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COMMUNICATION

ZrCl₄-promoted facile synthesis of indole derivatives

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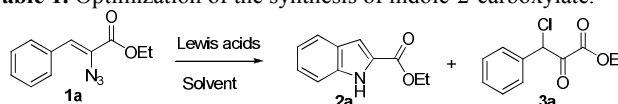
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Zirconium(IV) chloride effectively activates the nitrogen (N₂) extrusion from aryl azidoacrylates followed by annulation to provide the desired indole products in moderate to good yields. The reaction proceeds at low temperature and in short reaction time and is applicable to a variety of substrates.

Methodologies for the synthesis of indole derivatives have been continuously developed over the past several decades due to both naturally-occurring and synthetic indoles exhibiting a broad range of biological activities.¹ Several strategies for indole construction have been reported including the synthesis of indole-2-carboxylate derivatives² of which aryl azidoacrylates have been one of the best precursors. Typically, the aryl azidoacrylate derivatives can be converted into indole-2-carboxylates using the Hemetsberger reaction which requires high temperature.³ Recently, Driver has developed a new catalyst, rhodium(II) perfluorobutyrate, which can activate aryl azidoacrylates for the formation of indole-2-carboxylates *via* C-H amination at relatively low temperatures (room temperature to 60 °C).⁴ Subsequently, commercially available iron(II) triflate was also reported as an effective catalyst for this transformation at 80 °C.⁵ However, both catalysts still require high reaction temperatures and long reaction times. Herein, we report for the first time that ZrCl₄ is an effective reagent for such transformation at room temperature or lower in less than 30 minutes. We commenced the investigation using the unactivated phenyl

Table 1. Optimization of the synthesis of indole-2-carboxylate.



| Entry | Reagent/Additive (equiv) | Solvent | Time (min) | Temp (°C) | Yield of 2a (%) |
|-------|---|--------------------|----------------|----------------|-----------------|
| 1 | Lewis acids | DCE | - ^b | - ^b | 0-14 |
| 2 | HfCl ₄ (1.0) | DCE | 1 | rt | 42 |
| 3 | ZrCl ₄ (1.1) | DCE | 1 | rt | 40 |
| 4 | ZrCl ₄ (1.1) | DCE | 5 | 0 | 46 |
| 5 | ZrCl ₄ /AgNO ₃ (1.1:0.1) | DCE | 60 | 0 | 28 |
| 6 | ZrCl ₄ /AgNO ₃ (1.4:0.1) | DCE | 20 | 0 | 70 |
| 7 | ZrCl ₄ /AgNO ₃ (1.4:1.0) | DCE | 10 | 0 | - |
| 8 | ZrCl ₄ /AgNO ₃ (0.1:0.2) | DCE | 30 | 0 | trace |
| 9 | ZrCl ₄ /Ag ₂ O (1.4:0.1) | DCE | 20 | 0 | - |
| 10 | ZrCl ₄ /KOAc (1.4:0.1) | DCE | 30 | 0 | - |
| 11 | ZrCl ₄ /K ₂ CO ₃ (1.4:0.1) | DCE | 30 | 0 | - |
| 12 | AgNO ₃ (1.0 eq) | DCE | 30 | rt | NR |
| 13 | ZrCl ₄ /AgNO ₃ (1.4:0.1) | CH ₃ CN | 25 | 0 | NR |
| 14 | ZrCl ₄ /AgNO ₃ (1.4:0.1) | DCM | 25 | 0 | NR |
| 15 | ZrCl ₄ /AgNO ₃ (1.4:0.1) | PhCH ₃ | 25 | 0 | NR |
| 16 | ZrCl ₄ /AgNO ₃ (1.4:0.1) | THF | 25 | 0 | NR |

[a] Isolated yield. [b] 1 eq of BF₃·OEt₂ = NR (rt, 6 h), 1 eq of AlCl₃ = complex mixture (rt, 30 min), 10 mol% of In(OTf)₃ = 14% (reflux, O/N), 20 mol% of Yb(OTf)₃ = trace (reflux, O/N)

azidoacrylate (**1a**) as a screening substrate and started our study with several Lewis acids including BF₃·OEt₂, AlCl₃, In(OTf)₃, Yb(OTf)₃, HfCl₄ and ZrCl₄. We found that only ZrCl₄ and HfCl₄ were promising as the reactions went to completion within a few minutes at room temperature and provided the desired product (**2a**) in acceptable yields (entries 2-3, Table 1). Among metal catalysts reported to effect such a transformation, ZrCl₄ is much less expensive, hence more economically advantageous. We then decided to select ZrCl₄ as the reagent for this transformation.⁶ In our optimization process, we encountered a competitive reaction which resulted in the formation of by-product **3a** in a significant amount. To reduce the formation of by-product **3a**, a lower temperature (0 °C, entry 4) was employed and found to improve the yield to 46%. Due to the polymeric structure with octahedral coordination geometry around the metal centers,⁷ ZrCl₄ and HfCl₄ could not be

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dissolved in DCE and, as a result, the corresponding reactions were heterogeneous. To improve the efficiency of $ZrCl_4$, we envisioned that breaking up the polymeric structure of $ZrCl_4$ might enhance the efficiency of this transformation. As reported in the literature⁸ that $AgNO_3$ could remove the chloride ligand from a metal center complex, we thought that the silver salt could abstract chloride ligand from $ZrCl_4$ resulting in depolymerization of its polymeric structure into short chains thereby increasing the reactivity of $ZrCl_4$ in the reaction. Therefore 0.1 equivalent of $AgNO_3$ was added to the reaction mixture (Table 1, entry 5). Unfortunately, the result was an incomplete reaction after 20 min as monitored by TLC. When this reaction was allowed to proceed longer (60 min), side reactions were observed and we obtained only 28% yield of the desired indole. Then we attempted to enhance the conversion by increasing the amount of $ZrCl_4$ to 1.4 equivalents and we found the reaction went to completion within 20 min at 0 °C to provide the desired product in 70% yield (entry 6). However, when 1.0 equivalent of $AgNO_3$ was employed, the reaction provided a complex mixture (entry 7). In this

entry, we initially observed the formation of the desired product by TLC but this product gradually disappeared from the decomposition under the reaction conditions. We believed this was due to the increased amount of $AgNO_3$ which led to the excess amount of short chain $ZrCl_4$ species from the depolymerization resulting in disintegration of the indole product. Furthermore, we also examined the reaction using a catalytic amount of $ZrCl_4$ (0.1 equivalent) and $AgNO_3$ (0.2 equivalent) (entry 8). Only trace amount of indole product **2a** was observed attributing to incomplete conversion of the azidoacrylate precursor **1a**. In addition, no conversion of compound **1a** was obtained when $ZrCl_4$ was excluded in the reaction mixture (entry 9). Therefore, stoichiometric amount of $ZrCl_4$ was needed for this transformation.⁹ Additionally, the use of different additives such as Ag_2O , KOAc, and K_2CO_3 (entries 10-12) were also explored. Unfortunately, these proved detrimental to the reactions, providing only mixtures of unidentifiable by-products. We also investigated the effect of solvents and found DCE to be well-suited for this

Table 2. Scope of aryl azidoacrylates

| entry | substrate | product | Temp/Time | Yield (%) | substrate | product | Temp/Time | Yield (%) ^a |
|----------------|-----------|---------|--------------------|-----------|-----------|---------|--------------------|------------------------|
| 1 | | | 0 °C (20 min) | 70 | 10 | | 0 °C (10 min) | 65 |
| 2 | | | 15 °C (3 min) | 75 | 11 | | rt (30 min) | 22 |
| 3 | | | 15 °C (10 min) | 69 | 12 | | 0 °C → rt (30 min) | 63 |
| 4 | | | 15 °C (10 min) | 69 | 13 | | 0 °C → rt (10 min) | 63 |
| 5 | | | 0 °C → rt (5 min) | 44 | 14 | | 0 °C → rt (10 min) | 61 ^b |
| 6 | | | 0 °C (15 min) | 80 | 15 | | 15 °C (20 min) | 56 ^b |
| 7 | | | 0 °C → rt (5 min) | 48 | 16 | | 0 °C (10 min) | 54 |
| 8 ^b | | | 0 °C → rt (10 min) | 79 | 17 | | 15 °C (1 min) | 88 |
| 9 | | | 0 °C (10 min) | 71 | | | | |

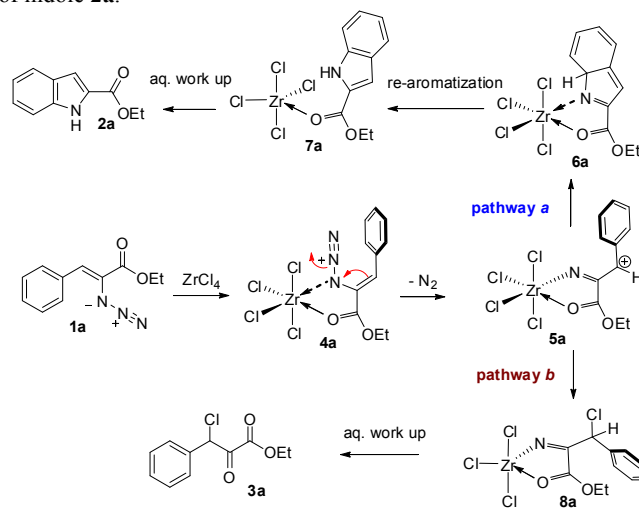
^a) Isolated yield. ^b) Combined yield of separable regioisomeric products; **2nX** = 31%, **2nY** = 30%, **2oX** = 38%, and **2oY** = 18%.

transformation while there was no reaction in CH₃CN, DCM, toluene or THF (entries 13-16). We therefore used 1.4 equivalent of ZrCl₄ and 0.1 equivalent of AgNO₃ in DCE as our optimal conditions.

To study the scope of this reaction, we then applied the optimal conditions to a variety of aryl azidoacrylate derivatives and the results are summarized in Table 2. *o*-Tolyl azidoacrylate and *o*-ethylphenyl azidoacrylate (entries 2-3) provided the desired products in good yields. The reaction of *p*-*tert*-butylphenyl azidoacrylate (1d, entry 4) also proceeded well under these conditions and furnished the corresponding indole in 69% yield. Unfortunately, when *p*-biphenyl azidoacrylate was subjected to this transformation, the yield dropped to 44% and we observed the formation of by-product 3e in a significant amount (42%). The results implied that the *p*-phenyl substituent increased the electrophilicity of the benzylic position of carbocation intermediate 5 (Scheme 1) which induced the nucleophilic attack by a chlorine atom from the zirconium complex. α -Naphthyl azidoacrylate was successfully converted to indole 2f in 80% yield, whereas β -naphthyl azidoacrylate gave product 2g in lower yield (48%) as the only isolable regioisomer. In the latter case, we observed a purple-colored reaction which we suspected was a sign of decomposition. *p*-Halogen-substituted phenyl azidoacrylates (entries 8-10) were effectively transformed to indole products in good efficiency. By contrast, when a substrate containing an electron-withdrawing nitro group (entry 11) was attempted, a low conversion was observed and the corresponding product was obtained in low yield. This could be attributed to the strong electron-withdrawing effect of the *p*-nitro group which prevented the nitrogen extrusion. Subsequently, *o*-halogen-substituted phenyl azidoacrylates (entries 12-13) were examined and found to provide the corresponding indoles in good yields. In the cases of *m*-chlorophenyl azidoacrylate and *m*-fluoro-*p*-tolyl azidoacrylate (entries 14-15), we obtained a mixture of regioisomeric products in moderate to good overall yields. The products were obtained in approximately a 1:1 ratio for the chloro-substituted indoles whereas in the fluoro-substituted case, the desired products were obtained in a 2:1 ratio. Interestingly, *m*-methoxyphenyl azidoacrylate (entry 16) provided a single regioisomeric product. In this entry, the purple-colored reaction mixture was also observed and the reaction produced the desired product in moderate yield. The reaction of polysubstituted phenyl azidoacrylate (entry 17) proceeded well, affording the indole product in excellent yield. From these results, we can draw a trend that aryl azidoacrylates *p*-substituted with electron-withdrawing groups such as phenyl and nitro groups (entries 5 and 11), led to the formation of the indole product in low yields whereas substrates containing electron-donating substituents in the *para*-position (*t*-Bu, Br, and OCH₃; entries 4, 8, and 17, respectively) could provide the desired indole products in higher yields.

The proposed mechanism for the formation of the indole 2a and by-product 3a is shown in Scheme 1. Since Zr(IV) are highly oxophilic which can form a stable metal-oxygen complex^{7,10} and also have a good chelation with the nitrogen donor¹¹ thus the coordinations of ZrCl₄ with the nitrogen and carbonyl group of the aryl azidoacrylate occurred in the initial step to generate the hexacoordinate zirconium complex 4.¹² This complex subsequently undergoes a slight rearrangement of bonds and a nitrogen extrusion to provide zirconium complex 5. This is the important key intermediate which could undergo two competing reaction pathways to form the indole product 2a (pathway a) or chlorinated-product 3a (pathway b). In partway a, an intramolecular nucleophilic aromatic substitution-type of complex 5 provides the cyclization intermediate complex 6 which rearomatizes and hydrolyzes upon workup to the desired indole 2a. For the formation of chlorinated-product 3a, the carbocation complex 5 could undergo an intramolecular chlorine atom transfer

(pathway b) to form the pentacoordinate zirconium complex 8.¹³ This complex is then further hydrolyzed during workup to give by-product 3a.¹⁴ DFT calculations were performed to understand the reaction pathways of these transformation as shown in Figure 1. The conversion of intermediate 5 to indole 2a is thermodynamically more favorable (pathway a) than the conversion to compound 3a via the chlorine atom transfer (pathway b) (Figure 1). In addition, the activation energies of pathway b is significantly larger than pathway a (TS4-TS2 = 6.2 kcal/mol), which explains the exclusive formation of indole 2a.



Scheme 1. Proposed mechanism for the formation of indole 2 and by-product 3.

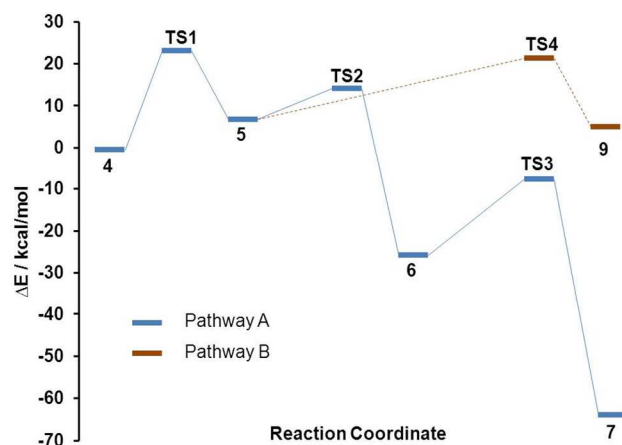


Figure 1. The calculated DFT energy profiles¹⁵ associated for the two mechanisms proposed in Scheme 1 (see SI for further details).

Conclusions

In conclusion, a cost-effective synthesis of indole derivatives is presented. We have established the use of commercially available and inexpensive zirconium(IV) chloride as a novel reagent to promote the nitrogen extrusion of aryl azidoacrylates followed by an annulation process at low temperature and in short reaction time to give the desired indole products in moderate to good yields. This provides a fast and mild synthetic protocol for the synthesis of indole derivatives which is applicable to a variety of substrates.

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- 15 Quantum chemical calculations were performed using the M06 density functional theory (DFT) method, with the LANL2DZ basis set in the Gaussian 09 program. Minima and transition states were confirmed as stationary points using the results from frequency calculations. Minima showed positive frequencies while transition states showed a single negative frequency corresponding to the expected reaction coordinates. For more details, see the supporting information.