ORGANIC
LETTERS

2009
Vol. 11, No. 19
4262−4265

Iron Trichloride-Promoted Cyclization of *o*-Alkynylaryl Isocyanates: Synthesis of 3-(Chloromethylene)oxindoles

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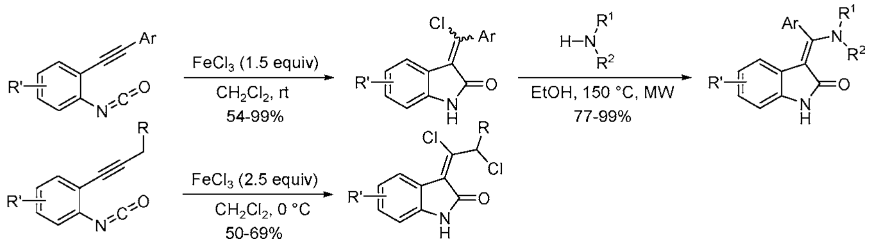
Received June 30, 2009

ABSTRACT



Iron trichloride promotes the cationic cyclization of *o*-(arylethynyl)aryl isocyanates leading to 3-(arylchloromethylene)oxindoles which can be stereoselectively converted to (*Z*)-3-(aminomethylene)oxindoles under straightforward conditions. When the alkyne is substituted by an alkyl group, activation of the allylic C−H bond also occurs producing 1,2-(dichloroalkylidene)oxindoles.

Oxindoles constitute an important class of heterocycles. In particular, substituted 3-methyleneoxindoles have elicited considerable synthetic interest due to their occurrence in many biologically active substances.[1] As a consequence, numerous strategies have been developed for the synthesis of 3-methyleneoxindoles possessing a trisubstituted or tetrasubstituted alkene with alkyl or aryl groups at the exocyclic olefinic carbon. The most representative routes feature the nucleophilic addition of oxindoles to carbonyl compounds,[1,2] Heck reactions,[3] radical cyclizations,[4] transition-metal-catalyzed domino processes with α,*β*-acetylenic amides derived from 2-haloanilines[5−7] or anilines (proceeding with arene ortho C−H bond activation),[8] carbonylation of 2-alkynylanilines,[9] carbopalladation−Stille coupling reactions with

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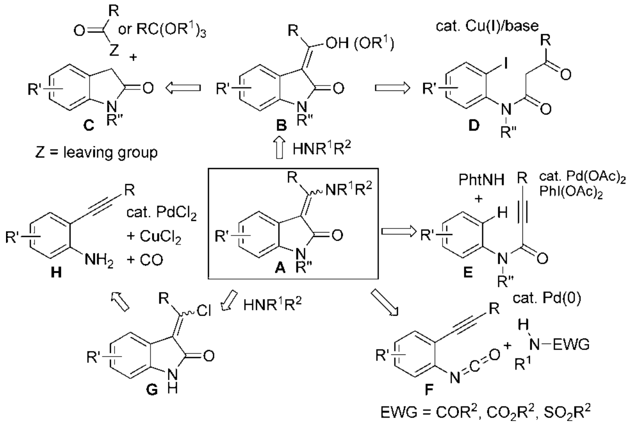
10.1021/ol9014877 CCC: $40.75

carbamoyl chlorides derived from 2-alkynylanilines,[10] and Pd- or Rh-catalyzed cyclizations of 2-alkynylaryl isocyanates in the presence of an external nucleophile.[11,12]

Substituted 3-methyleneoxindoles in which the exocyclic alkene is substituted by a heteroatom also constitute an important class of functionalized oxindoles, especially 3-(aminomethylene)oxindoles which have been identified as protein kinases inhibitors.[13] Several strategies have been developed to synthesize this class of oxindoles of type **A**. One of the most straightforward route involves the reaction of amines with enol ethers derived from 3-acyloxindoles **B**. The latter compounds are usually prepared by condensation of oxindoles **C** with activated acyl derivatives or orthoesters.[13] Another route to 3-acyloxindoles **B** capitalizes on the copper-catalyzed intramolecular arylation of β-keto amides **D**.[14] Metal-catalyzed reactions that allow access to 3-methyleneoxindoles bearing alkyl or aryl substituents on the exocyclic alkene have been successfully extended to some classes of nitrogen nucleophiles. Thus, in the presence of phthalimide (PhtNH), a catalytic amount of $Pd(OAc)_2$, and $PhI(OAc)_2$, α,β-acetylenic amides **E** undergo *syn*-amino-palladation, followed by arene C−H bond activation and reductive elimination, leading to 3-(aminomethylene)oxindoles **A**.[15] Pd-catalyzed cyclizations involving 2-alkynylaryl isocyanates **F** with amides, carbamates, or sulfonamides as external nucleophiles have also been recently reported.[16] Another class of potential precursors to oxindoles of type **A** are 3-(chloromethylene)oxindoles **G**, which have been prepared by chlorination of 3-acyloxindoles **B**.[13,17] A complementary route from 2-alkynylanilines, involving a chloropalladation−carbonylation sequence (cat. $PdCl_2$, excess $CuCl_2$, CO atmosphere), has also been described (Scheme 1).[18]

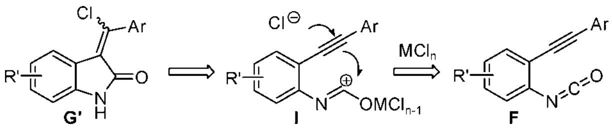
Scheme 1. Routes toward 3-(Aminomethylene)oxindoles



Herein, we report a new route toward 3-(chloromethylene)oxindoles **G** relying on the iron trichloride-promoted cationic cyclization of 2-alkynylaryl isocyanates. Additionally, straightforward conditions for their subsequent stereoselective transformation into 3-(aminomethylene)oxindoles have been developed.

In our retrosynthetic analysis, the formation of the exocyclic double bond in 3-(arylchloromethylene)oxindoles of type **G′** was envisaged by addition of a chloride ion to a developing vinylic carbocation resulting from the nucleophilic attack of the alkyne onto an imidoyl cation **I**. The latter species would be generated by activation of isocyanates **F** with a Lewis acidic metal salt (MCl_n) (Scheme 2).

Scheme 2. Synthesis of 3-(Arylchloromethylene)oxindoles



Activation of isocyanates by Lewis or protic acids has been used in modified Bischler−Napieralski reactions,[19] but to

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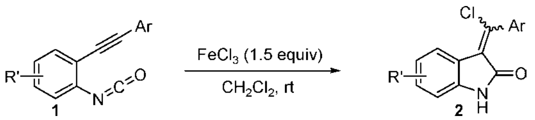
our knowledge, alkynes have not been used as π-nucleophiles to intercept the resulting imidoyl cation.[20] Although several Lewis acidic metal chlorides could be considered, $FeCl_3$ was selected for its ease of handling and environmentally benign character.[21] Additionally, cationic cyclizations involving oxycarbenium ions[22] or enoates[23] as electrophilic species and alkynes, as π-nucleophiles, have been efficiently promoted by $FeCl_3$.

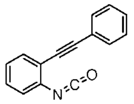
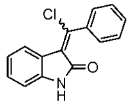
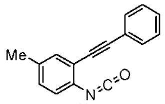
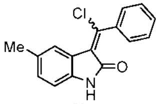
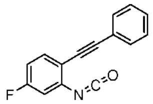
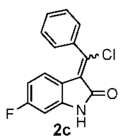
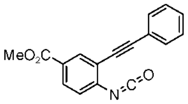
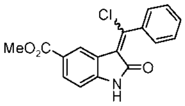
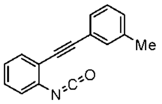
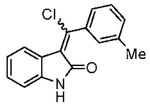
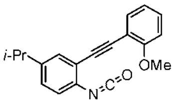
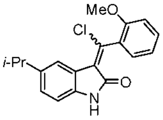
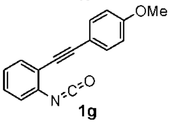
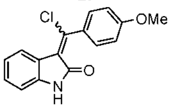
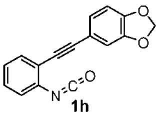
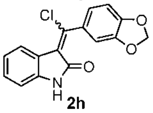
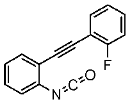
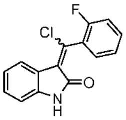
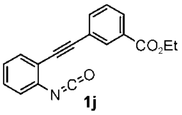
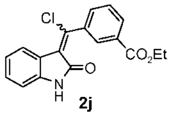
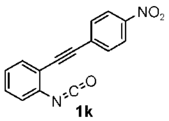
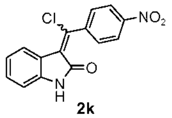
Thus, several 2-alkynylaryl isocyanates **1a**−**k** were synthesized and treated with $FeCl_3$ [(1.5 equiv), CH_2Cl_2, rt, 1−12 h]. A smooth reaction took place, and the corresponding 3-(arylchloromethylene)oxindoles **2a**−**k** were isolated in good to excellent yields (54−99%) as mixtures of geometric isomers (Table 1).[24] The *E*/*Z* ratio seems to result from kinetic control and was not altered by extended reaction times or resubjection of the mixture of geometric isomers to $FeCl_3$. Although an *anti*-addition process across the alkyne was anticipated, isomerization of the developing vinylic cation, stabilized by the aromatic group, presumably occurred. The reaction tolerates esters, methyl ethers, benzodioxole, and nitro groups. A high regioselectivity was observed in all cases. Despite the presence of a *p*-nitrophenyl substituent on the alkyne in isocyanate **1k**, the regioselectivity was still in favor of a 5-*exo-dig* cationic cyclization process leading to **2k**, whose structure was unambiguously confirmed by a chemical correlation.[25]

The lack of stereoselectivity observed in the cationic cylizations of isocyanates **1a**−**k** leading to 3-(arylchloromethylene)oxindoles **2a**−**k** was in fact of little importance for the subsequent substitution of the chlorine atom with an amine by a 1,4-addition−elimination process.

We found that this transformation could be accomplished under straightforward conditions and in very high yields using microwave irradiation.[26,27] The scope of the reaction under these conditions (EtOH, 150 °C) is broad since ammonia, primary and secondary aliphatic amines (acyclic or cyclic), as well as *p*-anisidine all reacted well with substrate **2a** (R′ = H, Ar = Ph), providing the corresponding 3-(aminoarylmethylene)oxindoles **3**−**8** (83−99%).[28] The reaction was next generalized to other 3-(arylchloromethylene)oxindoles bearing substituents on the aromatic rings with different amines. The reactions proceeded equally well to afford compounds **9**−**17** (77−99%) (Scheme 3). In all cases,

Table 1. Synthesis of 3-(Arylchloromethylene)oxindoles



isocyanates	products	*E*/*Z* ratio	yield
 **1a**	 **2a**	70:30	95%
 **1b**	 **2b**	75:25	77%
 **1c**	 **2c**	40:60	75%
 **1d**	 **2d**	65:35	84%
 **1e**	 **2e**	75:25	99%
 **1f**	 **2f**	35:65	86%
 **1g**	 **2g**	70:30	89%
 **1h**	 **2h**	85:15	93%
 **1i**	 **2i**	75:25	54%
 **1j**	 **2j**	75:25	71%
 **1k**	 **2k**	90:10	61%

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(20) Recently, TfOH-promoted tandem Friedel−Crafts alkenylation−cyclization of 2-alkynylphenyl isothiocyanates has been disclosed; see: Otani, T.; Kunimatsu, S.; Takahashi, T.; Nihei, H.; Saito, T. *Tetrahedron Lett.* **2009**, *50*, 3853–3856.

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(24) The *E*/*Z* ratio was determined by ^{1}H NMR. The chemical shift of the aromatic proton H4 serves as a reliable diagnostic for the configurational assignment; see the Supporting Information.

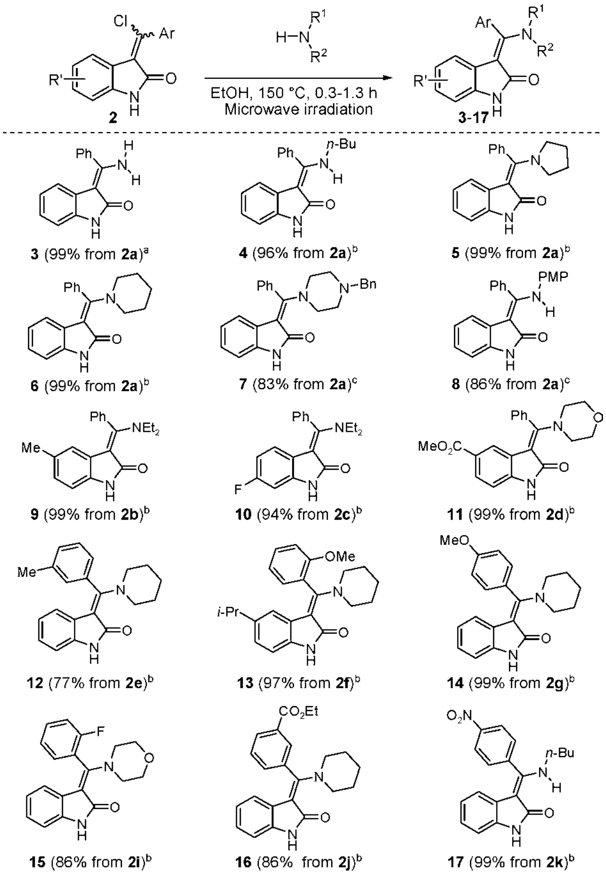
(25) See the Supporting Information.

(26) A few examples of such reactions have been previously reported, with 3-(chloromethylene)oxindoles bearing an acyl group on the nitrogen, by heating with an amine.[13c,17b] Enol ethers derived from 3-acyloxindoles have been more extensively used as substrates.[13]

(27) Kappe, C. O. *Angew. Chem., Int. Ed.* **2004**, *43*, 6250–6284.

(28) Treatment of **1a** under similar conditions [piperidine (2 equiv), EtOH, microwave, 150 °C, 0.3 h] only led to the corresponding ethyl carbamate (55%) and urea (45%) resulting from addition of ethanol and piperidine, respectively, to the isocyanate.

Scheme 3. Synthesis of 3-(Aminoarylmethylene)oxindoles

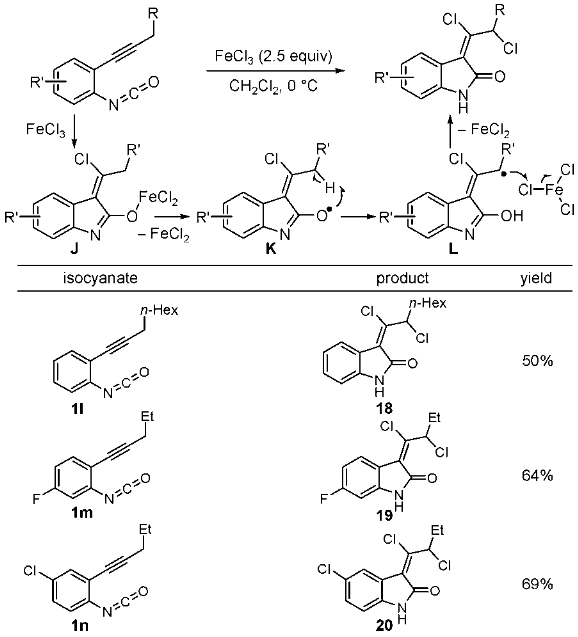


[a] With 30% aq NH_4OH (8 equiv). [b] R^1R^2NH (2 equiv). [c] R^1R^2NH (1 equiv), *i*-Pr_2NEt (1 equiv). PMP = 4-methoxyphenyl.

a single *Z*-geometric isomer was formed.[29] This result was not surprising when a primary amine was used as a nucleophile due to the intramolecular hydrogen bond that can exist between the amino group and the carbonyl group of the amide. In fact, whatever the amine, the stereochemical preference is likely to result from thermodynamic control.[1f]

The reactivity of isocyanates **1l**−**n**, in which the alkyne is substituted by a *n*-alkyl group, was also examined in the $FeCl_3$-promoted cationic cyclization. Interestingly, these compounds behave differently as more $FeCl_3$ (2.5 equiv) was required to ensure complete consumption of the starting material. After optimization of the conditions (CH_2Cl_2, 0 °C), 3-(1,2-dichloroalkylidene)oxindoles **18**−**20**, in which the allylic C−H bond of the alkyl chain has been functionalized in the form of a C−Cl bond, were isolated as single geometric isomers (50−69%). The formation of oxindoles **18**−**20** was explained by a stereoselective cationic cyclization, with attack of the imidoyl cation by the alkyne and addition of chloride ion in an *anti* fashion, producing the corresponding 3-(chloroalkylidene)oxindole iron alkoxide **J**. Homolytic scission of the O−Fe bond[30] would generate an oxy radical **K** able to promote a remarkably efficient 1,5-hydrogen abstraction leading to the allylic radical **L**. Chlorine atom transfer from $FeCl_3$ would then produce the corresponding oxindoles **18**−**20** and $FeCl_2$ (Scheme 4).[31]

Scheme 4. Reactivity of 2-(*n*-Alkylethynyl)aryl Isocyanates



In conclusion, we have reported that iron trichloride promotes an efficient cationic cyclization of 2-(arylethynyl)aryl isocyanates to 3-(arylchloromethylene)oxindoles, which can be subsequently stereoselectively converted to (*Z*)-3-(aminoarylmethylene)oxindoles. For 2-(*n*-alkylethynyl)aryl isocyanates, the $FeCl_3$-promoted cationic cyclization is followed by C−H bond functionalization leading to 3-(1,2-dichloroalkylidene)oxindoles. Further applications of isocyanates in cationic cyclizations are being investigated.

Acknowledgment. One of us (G.C.) thanks the MRES for a grant.

Supporting Information Available: Experimental procedures and ^1H and ^{13}C NMR data for all compounds and chemical correlation confirming the structure of oxindole **2k**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL9014877

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(29) The chemical shift of the oxindole proton H4 (5.32−6.30 ppm) supported the *Z* configuration of those compounds, and the configuration of **14** was unambiguously confirmed by NMR (NOE).

(30) (a) Ito, Y.; Fujii, S.; Saegusa, T. *J. Org. Chem.* **1976**, *41*, 2073–2074. (b) Blanco, L.; Mansouri, A. *Tetrahedron Lett.* **1988**, *29*, 3239–3242.

(31) The presence of $FeCl_2$ was confirmed by hydrolysis of the reaction mixture and addition of phenanthroline (phen) followed by qualitative detection of the $(phen)_3Fe(II)$ complex (λ_{max} = 511 nm).