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Synthetic Methods

Synthesis of Pyrrolo[2,3-*d*]pyrimidines by Copper-Mediated Carbomagnesiations of *N*-Sulfonyl Ynamides and Application to the Preparation of Rigidin A and a 7-Azaserotonin Derivative

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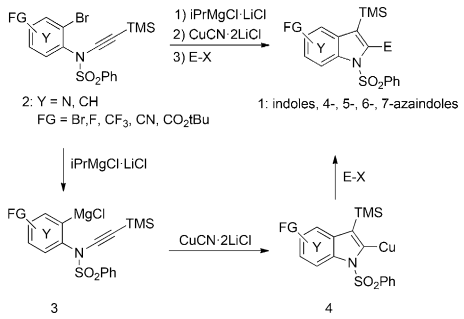
Abstract: The treatment of readily available *N*-alkynyl-5-iodo-6-sulfamido-pyrimidines with *i*PrMgCl·LiCl followed by a transmetalation with CuCN·2 LiCl produces, after intramolecular carbocupration, metalated pyrrolo[2,3-*d*]pyrimidines. Quenching of these pyrimidines with allylic halides or acid chlorides results in polyfunctional pyrrolo[2,3-*d*]pyrimidines. Further reaction with ICl and a Negishi cross-coupling, using PEPPSI-*i*Pr as the catalyst, furnishes fully substituted N-heterocycles. A formal synthesis of the marine alkaloid rigidin A has been achieved as well as the preparation of a derivative of 7-azaserotonine, related to the natural hormone serotonin.

Introduction

The preparation of condensed N-heterocyclic molecules is of great importance due to their biological properties.[1,2] Whereas the preparation of indoles is well established, the synthesis of highly substituted azaindoles is still a synthetic challenge. Recently, we and others developed a new preparation of functionalized indoles[3] and azaindoles[4] of type **1** from bromo *N*-sulfonyl ynamides[7] of type **2** (Scheme 1) using an intramolecular carbocupration[5] triggered by a Br–Mg exchange performed with *i*PrMgCl·LiCl.[6] The resulting organomagnesium reagent **3** undergoes a room temperature cyclization in the presence of CuCN·2 LiCl[8] leading to cuprated intermediates of type **4**, which, after quenching with various electrophiles, afford functionalized N-heterocycles of type **1**. Since azaindoles and pyrrolo[2,3-*d*]pyrimidines are common N-heterocycles found in natural products and in drug candidates, we have further investigated the preparation of relevant natural products and derivatives such as the marine alkaloid rigidin A[9] (**5**) as well as a derivative of 7-azaserotonin[10] (**6**), related to the natural hormone serotonin (**7**)[11] (Scheme 2).



Scheme 1. Copper-mediated carbomagnesation of ynamides of type **2** leading to indoles and azaindoles of type **1**.

Scheme 2. Natural products rigidin A, 7-azaserotonin, and serotonin.

Results and Discussion

As a model system for the preparation of rigidin A, we first prepared an *N*-sulfonyl ynamide derived from 2,4-dimethoxypyrimidine (**8**) with a double magnesiation/iodolysis sequence[12] using TMPMgCl·LiCl[13] (TMP = 2,2,6,6-tetramethylpiperidyl) and iodine to afford 5,6-diiodo-dimethoxypyrimidine (**9**) in 65% overall yield (Scheme 3). Copper-catalyzed amination[14] with *p*-toluenesulfonamide in the presence of Cs_2CO_3 in MeCN provided pyrimidyl *N*-sulfonylamide (**10**) in 68% yield. After metalation with KHMDS (HMDS = phexamethyldisilazane), treatment with phenyl((trimethylsilyl)ethynyl)iodonium triflate[15] afforded 6-substituted pyrimidyl *N*-sulfonyl ynamide (**11**).

Compound **11** was then submitted to an I–Mg exchange using *i*PrMgCl·LiCl (THF, −40 °C, 2 h). After full conversion,[16] the intermediate magnesium reagent of type **3** underwent transmetalation to the corresponding copper species using CuCN·2 LiCl. A smooth *trans*-carbocupration proceeded at 25 °C within 16 h leading to heterocyclic intermediate of type **4**. After hydrolysis, the pyrrolo[2,3-*d*]pyrimidine (**12a**) was obtained in 67% isolated yield (Table 1, entry 1). Allylation of the

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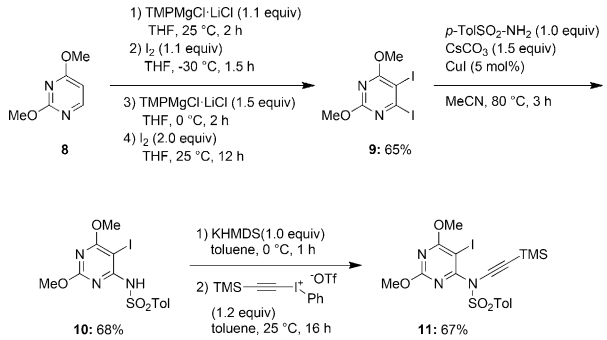
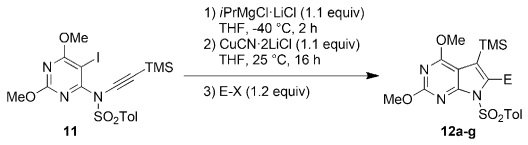
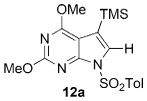
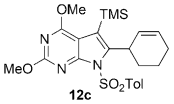
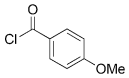
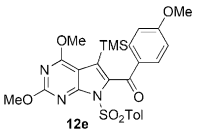
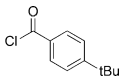
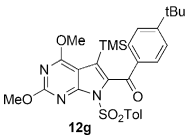
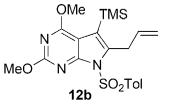
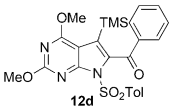
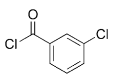
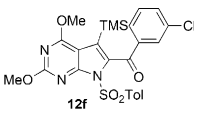


Scheme 3. Preparation of the *N*-sulfonyl ynamide (**11**).

copper intermediate of type **4** with allyl bromide or 2-cyclohexenyl bromide provided the allylated products (**12b–c**) in 57–81% yield (entries 2–3). Finally acylation with various aromatic acid chlorides furnished the substituted benzoylated N-heterocycles (**12d–g**) in 53–77% yield (entries 4–7).

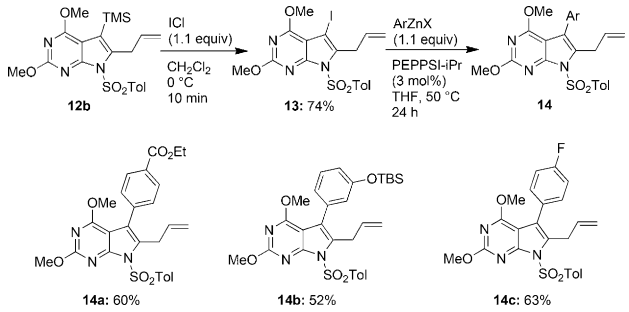
Table 1. Functionalized pyrrolo[2,3-*d*]pyrimidines of type **12** obtained by copper-mediated carbomagnesiation of ynamide **11** and subsequent reaction with various electrophiles (E–X).



Entry	Electrophile	Product	Yield [%][a]
1	H_2O	 **12a**	67
2		 **12c**	81
3		 **12e**	57
4		 **12g**	67
5		 **12b**	71
6		 **12d**	77
7		 **12f**	53

[a] Isolated yield of analytically pure products.

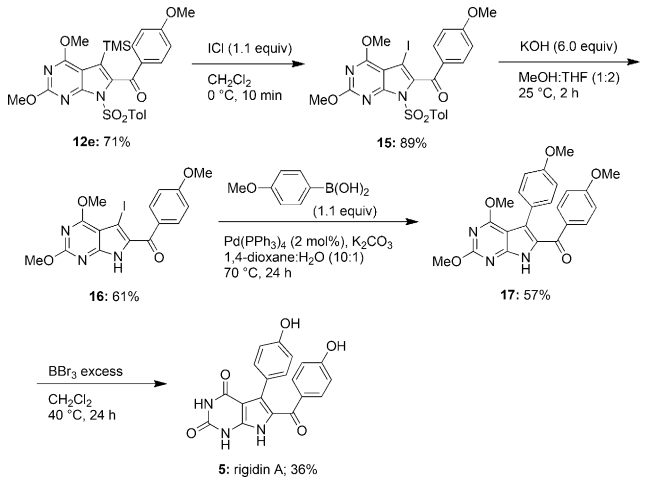
We further demonstrated that the 3-TMS-substituted pyrrolo[2,3-*d*]pyrimidine (**12b**) can be readily converted into the corresponding iodide (**13**) by using ICl[17] in CH_2Cl_2 (0 °C, 10 min) in 74% yield. Negishi cross-coupling[18] with various zinc reagents[19] using PEPPSI-IPr[20] furnished the arylated products (**14a–c**) in 52–63% yield (Scheme 4).



Scheme 4. Transformation of the TMS-substituted pyrrolo[2,3-*d*]pyrimidine **12b** to the 3-iodocompound **13** followed by Negishi cross-couplings.

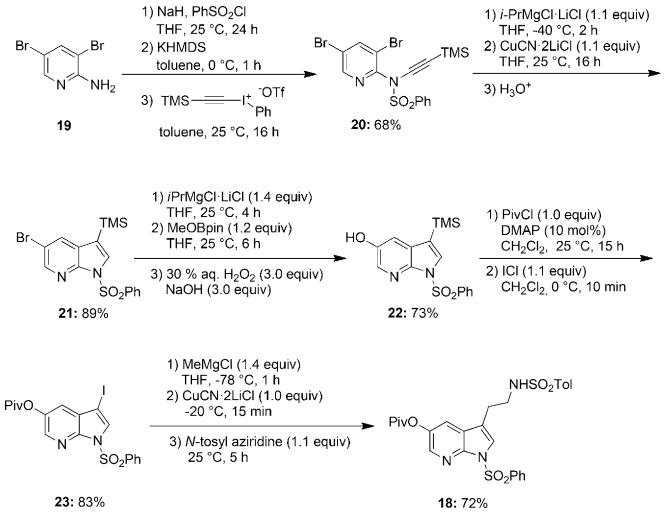
With these results in hand, we applied this method to the synthesis of marine natural product rigidin A (**5**; Scheme 5). Thus, the iodolysis of **12e** with ICl provided the 3-iodo-derivative (**15**) in 89% yield. Desulfonylation with KOH in a mixture of MeOH:THF led to the pyrrolo[2,3-*d*]pyrimidine (**16**) in 61% yield. The N-heterocycle **16** was further converted to rigidin A (**5**), according to the procedure of Sakamoto,[21] in two steps. A Suzuki reaction[22] afforded the fully substituted heterocycle **17** (57% yield), followed by a deprotection of the four methoxy-substituents leading to rigidin A (**5**) in five steps starting from the *N*-sulfonyl ynamide (**11**) in about 8% overall yield.

Finally, we performed a short synthesis of a derivative of 7-azaserotonine (**18**) starting from commercially available 2-amino-3,5-dibromopyridine (**19**) (Scheme 6). First, the phenylsulfonylation of the pyridine **19** with $PhSO_2Cl$ followed by its conversion to the corresponding ynamide **20** using KHMDS and phenyl((trimethylsilyl)ethynyl)iodonium triflate proceeded in about 68% overall yield. Regioselective Br–Mg exchange



Scheme 5. Synthesis of rigidin A (**5**).

with *i*PrMgCl·LiCl followed by a transmetalation with CuCN·2 LiCl provided, after an intramolecular carbocupration (25 °C, 16 h), the azaindole **21** in 89% yield. A second Br–Mg exchange followed by a borylation with methoxyboronic acid pinacol ester[23] and subsequent oxidation (30% H_2O_2, NaOH, 25 °C, 15 h) provided the 5-hydroxyazaindole **22** in 73% yield. Protection of the free phenolic hydroxyl group with pivaloyl chloride and iodination with ICl furnished the 3-iodoazaindole **23** in 83% yield. I–Mg exchange of **23** with MeMgCl and transmetalation with CuCN·2 LiCl, followed by an opening[24] of *N*-tosyl aziridine (25 °C, 5 h) gave the *N*-sulfonyl azaserotine derivative **18** in 72% yield.[25] The overall yield of the 7-azaserotonine derivative **18** was approximately 26% for 7 steps beginning with the aminopyridine (**19**).



Scheme 6. Synthesis of a derivative of *N*-sulfonylated 7-azaserotonin **18**.

Conclusions

In summary, we have reported a room temperature, intramolecular copper-mediated carbomagnesiation procedure for the synthesis of functionalized pyrrolo[2,3-*d*]pyrimidines of type **12** and 7-azaindole derivatives. Further functionalization of these N-heterocycles gave access to the marine alkaloid rigidin A and a derivative of 7-azaserotonin.

Experimental Section

Typical procedure for intramolecular copper-mediated carbomagnesations: To a solution of ynamide **11** (1.0 equiv) in THF (0.5 M) *i*PrMgCl·LiCl (1.22 M in THF, 1.1 equiv) was added dropwise at −40 °C and stirred at this temperature for 2 h. After addition of THF (0.05 M), CuCN·2 LiCl (1.0 M in THF, 1.1 equiv) was added and the solution was stirred at 25 °C for 24 h. The reaction mixture was then cooled to −30 °C, quenched with an electrophile (1.2 equiv), and slowly allowed to warm to 25 °C. After addition of aqueous NH_4Cl:NH_3 solution (19:1), the reaction mixture was extracted with EtOAc, the organic layers were dried ($MgSO_4$), and concentrated in vacuo. The crude residue was purified by flash column chromatography on silica gel to yield the corresponding products of type **12**.

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Keywords: azaserotonin · carbomagnesation · cyclisation · *N*-heterocycles · rigidin A

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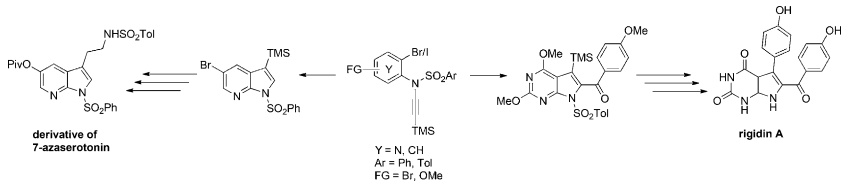

On the route to biomolecules: A mild and general intramolecular copper-mediated carbomagnesiation procedure was developed for the synthesis of functionalized N-heterocycles starting from readily available ynamides. Subsequent reactions offer short synthetic routes to biologically relevant molecules such as rigidin A or a derivative of 7-azaserotonin.

Synthetic Methods

*J. Nickel, M. Fernández, L. Klier, P. Knochel**

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Synthesis of Pyrrolo[2,3-*d*]pyrimidines by Copper-Mediated Carbomagnesiations of *N*-Sulfonyl Ynamides and Application to the Preparation of Rigidin A and a 7-Azaserotonin Derivative