Concurrent α-Iodination and N-Arylation of Cyclic β-Enaminones

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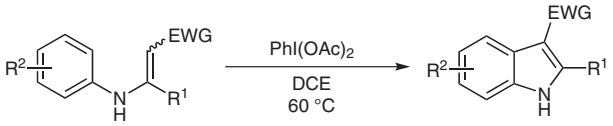
Abstract: A variety of N-substituted 3-aminocyclohex-2-enones were converted into the corresponding N-arylated α-iodo enaminones in high yields via concurrent α-iodination and N-arylation mediated by $ArI(OAc)_2$. A mechanism is postulated to account for the reaction differences between the cyclic and the acyclic β-enaminones, which undergo predominant α-acetoxylation under the same reaction conditions.

Key words: polyvalent iodine compounds, α-iodination, PIDA, α-iodo enaminones, 3-aminocyclohex-2-enones

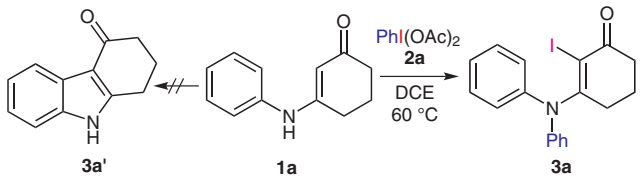
The organic chemistry of polyvalent iodine compounds has experienced an unprecedented explosive development since the early 1990s. This surging interest in organic iodine reagents is mainly due to the fact that the chemical properties and the reactivity of the iodine species are similar to heavy-metal congeners, such as Hg(II), Tl(III), Pd(IV), but without the toxic and environmental problems associated with these metal reagents.[1]

Among the many polyvalent iodine reagents, phenyliodine bis(trifluoroacetate) (PIFA) and phenyliodine(III) diacetate (PIDA) have been applied extensively to construct C–N or C–C bonds leading to heterocyclic compounds.[2] Recently, we reported a novel C–C bond formation strategy for indole synthesis via PIDA-mediated oxidation of the *N*-aryl enamines (Scheme 1).[2c] In order to enlarge the substrate scope and generality of the method, we applied the reaction conditions (PIDA, 60 °C, DCE) to the similar N-substituted cyclic enaminone **1a** in hopes of achieving the desired cyclized product **3a′**. However, an unexpected N-arylated α-iodo enaminone **3a** (confirmed by X-ray crystal analysis,[3] Figure 1) was achieved in 85% yield, with no formation of the desired cyclized **3a′** (Scheme 2).

Numerous methods have been described for the preparation of α-iodo enaminone compounds,[4] which can be readily converted to a range of α-functionalized enaminones via a transition-metal-catalyzed cross-coupling reaction.[5] However, a literature survey indicated that there are few examples of a general, one-pot α-iodination and N-arylation of secondary enaminones mediated by $ArI(OAc)_2$, although a similar two-step chemical process has already been observed for 2-amin-o-1,4-naphthoquinone compounds and 4-aminocoumarin derivatives by Varvoglis's group.[6] As a complementary work to this interesting class of reaction and an exceptional case that supplements our preliminary findings,[2c] we wish to report herein this unexpected one-pot α-iodination and N-arylation process of 3-aminocyclohex-2-enones mediated by $ArI(OAc)_2$.



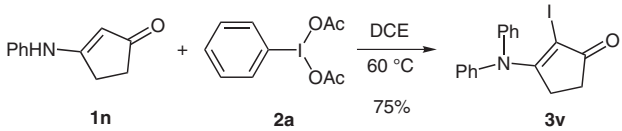
Scheme 1



Scheme 2

One feature of the reaction is that both the aryl and iodo moiety in $ArI(OAc)_2$ are incorporated into the final product, while for most oxidative reactions mediated by $PhI(OAc)_2$, phenyl iodide is always released as a byproduct.

A variety of 3-arylaminocyclohex-2-enone derivatives, which were readily prepared via the condensation of cyclohexane-1,3-dione and the corresponding anilines,[7] were firstly treated with PIDA under optimal conditions[8] to investigate the scope and generality of the reaction. The results listed in Table 1 indicated that both electron-donating and electron-withdrawing aromatic substituents could be tolerated in the process. For the substrates with electron-withdrawing groups, the reaction yields achieved were relatively higher (entries 2–6, Table 1). Furthermore, five-membered β-enaminone **1n** could also be transferred into the corresponding N-arylated α-iodo enaminone **3v** in good yield by using the method (Scheme 3).



Scheme 3

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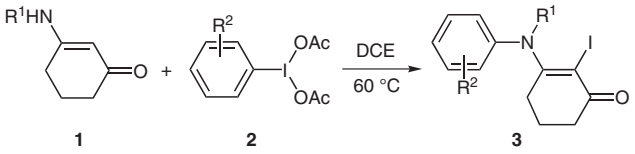
Table 1 α-Iodination and N-Arylation of Cyclic 3-Aminocyclohex-2-enones **1** Mediated by $ArI(OAc)_2$[a]

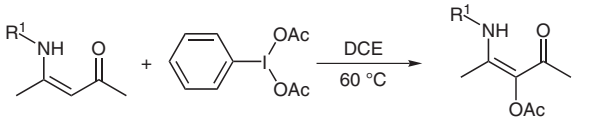


1 2 3

Entry	R^1 in **1**		R^2 in **2**		**3**	Yields (%)[b]
1	Ph	**1a**	H	**2a**	**3a**	85
2	4-$F_3CC_6H_4$	**1b**	H	**2a**	**3b**	74
3	4-BrC_6H_4	**1c**	H	**2a**	**3c**	75
4	4-$O_2NC_6H_4$	**1d**	H	**2a**	**3d**	89
5	2,4-$F_2C_6H_3$	**1e**	H	**2a**	**3e**	85
6	2-ClC_6H_4	**1f**	H	**2a**	**3f**	72
7	3,4-$Me_2C_6H_3$	**1g**	H	**2a**	**3g**	77
8	4-$MeOC_6H_4$	**1h**	H	**2a**	**3h**	60
9	4-MeC_6H_4	**1i**	H	**2a**	**3i**	85
10	4-$MeOC_6H_4$	**1h**	4-O_2N	**2b**	**3j**	57
11	4-BrC_6H_4	**1c**	4-Br	**2c**	**3k**	71
12	4-$O_2NC_6H_4$	**1d**	3-O_2N	**2d**	**3l**	57
13	2,4-$F_2C_6H_3$	**1e**	4-O_2N	**2b**	**3m**	63
14	2-ClC_6H_4	**1f**	3-O_2N	**2d**	**3n**	85
15	Ph	**1a**	4-Me	**2e**	–	n.d.[c]
16	4-$O_2NC_6H_4$	**1d**	4-Me	**2e**	–	n.d.[c]
17	Bn	**1j**	4-O_2N	**2b**	**3o**	84
18	Bn	**1j**	4-O_2N	**2b**	**3p**	91
19	Bn	**1j**	4-Br	**2c**	**3q**	57
20	Bn	**1j**	2-Cl	**2f**	**3r**	62
21	Bn	**1j**	4-MeO_2C	**2g**	**3s**	65
22	$Ph(CH_2)_2$	**1k**	4-O_2N	**2b**	**3t**	86
23	*c*-C_6H_{11}	**1l**	4-O_2N	**2b**	**3u**	35[d]
24	H	**1m**	H	**2a**	–	n.d.[c]

[a] Conditions: all reactions were carried out by adding dropwise 1.3 equiv of $ArI(OAc)_2$ in DCE to a 60 °C solution of 1.0 equiv of substrate **1** in DCE under N_2 protection.
[b] Isolated yields after silica gel chromatography.
[c] n.d. = not detected.
[d] With concomitant formation of other unidentified byproducts.

In order to realize a versatile N-arylation of the α-iodo enaminones, a series of aryliodine diacetates were prepared[9] and applied to the method. It was found that when the PIDA derivatives bear aromatic electron-withdrawing substituents, the reactions went smoothly to afford the corresponding products (entries 10–14, Table 1). Surprisingly, when substrate **1a** and **1d** were treated with PIDA analogue **2e**, differing from PIDA by only one *para*-methyl group, no expected N-arylated and α-iodonated products were achieved in either case. This result might indicate that an aromatic electron-rich polyvalent iodine(III) reagent is ineffective for this transformation.



Scheme 4

Encouraged by the above results, we decided to study whether N-alkylated 3-aminocyclohex-2-enones could be applied to this α-iodination and N-arylation process. The results in Table 1 (entries 17–23) demonstrated that the N-alkylated and N-arylated α-iodocyclohex-2-enones **3o–u** could also be successively obtained via this α-iodination and N-arylation approach. However, when nonsubstituted primary enaminone **1m** was subjected to the same reaction conditions, a complex mixture was obtained and no desired N-arylated α-iodo enaminone was separated.

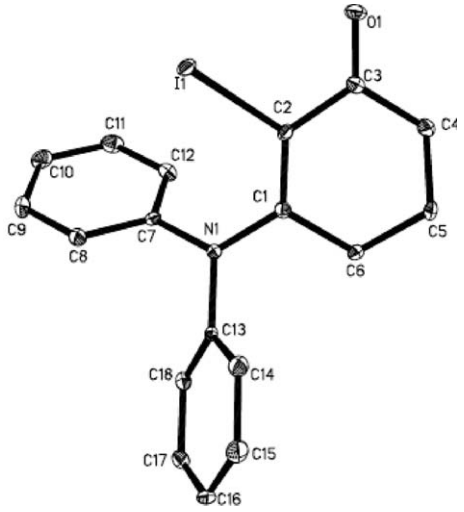
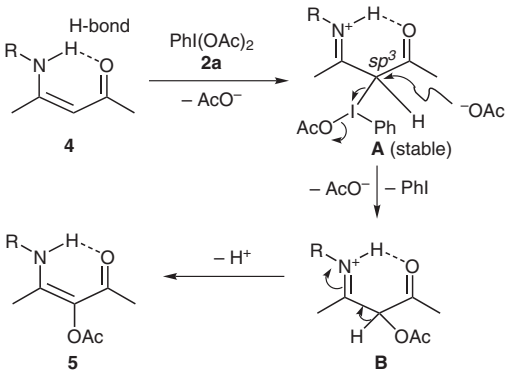


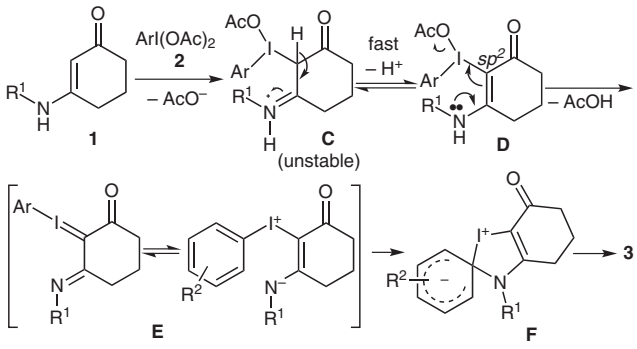
Figure 1 X-ray crystallography of **3a**

Interestingly, exceptional results were obtained for the cases when acyclic β-enaminones were used as substrates. Under the exact same reaction conditions, acyclic β-enaminone **4a–c** afforded α-acetoxylated[10] product **5a–c** in 73–85% yields, with no detection of the desired N-arylated α-enaminones in each case (Scheme 4).

A plausible mechanism is proposed to explain why the acyclic β-enaminone **4** and cyclic β-enaminone **1** would afford different products under the same $ArI(OAc)_2$ conditions. Due to the existence of an H-bond, the acyclic β-enaminone with the *Z*-configuration would exist as the sole isomer.[11] Firstly, the reaction of acyclic β-enaminone with $PhI(OAc)_2$ would give an α-iodo iminium salt **A**, which is proposed to be a stable intermediate for the existence of an intramolecular H-bond. Next, one possible pathway is that the generated acetate anion would nucleophilically attack the sp^3-carbon center, releasing one molecule of phenyl iodide and acetate anion.[12] Finally, capture of the acidic proton by the acetate anion would transform **B** into the α-acetoxylated β-enaminone **5** (Scheme 5). While for the cyclic β-enaminones, the C=N double bond would undoubtedly adopt the *E*-configuration, and the H-bond cannot be formed between the N–H and the carbonyl group because of the spatial distance. Similarly, α-iodo iminium salt **C** would firstly be formed from **1** and **2**. However, intermediate **C** is greatly unstable because of the presence of a ring system and the lack of H-bond; it would deprotonated instantly to give the stabilized cyclic α-iodo enaminone **D**. Due to the fact that substitution of an acetate anion (if formed) cannot occur at a sp^2-carbon center, intermediate **D** would be converted to iodine-nitrogen 1,4-dipoles **E**.[6] Finally, the *ipso* attack of the negative nitrogen on the phenyl ring, through a five-membered cyclic intermediate **F**,[13] would afford the cyclic N-arylated α-iodo enaminone **3** (Scheme 6). The formation of the cyclic intermediate **F** seemingly accounts for the experimental fact that an electron-withdrawing R^2 substituent was beneficial while an electron-donating R^2 group was ineffective for the reaction (entries 10–16, Table 1), since the stability of intermediate **F** would be greatly deactivated in the latter case.



Scheme 5



Scheme 6

In conclusion, we have described that when the cyclic N-substituted 3-aminocyclohex-2-enones were treated with $ArI(OAc)_2$, both the aryl and iodo moiety of $ArI(OAc)_2$ would be incorporated into the product.[14] The cyclic N-arylated α-iodo β-enaminones could be obtained in high

yields by this method. While for the acyclic β-enaminones, one acetoxy group of $ArI(OAc)_2$ was transferred to the product to give selectively the acyclic α-acetoxylated β-enaminones in good yields.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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References and Notes

(1) (a) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2008**, *108*, 5299. (b) Stang, P. J. *J. Org. Chem.* **2003**, *68*, 2997. (c) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2002**, *102*, 2523. (d) Stang, P. J.; Zhdankin, V. V. *Chem. Rev.* **1996**, *96*, 1123. (e) Richardson, R. D.; Wirth, T. *Angew. Chem. Int. Ed.* **2006**, *45*, 4402. (f) Wirth, T. *Angew. Chem. Int. Ed.* **2005**, *44*, 3656. (g) Moriarty, R. M.; Prakash, O. *Hypervalent Iodine in Organic Chemistry: Chemical Transformations*; Wiley-Interscience: New York, **2008**. (h) Moriarty, R. *J. Org. Chem.* **2005**, *70*, 2893. (i) Varvoglis, A. *Hypevalent Iodine in Organic Synthesis*; Academic Press: London, **1997**. (j) Varvoglis, A. *The Organic Chemistry of Polycoordinated Iodine*; VCH Publishers: New York, **1992**. (k) Varvoglis, A. *Tetrahedron* **1997**, *53*, 1179.

(2) (a) Du, Y.; Liu, R.; Linn, G.; Zhao, K. *Org. Lett.* **2006**, *8*, 5919. (b) Li, X.; Du, Y.; Liang, Z.; Li, X.; Pan, Y.; Zhao, K. *Org. Lett.* **2009**, *11*, 2643. (c) Yu, W.; Du, Y.; Zhao, K. *Org. Lett.* **2009**, *11*, 2417. (d) Tellitu, I.; Serna, S.; Herrero, M. T.; Domínguez, E.; Sanmartin, R. *J. Org. Chem.* **2007**, *72*, 1526. (e) Huang, J.; Liang, Y.; Pan, W.; Yang, Y.; Dong, D. *Org. Lett.* **2007**, *48*, 5345. (f) Fan, R.; Wen, F.; Qin, L.; Pu, D.; Wang, B. *Tetrahedron Lett.* **2007**, *48*, 7444. (g) Correa, A.; Tellitu, I.; Domínguez, E.; Sanmartin, R. *J. Org. Chem.* **2006**, *71*, 3501. (h) Aggarwal, R.; Sumran, G.; Saini, A.; Singh, S. *Tetrahedron Lett.* **2006**, *62*, 11100. (i) Ciufolini, M.; Braun, N.; Canesi, S.; Ousmer, M.; Chang, J.; Chai, D. *Synthesis* **2007**, 3759. (j) Shigehisa, H.; Takayama, J.; Honda, T. *Tetrahedron Lett.* **2006**, *47*, 7301. (k) Braun, N.; Ousmer, M.; Bray, J.; Bouchu, D.; Peters, K.; Peters, E.; Ciufolini, M. *J. Org. Chem.* **2000**, *65*, 4397.

(3) **Compound 3a**
Crystallized in the monoclinic space group P2 (1)/c with cell dimensions: a = 10.497 (2) Å, b = 13.607 (3) Å, c = 11.987 (2) Å, α = 90°, β = 114.36 (3)°, γ = 90°, V = 1559.9 (5) Å^3, D_c = 1.657 g/cm^3, Z = 4. CCDC: 753753.

(4) (a) Krafft, M.; Cran, J. *Synlett* **2005**, 1263. (b) Campos, P.; Tan, C.; Rodriguez, M. *Tetrahedron Lett.* **1995**, *36*, 5257. (c) Kozmin, S.; Iwama, T.; Huang, Y.; Rawal, V. *J. Am. Chem. Soc.* **2002**, *124*, 4628. (d) Campos, P.; Arranz, J.; Rodriguez, M. *Tetrahedron Lett.* **1997**, *37*, 8397. (e) Sakamoto, T.; Kondo, Y.; Yamanaka, H. *Synthesis* **1984**, 252. (f) Habib, N.; Kappe, T. *J. Heterocycl. Chem.* **1984**, *21*, 385. (g) Matsuo, K.; Ishida, S.; Takuno, Y. *Chem. Pharm. Bull.* **1994**, *42*, 1149.

(5) (a) Negishi, E. *J. Organomet. Chem.* **1999**, *576*, 179. (b) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (c) Yoshioka, N.; Lahti, P. M.; Kaneko, T.; Kuzumaki, Y.; Tsuchida, E.; Nishide, H. *J. Org. Chem.* **1994**, *59*, 4272. (d) Farina, V. *Pure Appl. Chem.* **1996**, *68*, 73.

(6) (a) Papoutsis, I.; Spyroudis, S.; Varvoglis, A. *Tetrahedron Lett.* **1996**, *37*, 913–916. (b) Papoutsis, I.; Spyroudis, S.; Varvoglis, A.; Raptopoulou, C. *Tetrahedron* **1997**, *53*, 6097–6112.

(7) Rao, V. V. R.; Wentrup, C. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1232.

(8) (a) CaH_2-dried EtOAc, THF, MeCN, and CH_2Cl_2 were also tested as solvents, but were not superior to DCE. (b) The conversion was very slow at 40 °C.

(9) (a) Kazmierczak, P.; Skulski, L. *Synthesis* **1998**, 1721. (b) Kazmierczak, P.; Skulski, L.; Kraszkiewicz, L. *Molecules* **2001**, *6*, 881.

(10) For a previous example relative to this: Zhang, P. F.; Chen, Z. C. *J. Chem. Res., Synop.* **2001**, 150.

(11) For the evidence of assigning *Z*-configuration for such acyclic β-enaminone compounds, see: Ramtohul, Y. K.; Chartrand, A. *Org. Lett.* **2007**, *9*, 1029.

(12) For a similar nucleophilic substitution process in which water was acted as nucleophile, see: Moriarty, R. M.; Berglund, B. A.; Penmasta, R. *Tetrahedron Lett.* **1992**, *33*, 6065.

(13) For a similar migration process relative to iodine–oxygen 1,4-dipoles, see: Takaku, M.; Hayashi, Y.; Nozaki, H. *Tetrahedron* **1970**, *26*, 1243.

(14) **General Procedure for α-Iodination and N-Arylation of β-Enaminones**
To a solution of substrate **1** (1.0 mmol) in dried DCE (10 mL) was added dropwise a solution of aryliodine diacetate **2** (1.3 mmol) in dried DCE (10 mL) at 60 °C under nitrogen atmosphere. After the addition, the reaction mixture was stirred at this temperature until the conversion was complete as indicated by TLC. Then the mixture was cooled to r.t., treated with sat. aq $NaHCO_3$ (40 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layer was dried over Na_2SO_4 and evaporated under reduced pressure to remove the solvent. The residue was purified by column chromatography using a mixture of PE and EtOAc as eluent to afford the product.
Compound **3a**: yellow solid, mp 106–108 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.32 (t, J = 7.9 Hz, 4 H), 7.14 (t, J = 7.4 Hz, 2 H), 7.02 (d, J = 7.7 Hz, 4 H), 2.75–2.65 (m, 2 H), 2.58 (t, J = 6.0 Hz, 2 H), 2.04–1.91 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.09, 166.95, 145.20, 129.52, 125.45, 125.22, 95.80, 37.54, 34.04, 21.38. ESI-LRMS: m/z = 390.2 [M + H$^+$].
Compound **5a**: yellow solid, mp 102–104 °C. ^{1}H NMR (400 MHz, DMSO): δ = 7.51 (dd, J = 4.8, 2.5 Hz, 3 H), 7.35 (dd, J = 7.7, 1.9 Hz, 2 H), 2.43 (s, 3 H), 2.35 (s, 3 H), 2.22 (s, 3 H). ESI-LRMS: m/z = 271.9 [M + K$^+$]. The spectroscopic data for all the new compounds could be found in the Supporting Information.