Azaindole Synthesis

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Preparation of Functionalized Indoles and Azaindoles by the Intramolecular Copper-Mediated Carbomagnesiation of Ynamides**

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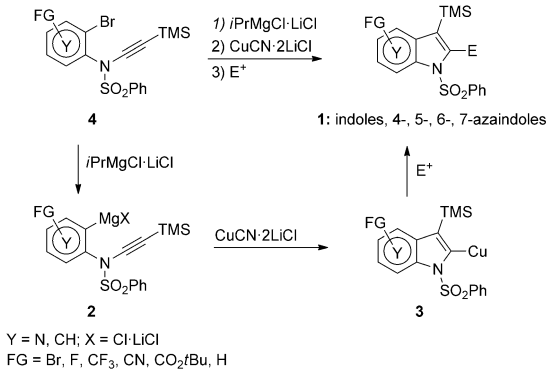
Dedicated to Professor Wolfgang Steglich on the occasion of his 80th birthday

Indoles are among the most important heterocycles and are a key structural element for a vast number of biologically active molecules (pharmaceuticals and agrochemicals).[1] The widespread utility of indoles has stimulated the development of numerous methodologies for their synthesis.[2] Also, the closely related azaindoles have recently received a lot of attention due to their potential biological properties.[3] A frequently employed strategy for azaindole synthesis is to start with substituted pyridines and to build up the pyrrole ring. Due to the electron-deficient nature of the pyridine ring, many classical indole preparations either do not proceed or are not efficient.[4] Thus, a synthetic method for the preparation of indoles as well as the various isomeric azaindoles (4-, 5-, 6-, or 7-azaindoles) would be highly desirable.

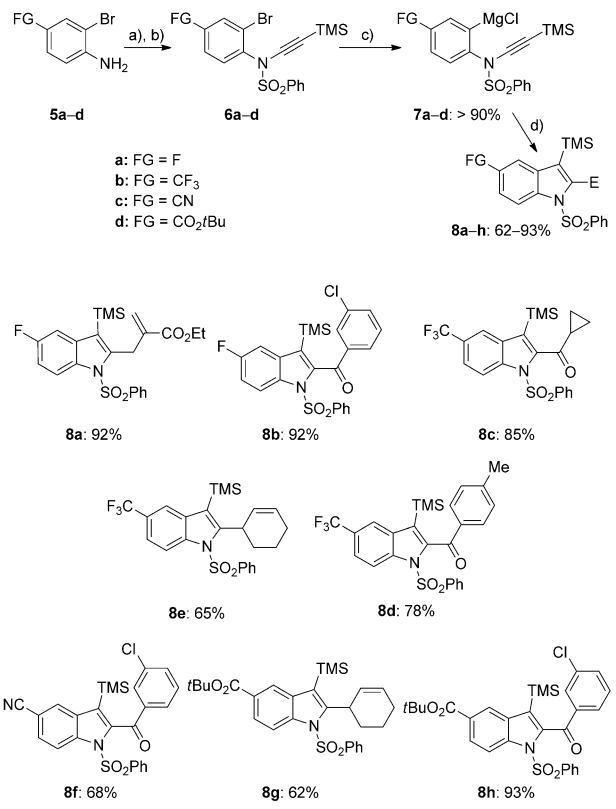
Recently, we have described a general preparation of functionalized benzo[*b*]thiophenes and benzo[*b*]thieno[2,3-*d*]thiophenes by means of an intramolecular catalytic carbocupration[5] reaction.[6] Carbocuprations are very powerful addition reactions for the construction of complex stereodefined organic molecules[7] and their intramolecular version is very attractive for constructing heterocyclic organometallic compounds.[8]

Herein, we report a mild and general one-pot preparation of indoles and azaindoles of type **1** by means of the new 5-*endo*-dig[9] copper-mediated intramolecular carbometalation of magnesiated derivatives of type **2**, leading to cuprated heterocyclic intermediates of type **3**, which after quenching with various electrophiles afford functionalized N-heterocycles of type **1** (Scheme 1). The magnesiated intermediates were readily prepared from the corresponding bromoynamides[10] of type **4** by a bromine–magnesium exchange.

First, we tested the intramolecular carbocupration for the preparation of polyfunctional indoles. The required bromoynamides of type **4** are available in two straightforward steps starting from the corresponding 2-bromoanilines (**5a–d**; Scheme 2). After N-sulfonylation of anilines **5a–d** and N-ethynylation using potassium hexamethyldisilazane



Scheme 1. Preparation of indoles and 4-, 5-, 6-, and 7-azaindoles by the copper-mediated carbomagnesiation of ynamides of type **4**.



Scheme 2. Preparation of functionalized indoles of type **8** by the copper-mediated carbomagnesiation of ynamide **6**. Reagents and conditions: a) $PhSO_2Cl$ (1.2 equiv), pyridine (3.0 equiv), CH_2Cl_2, 25 °C, 46–95 %; b) KHMDS (1.0 equiv), toluene, 0 °C, 1 h, then phenyl[(trimethylsilyl)ethynyl]iodonium triflate (1.2 equiv), 25 °C, 16 h, 45–79 %; c) *i*PrMgCl·LiCl (1.1 equiv), THF, −20 °C to 0 °C, 0.25 to 1.0 h; d) CuCN·2 LiCl (30–100 mol %), E^+ (0.9 equiv), 62–93 %.

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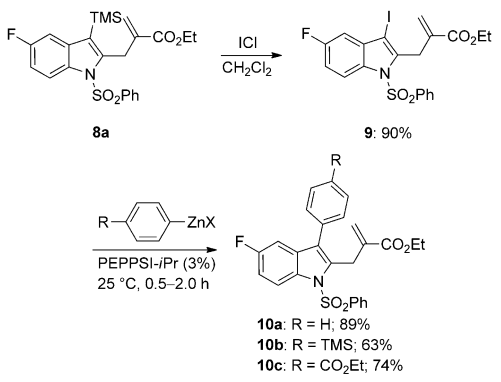
(KHMDS) and phenyl[(trimethylsilyl)ethynyl]iodonium triflate,[11] the corresponding ynamides **6a–d** were obtained in 45–79% yield.[12] Subsequent treatment of ynamide **6a** with *i*PrMgCl·LiCl[13] provided the corresponding magnesium reagent **7a** within 0.5 h at −10 °C in over 90% yield.[14] In the presence of a catalytic amount of CuCN·2 LiCl[15] (30 mol%) **7a** underwent a smooth cyclization (25 °C, 24 h)[16] producing a 2-metalated indole derivative (of type **3**; Scheme 1). A subsequent allylation reaction with ethyl 2-(bromomethyl)acrylate[17] (0.9 equiv) afforded the polyfunctional indole **8a** in 92% yield (Scheme 2).[18] Similarly, acylation of **7e** with 3-chlorobenzoyl chloride furnished the 2-acylated indole **8b** in 92% yield. The CF_3-substituted ynamide **6b** reacted smoothly with *i*PrMgCl·LiCl (−20 °C, 15 min) to give the corresponding magnesium reagent **7b**. However, in this case the addition of one equivalent of CuCN·2 LiCl was necessary to achieve complete ring closure (25 °C, 8 h). Alternatively, with microwave irradiation[19] of the reaction mixture (50 °C, max. 100 W) the ring closure reaches completion within 1.5 h. The resulting 2-metalated indole reacted with various electrophiles in good yields. Thus, acylations with cyclopropanecarbonyl chloride and 4-methylbenzoyl chloride provided the desired ketones **8c** and **8d** in yields of 85 and 78%, respectively. Similarly, the allylation with 3-bromocyclohexene afforded the functionalized indole **8e** in 65% yield.

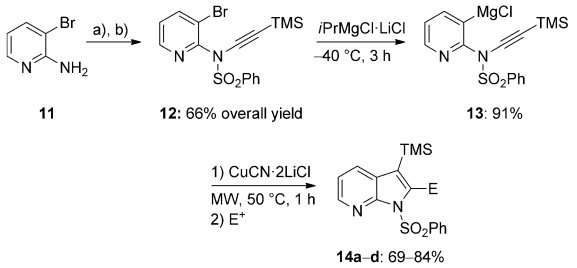
In the case of the cyano-substituted ynamide **6c**, the Br/Mg exchange with *i*PrMgCl·LiCl was complete at −5 °C in 0.5 h and for the more sensitive ester-substituted ynamide **6d**, the exchange was carried out at −20 °C in 1 h. The use of stoichiometric amounts of CuCN·2 LiCl avoids side reactions in both cases. Again when microwave irradiation (50 °C, max. 100 W) was applied, the ring closure was complete within 0.75–1 h (instead of 25 °C, 16 h). Subsequent acylation of the corresponding cyano-substituted 2-metalated heterocycle gave indole **8f** in 68% yield. Likewise, allylation and acylation of reagent **7d** afforded indoles **8g** and **8h** in yields of 62 and 93%, respectively (Scheme 3).

The TMS substituent in indoles of type **8** can be used as a handle for further functionalization in position 3. Thus, the TMS-substituted indole **8a** was converted into iodide **9** (ICl (1.1 equiv), CH_2Cl_2, 0 °C, 5 min, 90%;[20] Scheme 3). Iodoindole **9** undergoes Negishi cross-coupling reactions[21] with various zinc reagents[22] in the presence of 3 mol% PEPPSI-*i*Pr[23] to provide the 2,3-disubstituted indoles **10a–c** in 63–89% yield (Scheme 3).



Scheme 3. Transformation of the TMS-substituted indole **8a** into the 3-iodoindole **9** and subsequent Negishi cross-couplings.

Remarkably, this versatile indole synthesis was successfully extended to the preparation of 4-, 5-, 6-, and 7-azaindoles. For the synthesis of 7-azaindoles, we used commercial 2-amino-3-bromopyridine (**11**) as the starting material. The synthesis of the corresponding ynamide **12** was achieved in two steps as described above (66% overall yield). Treatment of ynamide **12** with *i*PrMgCl·LiCl (1.1 equiv, −45 °C, 1 h) provided the heteroarylmagnesium reagent **13** in roughly 91% yield. Upon subsequent microwave irradiation and reaction with CuCN·2 LiCl (1.0 equiv) at 50 °C the ring closure yielding **14** was complete within 1 h (Scheme 4).



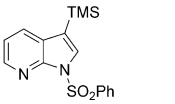
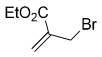
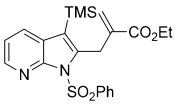
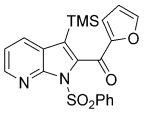
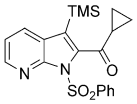
Scheme 4. Preparation of functionalized 7-azaindoles of type **14** by the copper-mediated carbomagnesiation of ynamide **12**. Reagents and conditions: a) $PhSO_2Cl$ (1.2 equiv), pyridine (3.0 equiv), CH_2Cl_2, 25 °C, 72 h, 80%; b) KHMDS (1.0 equiv), toluene, 0 °C, 1 h, then phenyl-[(trimethylsilyl)ethynyl]iodonium triflate (1.2 equiv), 25 °C, 16 h, 82%.

After quenching with water the corresponding 7-azaindole **14a** was isolated in 79% yield (Table 1, entry 1). Alternatively, allylation or acylation can be readily performed with ethyl 2-(bromomethyl)acrylate, furoyl chloride, or cyclopropanecarbonyl chloride to provide the desired 7-azaindoles **14b–d** in 69–84% yield (Table 1, entries 2–4).

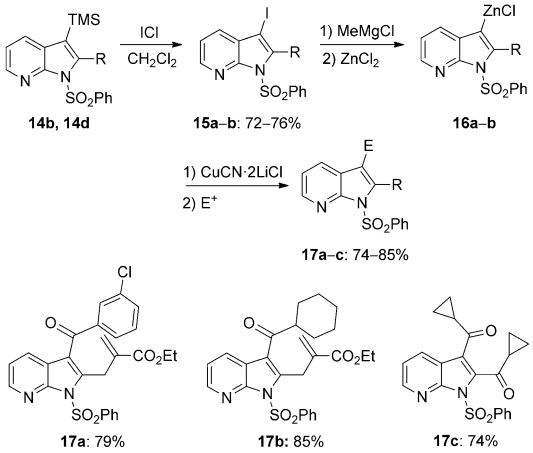
Further functionalization of 7-azaindoles **14b** and **14d** could be achieved by transformation of the TMS group using ICl (1.1 equiv) (CH_2Cl_2, 0 °C, 5 min, 64–72%) to provide the corresponding iodides **15a** and **15b**. Subsequent I/Mg exchange with MeMgCl (1.1 equiv, −78 °C, 0.5 h)[24] followed by transmetalation with $ZnCl_2$ (1.1 equiv) furnished the functionalized Zn reagents **16a–b** which reacted smoothly with 3-chlorobenzoyl chloride, cyclohexanecarbonyl chloride, and cyclopropanecarbonyl chloride to give the respective 2,3-disubstituted azaindoles **17a–c** in 74–85% yield (Scheme 5).

The subclass of 4- and 6-azaindoles is readily available using this new method. The standard two-step conversion of the commercial 2-bromopyridin-3-amine (**18**) provides the desired ynamide **19** in 56% overall yield. This precursor **19** undergoes a Br/Mg exchange reaction with *i*PrMgCl·LiCl (1.5 equiv, −40 °C, 24 h) at position 2 providing, after copper-mediated ring closure, 4-azaindole **20** in 52% yield (Scheme 6).[25] Remarkably, starting from the same ynamide **19**, the present methodology can be used to prepare 6-azaindoles by means of selective C–H activation mediated by

Table 1: Functionalized 7-azaindoles of type **14** obtained by the copper-mediated carbomagnesiation of ynamide **12** and subsequent reaction with various electrophiles.

Entry	Substrate	Electrophile[a]	Product[b]
1	**12**	H_2O	 **14a**: 79%
2	**12**		 **14b**: 84%
3	**12**		 **14c**: 69%
4	**12**		 **14d**: 84%

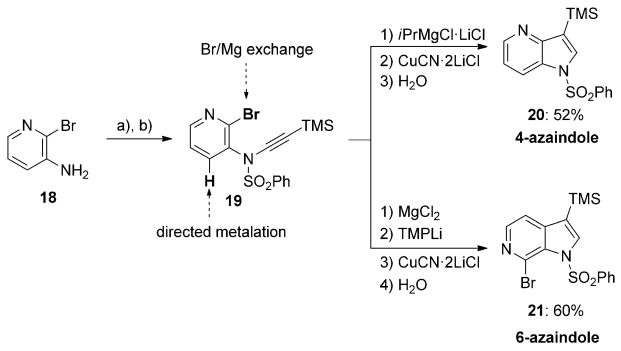
[a] 0.9 equiv of electrophile was used. [b] Yield of analytically pure product.



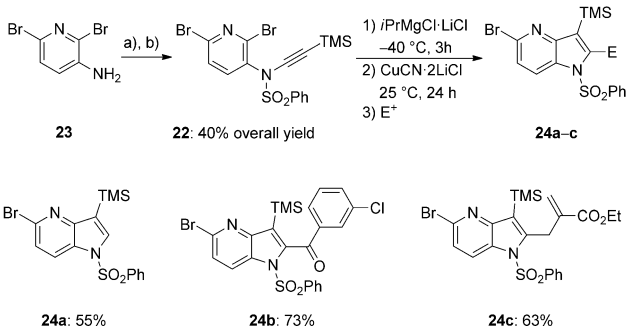
Scheme 5. 2,3-Disubstituted 7-azaindoles of type **17** obtained by transformation of the TMS-substituted 7-azaindoles **14b** and **14d**.

TMPLi.[26] Thus, the 2,3-substituted pyridine **19** was conveniently metalated with TMPLi (1.1 equiv) in the presence of $MgCl_2$ (1.2 equiv) at −78 °C within 0.5 h at position 4. Subsequent copper-mediated cyclization (25 °C, 48 h) followed by hydrolysis afforded 6-azaindole **21** in 60% yield.

Our methodology also provides simple access to more functionalized 4-azaindoles. The required ynamide **22** is available in two straightforward steps starting from 3-amino-2,6-dibromopyridine[27] (**23**) (40% overall yield, Scheme 7). A Br/Mg exchange performed on **22** with *i*PrMgCl·LiCl at −40 °C within 3 h affords, after copper-



Scheme 6. Reaction pathways for the conversion of ynamide **19** into 4-azaindole **20** and 6-azaindole **21**. Reagents and conditions: a) $PhSO_2Cl$ (1.2 equiv), pyridine (3.0 equiv), CH_2Cl_2, 25 °C, 1 h, 76%; b) KHMDS (1.0 equiv), toluene, 0 °C, 1 h, then phenyl[(trimethylsilyl)ethynyl]iodonium triflate (1.2 equiv), 25 °C, 16 h, 74%.

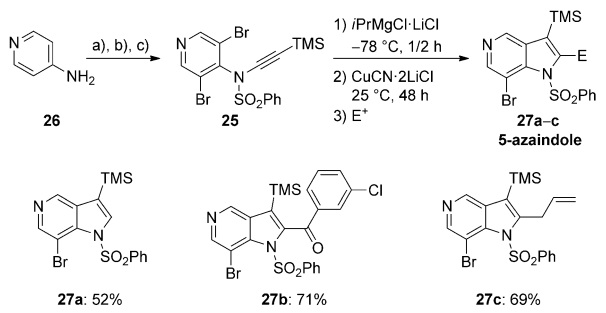


Scheme 7. Preparation of functionalized 4-azaindoles of type **24** by the copper-mediated carbomagnesiation of ynamide **22**. Reagents and conditions: a) $PhSO_2Cl$ (1.2 equiv), pyridine (3.0 equiv), CH_2Cl_2, 0–25 °C, 12 h, 65%; b) KHMDS (1.0 equiv), toluene, 0 °C, 1 h, then phenyl[(trimethylsilyl)ethynyl]iodonium triflate (1.2 equiv), 25 °C, 16 h, 62%.

mediated ring closure (25 °C, 24 h) and subsequent hydrolysis, acylation with 3-chlorobenzoyl chloride, or allylation with ethyl 2-(bromomethyl)acrylate, the corresponding polyfunctional 4-azaindoles **24a–c** in 55-73% yield (Scheme 7). Interestingly, the bromine substituent at position 5 provides a convenient handle for further functionalization.

Finally, the present methodology was extended to the synthesis of 5-azaindoles. Thus, ynamide **25**, prepared in the standard way in three steps from the commercial 4-aminopyridine (**26**) underwent a smooth Br/Mg exchange reaction with *i*PrMgCl·LiCl at −78 °C in 0.5 h. CuCN·2 LiCl mediated cyclization (1.0 equiv, 25 °C, 48 h) led after aqueous workup to the 5-azaindole **27a** (Scheme 8). Allylation with allyl bromide as well as acylation with 3-chlorobenzoyl chloride provided the new azaindoles **27b** and **27c** in 71 and 69% yield, respectively.

In summary, we have reported a mild and general intramolecular copper-mediated carbomagnesiation procedure for the synthesis of functionalized indoles as well as 4-, 5-, 6-, and 7-azaindoles starting from readily available ynamides. Further functionalization of these N-heterocycles with various electrophiles gave access to highly functionalized



Scheme 8. Preparation of functionalized 5-azaindoles of type **27** by the copper-mediated carbomagnesiation of ynamide **25**. Reagents and conditions: a) NBS (2.0 equiv), CCl_4, 24 h 25 °C, 70%; b) NaH (2.0 equiv), $PhSO_2Cl$ (1.0 equiv), THF, 0–25 °C, 12 h, 51%; c) KHMDS (1.0 equiv), toluene, 0 °C, 1 h, then phenyl[(trimethylsilyl)ethynyl]iodonium triflate (1.2 equiv), 25 °C, 16 h, 39%.

N-heterocycles in good yields. The generation of the key magnesium intermediate for the cyclization through the use of *i*PrMgCl·LiCl tolerated a wide range of functional groups. An extension of this methodology to other heteroarenes is currently underway in our laboratories.

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