[ZnCl_4]^{2-}$ I^+ reagent in the reaction mixture. The reaction seems to be very sensitive to the nature of the substrate and we could not find any element to rationalise this behaviour.

Finally, it is noteworthy that, in spite of the presence of electron-withdrawing groups on the molecule which usually gave 4,5-disubstituted products,[9] the BTMA $ICl_2/ZnCl_2$ reagent seems to be very mild and selective, giving only 5-substituted products.

General Procedure Without Prereaction; Procedure B:

BTMA ICl_2 (30 mmol) and $ZnCl_2$ (30 mmol) were added to a solution of the substrate (10 mmol) dissolved in AcOH (30 mL). The mixture was stirred at 70 °C for 24 h, then diluted with Et_2O (100 mL) and washed with 0.1 N $Na_2S_2O_3$ (50 mL), with 0.1 N $NaHCO_3$ (20 mL), and with brine (20 mL). The organic phase was dried (Na_2SO_4). Removal of the solvent yielded a crude product which was purified by column chromatography or vacuum distillation.

General Procedure With Prereaction; Procedure C:

BTMA ICl_2 (30 mmol) and $ZnCl_2$ (30 mmol) were dissolved in AcOH (30 mL) and stirred at r.t. After 1 h the substrate (10 mmol), in a small volume of AcOH (ca. 5 mL) was added. The mixture was stirred at 70 °C for 24 h, and the mixture was diluted with Et_2O (100 mL) and washed with 0.1 N $Na_2S_2O_3$ (50 mL), with 0.1 N $NaHCO_3$ (20 mL), and then with brine (20 mL). The organic phase was dried (Na_2SO_4). Removal of the solvent yielded a crude product which was purified by column chromatography or vacuum distillation.

Methyl 4,5-diiodothiophene-2-carboxylate:

mp 100–102 °C.

^1H NMR ($CDCl_3$): $\delta = 7.79$ (s, 1 H), 4.01 (s, 3 H).

MS: $m/z = 394$ (M^+).

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