Unexpected α-Chlorination of Tertiary Enaminones using Benzyltrimethylammonium Dichloroiodate

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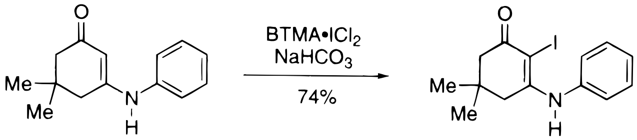
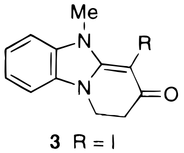
Benzyltrimethylammonium dichloroiodate (BTMA·ICl_2) has been reported by Matsuo and co-workers to be an efficient α-iodinating agent for enaminones.[1] For example, compound **1** gave a 74% yield of iodo enaminone **2** upon treatment with BTMA·ICl_2 (1 mol equiv) and $NaHCO_3$ in a 3:2 mixture of CH_2Cl_2 and MeOH.[1] In all, six examples of α-iodination of enaminones in good yield were reported using BTMA·ICl_2;[1] however, all of these cases involved secondary enaminones [i.e., N(R)H nitrogen substitution]. We report here that reaction of BTMA·ICl_2 with tertiary enaminones [N(R)R′ substitution] results exclusively in α-chlorination, possibly due to steric factors that influence the reaction course.

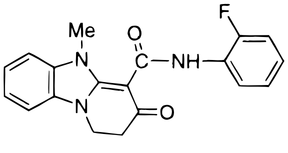


1 **2**

We required iodo enaminone **3** as a synthetic intermediate for the preparation of derivatives related to a CNS-active chemical series including **4**, a compound with a 0.26 nM IC_{50} for binding to the benzodiazepine site on $GABA_A$ receptors.[2] There are only a few reports describing iodo enaminone formation in the literature.[1,3,4] Reaction of **5** with BTMA·ICl_2 under the Matsuo conditions[1] resulted in the formation of α-chloro derivative **6** (80%), without *any* of expected iodo compound **3** being detected. Treatment of **5** with iodine and pyridinium dichromate,[5] and with iodine in pyridine,[6] resulted in a large number of diverse products (TLC analysis).



3 R = I
5 R = H
6 R = Cl



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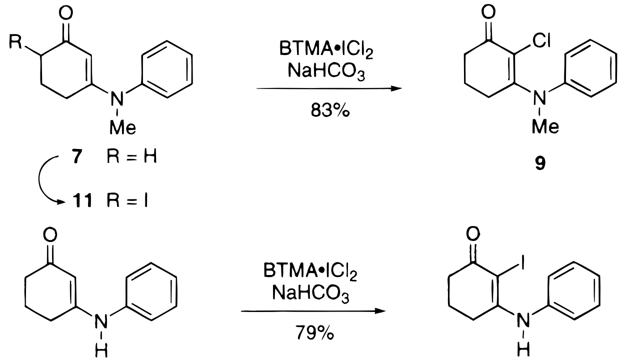
These unanticipated results prompted us to synthesize model enaminones **7** and **8**, prepared by reaction of 1,3-cyclohexanedione with *N*-methylaniline and aniline, respectively,[7] and then to examine their reaction with BTMA·ICl_2. Treatment of **7** with BTMA·ICl_2 cleanly afforded *exclusively* α-chloro enaminone **9** (83% yield), with none of the corresponding iodo derivative being observed (NMR, MS). Alternatively, secondary enaminone **8** produced ≥99% α-iodo enaminone **10** (79% yield), in keeping with the original Matsuo work.[1] Reaction of **7** with iodine in $CHCl_3$[3,4] afforded primarily iodination on the methylene adjacent to the carbonyl to give **11**.



9 **8** **10**

Additional experiments involving **7** in reaction with iodine and K_2CO_3, and *N*-iodosuccinimide in $CHCl_3$, resulted in polyiodination. These results highlight the mild and selective nature of the reaction of BTMA·ICl_2 for halogenation of enaminones and the remarkable chemical selectivity possible (chloro vs iodo) depending on the nature of the substrate. Recently, D'Auria and Mauriello reported that the complex between BTMA·ICl_2 and $ZnCl_2$ is a good chlorinating reagent for thiophenes and furans bearing a carbonyl group but serves as an iodinating reagent with other thienyl substrates, again pointing out the dual halogenating nature of BTMA·ICl_2.[8]

It has been postulated that the reactive iodinating species when using BTMA·ICl_2 in MeOH is methyl hypoiodate (MeOI).[9] In the case where chlorination competes with iodination, it is possible that an equilibrium between MeOH, BTMA·ICl_2, MeOI, and methyl hypochoridate (MeOCl) is a key feature of the reaction course. Therefore, we sought to shift this equilibrium deliberately to MeOCl by the addition of a large excess of chloride ion and see whether we could effect chlorination in a reaction for which only iodination had been observed previously. Benzyltriethylammonium chloride (10 mol equiv) was mixed with BTMA·ICl_2 and $NaHCO_3$ for 2 min prior to the introduction of **8**. In this experiment, **10** was produced as the major product with ca. 5% of the corresponding chloroenaminone formed as well. When the premixing time was increased to 1 h, ca. 20% of the chloro derivative was observed, demonstrating that the added chloride was able to enter the reaction manifold.

Another possible explanation is that secondary enaminones might undergo initial *N*-halogenation (chloro or iodo) followed by S_N2' displacement by iodide ion, which would be more nucleophilic than chloride ion. However,

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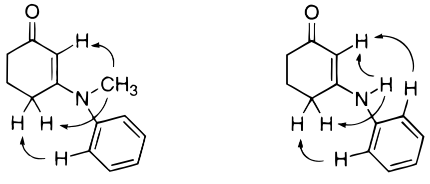

7 8

Figure 1. Observed NOE's for compounds **7** and **8**.

experiments in which we added a large excess of chloride ion (see above) argue against this proposal as only 20% of the corresponding chloro derivative was formed, whereas a larger effect would be expected if halide ion displacement was a distinct chemical step.

Yamada and co-workers have calculated the relative energetics of enaminone conformations using MINDO/2.[10] Their evaluation of **7** suggests that the *N*-methyl substituent prefers a perpendicular orientation relative to the cyclohexene ring, with a barrier to rotation of 2.1 kcal/mol. We performed NOE experiments on **7** and **8** in order to determine if there was a conformational difference between the two in solution, which could account for their divergent reactivity with BTMA·ICl_2. Secondary enaminone **8** exhibits an NOE ($CDCl_3$, ambient temperature) of the ortho protons of the phenyl ring and N*H* with both the enaminone vinyl and C-4 methylene protons (Figure 1). In contrast, **7** displayed an NOE interaction between NCH_3 and both the enaminone vinyl and C-4 methylene protons, but the ortho phenyl protons only demonstrated an NOE effect with the C-4 methylene. Thus, the phenyl group in **7** is positioned primarily away from the vinyl proton, perhaps in a gearing conformation in which the NMe is perpendicular to the cyclohexene ring, consistent with the MINDO/2 calculations. The NMe substituent of **7** is then able to interfere to a greater extent with the approach of an incoming electrophile, when compared with the corresponding NH in **8**. It is possible that this greater steric interference in the transition state for electrophilic addition to tertiary enaminone **7** is a reason why the smaller, less-reactive chlorine electrophile adds selectively.

The reaction of secondary enaminone **8** with BTMA·ICl_2 yields exclusively α-iodo enaminone **10**, consistent with earlier work.[1] Unexpectedly, however, treatment of tertiary enaminones **5** and **7** with BTMA·ICl_2 gave α-*chlorination* only. The versatility of BTMA·ICl_2 may enable it to be used more broadly in synthesis than originally expected.

Experimental Section

General Procedures. The ^{1}H-NMR spectra were recorded on either a 300 or 400 MHz spectrometer. Elemental analyses were conducted by Robertson Microlit Laboratories, Inc., Madison, NJ. Melting points were determined in open capillary tubes and are uncorrected. Chemical ionization mass spectra were recorded with ammonia as the reagent gas. The high-resolution mass spectral (HRMS) value was determined on a magnetic sector mass spectrometer, was referenced to poly(ethylene glycol), and is reported as ± one standard deviation. Most reagents and solvents were purchased and used without further purification.[10]

General Procedure for Halogenation with BTMA·ICl_2. To a solution of enaminone (1 mmol) in 2:1 CH_2Cl_2:MeOH (12 mL) at ambient temperature was added BTMA·ICl_2 (1 mmol) followed by $NaHCO_3$ (7 mmol). The resultant brown solution was allowed to stir for 30 min. The solid was filtered via vacuum filtration through a scintered glass funnel and the filtrate concentrated. The residue was dissolved in $CHCl_3$ (50 mL) and washed with H_2O (2 × 50 mL). The aqueous phase was extracted with $CHCl_3$ (2 × 25 mL), and the combined organic layers were washed with brine (2 × 50 mL), dried over Na_2SO_4, and concentrated to leave a dark brown product. The compound was purified by flash chromatography on silica gel eluting with 1% MeOH:CH_2Cl_2 to yield the halogenated enaminone listed below.

Chloro enaminone 6: yield, 188 mg (80%); mp 195−197 °C dec; TLC (CH_2Cl_2:MeOH:NH_4OH 99:9:1) $R_f = 0.5$; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.23 (m, 3H), 7.08 (d, 1H, $J = 7.3$ Hz), 4.08 (t, 2H, $J = 6.8$ Hz), 4.0 (s, 3H), 2.85 (t, 2H, $J = 6.8$ Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 179.96, 151.18, 134.06, 131.39, 123.52, 122.37, 108.87, 107.80, 82.90, 40.34, 34.76, 32.42; MS (CI) *m/z* 235 MH$^+$. Anal. Calcd for $C_{12}H_{11}N_2OCl$: C, 60.26; H, 4.64; N, 11.71; Cl, 14.82. Found: C, 60.12; H, 4.43; N, 11.51; Cl, 14.33.

2-Chloro-3-(*N*-methyl-*N*-phenylamino)cyclohex-2-enone (9). This compound was somewhat unstable at ambient temperature and was characterized quickly before decomposition: yield 196 mg (83%); TLC (CH_2Cl_2:MeOH:NH_4OH, 99:9:1) $R_f = 0.6$; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.35 (t, 2H, $J = 7.5$ Hz, 7.18 (t, 1H, $J = 7.5$ Hz), 7.10 (d, 2H, $J = 7.5$ Hz), 3.51 (s, 3H), 2.55 (m, 4H), 1.85 (m, 2H); MS (CI) *m/z* 236 MH$^+$; HRMS calcd for $C_{13}H_{14}NOCl$, 236.0842, found 236.0845 ± 0.0012.

2-Iodo-3-(*N*-phenylamino)cyclohex-2-enone (10): yield 248 mg (83%); mp 79−82 °C; TLC (CH_2Cl_2:MeOH:NH_4OH, 99:9:1) $R_f = 0.55$; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.45 (t, $J = 7.4$ Hz), 7.32 (t, 2H, $J = 7.4$ Hz), 7.15 (d, 2H, $J = 7.5$ Hz), 2.55 (m, 4H), 1.9 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 190.17, 163.18, 137.53, 129.38, 127.05, 125.86, 78.98, 36.42, 28.45, 21.92; MS (CI) *m/z* 314 MH$^+$. Anal. Calcd for $C_{12}H_{12}NOI$: C, 46.01; H, 3.86; N, 4.47; I, 40.55. Found: C, 46.31; H, 3.52; N, 4.27; I, 40.65.

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