Chinese Chemical Letters Vol. 16, No. 12, pp 1593-1596, 2005 1593
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Approach to N-Alkoxy-2-oxoindole for Mimicing SERMs Structure

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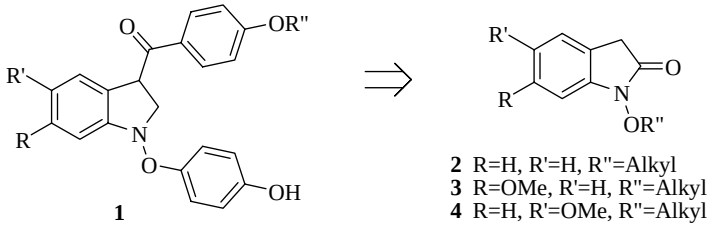
Abstract: Treatment of N-alkoxyamides with bis(trifluoroacetoxy)iodobenzene generated electron deficient nitrogen species, which readily cyclized onto aromatic ring to give N-alkoxy-2-oxoindoles. The effect of different substituent on aromatic ring to the electrophilic substitution was studied.

Keywords: N-Alkoxyamides, bis(trifluoroacetoxy)iodobenzene, intramolecular cyclization.

Selective estrogen receptor modulators (SERMs) are a class of compounds which can act as estrogen receptor agonists or estrogen receptor antagonists in some tissues[1]. Currently, two main classes of compounds—triphenylethlene and benzothiophene derivatives have been approved under research and development stage or in the clinical use. But these approved SERMs have some serious and potentially fatal side effects in the treatment of breast cancer and osteoporosis. It is quite necessary to synthesize novel compounds which have better therapeutic effects but minor side effects. For this aim our group designed novel compound **1** which could be obtained through the modification of N-alkoxy-2-oxoindole (**2**, **3** and **4**). Herein we reported the preparation of **2**, **3** and **4**.

Compounds **2**, **3** and **4** can be obtained by intramolecular aromatic substitution through the intermediates of N-acyl-N-alkoxynitrenium ions which can be generated by treatment of N-chloro-N-alkoxyamides with silver salts[2]. This reaction requires prior chlorination of amides and subsequent dechlorination with silver salt. Kikugawa and Kawase[3] used hypervalent iodine compounds to obtain intermediates having electron deficient nitrogen atom[4] directly from amides, which is an improved method for synthe-



1

2 R=H, R'=H, R"=Alkyl
3 R=OMe, R'=H, R"=Alkyl
4 R=H, R'=OMe, R"=Alkyl

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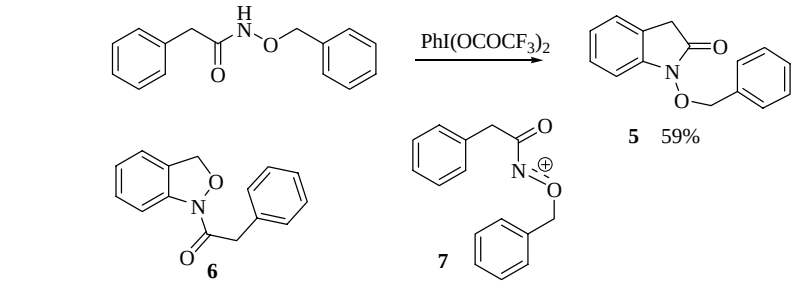
sizing compound **2**, **3** and **4** through intramolecular electrophilic substitution. In a typical procedure, a solution of N-alkoxyarylacetamide (2 mmol) in $CHCl_3$ (5 mL) was added to a stirred solution of bis(trifluoroacetoxy)iodobenzene (2.6 mmol) in $CHCl_3$ (10 mL) at 60℃ under N_2 atmosphere. The resulting solution was stirred for another 10 min, poured into saturated sodium carbonate, and then extracted with CH_2Cl_2. The combined organic phases were dried over anhydrous sodium sulfate, filtered and then the solvent was removed under reduced pressure. The residue was purified with column chromato- graphy to give the title compounds.

Results and Discussion

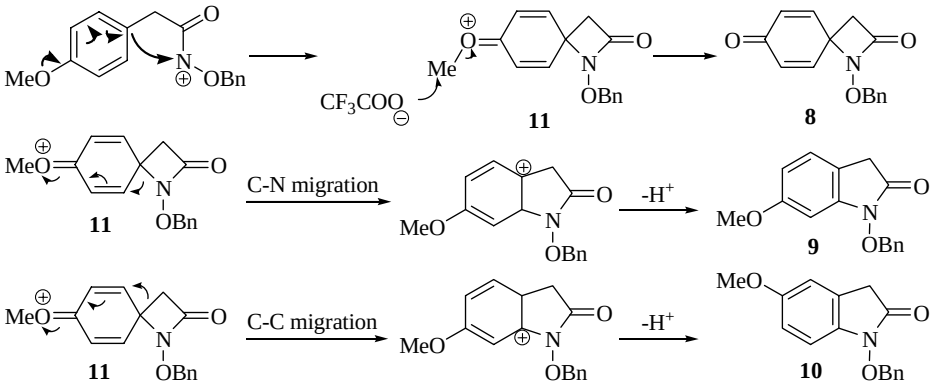
The electrophilic aromatic intramolecular substitution of N-alkoxyphenylacetamide with bis(trifluoroacetoxy)iodobenzene as oxidant was studied. Compound **5** was obtained, instead of cyclization product **6**.



The attack of nitrenium ion (transition **7**) onto the acyl side chain was facilitated by the exocyclic nature of N-O *pseudo* π bond, which made the formation of five-membered ring easier. However, for cyclization onto the alkoxy side chain, the N-O bond would be endocyclic in the transition state. In the result, the strain would increase consequently and five-membered ring formation would be more difficult.

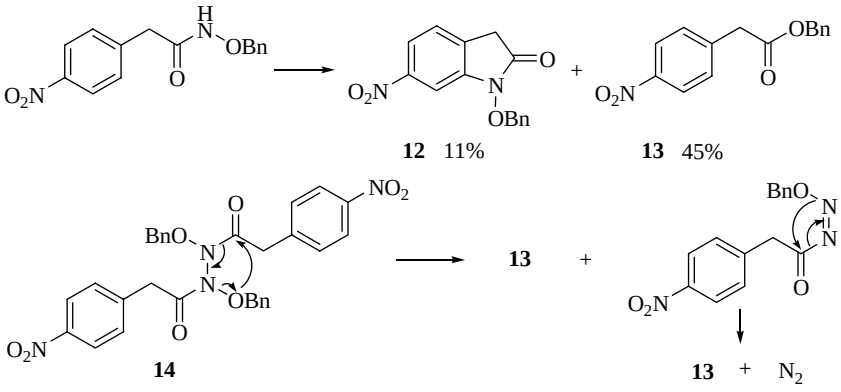
The electron-donating group on the aromatic ring would affect the electrophilic substitution reaction. The intramolecular cyclization of N-alkoxy-*p*-methoxyphenyl-acetamide was investigated.

The electron-donating group would increase the electron density on benzene ring, especially at its *ortho* and *para* positions. The products **8**, **9**, **10** were obtained from the intermediate **11**, and the mechanism was proposed as follows.



The C-C migration and C-N migration are similar with dienone-phenol rearrangement[5, 6].

The electron-withdrawing group would retard the electrophilic reaction. The experimental result of the reaction of N-alkoxy-*p*-nitrophenylacetamide with bis(trifluoroacetoxy)iodobenzene was shown in the following procedure. The yield of intramolecular cyclization **12** was poor and the main product was **13**. The mechanism of formation of **13** might be proposed as the decomposition of intermediate **14**.



Acknowledgments

We thank the supports from the Chung Kong Scholars Program Administered by the Ministry of Education, PRC and the Li Ka Shing Foundation, Hong Kong.

References and Notes

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7. Data of compound **5**: ^{1}H NMR ($CDCl_3$, δ_{ppm}, J Hz): 3.52 (s, 2H, -CH_2-), 4.20 (s, 2H, -CH_2-), 6.81 (br d, 1H, J=7.5, Ph-H), 7.05 (br t, 1H, J=7.5, Ph-H), 7.22 (br t, 1H, J=7.8, Ph-H), 7.37-7.40 (m, 4H, Ph-H), 7.50-7.53 (m, 2H, Ph-H); Compound **8**: ^{1}H NMR ($CDCl_3$, δ_{ppm}, J Hz): 2.89 (s, 2H, -CH_2-), 4.88 (s, 2H, -CH_2-), 6.18 (dd, 2H, J=2.1, J=8.1, Vinyl-H), 6.57 (dd, 2H, J=2.1, J=8.1, Vinyl-H), 7.28-7.36 (m, 5H, Ph-H); Compound **9**: ^{1}H NMR ($CDCl_3$, δ_{ppm}, J Hz): 3.46 (s, 2H, -CH_2-), 3.73 (s, 3H, -OCH_3), 5.18 (s, 2H, -CH_2-), 6.35 (d, 1H, J=2.4, Ph-H), 6.51 (dd, 1H, J=2.7, J=8.1, Ph-H), 7.07 (br d, 1H, J=7.8, Ph-H), 7.38-7.41 (m, 3H, Ph-H), 7.49-7.52 (m, 2H, Ph-H); Compound **10**: ^{1}H NMR ($CDCl_3$, δ_{ppm}, J Hz): 3.49 (s, 2H, -CH_2-), 3.76 (s, 3H, -OCH_3), 5.12 (s, 2H, -CH_2-), 6.66-6.74 (m, 2H, Ph-H), 6.81 (br s, 1H, Ph-H), 7.26-7.39 (m, 3H, Ph-H), 7.49-7.52 (m, 2H, Ph-H); Compound **12**: ^{1}H NMR ($CDCl_3$, δ_{ppm}, J Hz): 3.79 (s, 2H, -CH_2-), 5.16 (s, 2H, -CH_2-), 7.26-7.37 (m, 4H, Ph-H), 7.46 (br d, 2H, J=8.4, Ph-H), 8.19 (dd, 2H, J=1.2, J=6.9, Ph-H); Compound **13**: ^{1}H NMR ($CDCl_3$, δ_{ppm}, J Hz): 3.84 (s, 2H, -CH_2-), 5.25 (s, 2H, -CH_2-), 7.27-7.50 (m, 5H, Ph-H), 8.20-8.24 (m, 4H, Ph-H).

Received 1 April, 2005