ORGANIC LETTERS

2002
Vol. 4, No. 11
1819−1822

Preparation of Polyfunctional Heterocycles Using Highly Functionalized Aminated Arylmagnesium Reagents as Versatile Scaffolds

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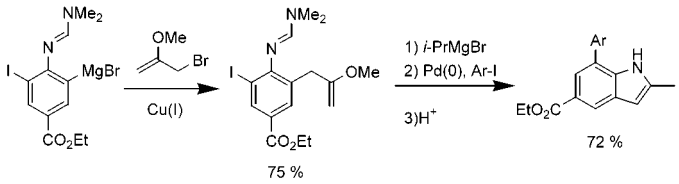
Received January 22, 2002

ABSTRACT



Functionalized Grignard reagents, derived from readily available *o*-iodoaniline derivatives and obtained via a straightforward iodine−magnesium exchange, can be used to prepare a wide range of polyfunctional indoles, quinolines, and quinazolinones.

The preparation of polyfunctional heterocycles by using multicoupling reagents[1] as versatile scaffolds has recently been extensively studied.[2] Such polyfunctional scaffolds allow the synthesis of a broad range of diversely functionalized heterocycles. Recently, we have reported that various polyfunctional aryl-, heteroaryl-, and alkenylmagnesium compounds[3] can be prepared using an iodine- or bromine-magnesium exchange reaction.[3,4] Aminated arylmagnesium compounds recently obtained by these methods[5] should be especially useful for the preparation of nitrogen-containing heterocycles.[6] Herein, we report that readily available functionalized *o*-iodoanilines or *o*-iodo-*p*-phenylenediamines can be converted, via organomagnesium intermediates, into polyfunctionalized indoles, quinolines, and quinazolinones. Thus, treatment of the amidine-protected diiodoamidine[7] **1a**

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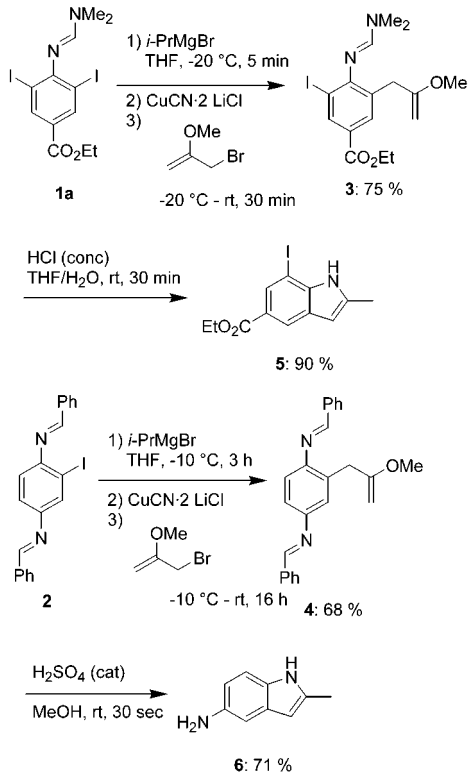
10.1021/ol025597x CCC: $22.00
Published on Web 04/30/2002

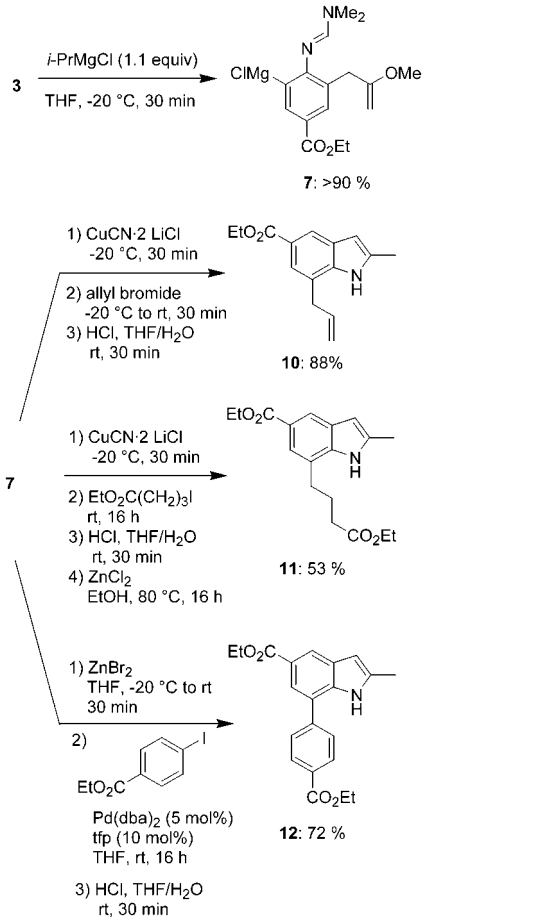
or the diimine derivative of 2-iodophenylenediamine,[8] **2**, with *i*-PrMgCl in THF (−20 °C, 5 min or −10 °C, 3 h, respectively) furnishes the corresponding mono-organomagnesium derivative in over 90% yield, as estimated by analysis of reaction aliquots. After transmetalation to the corresponding copper species with CuCN·2LiCl[9] and allylation with 2-methoxyallyl bromide,[10] the desired allylation products **3** and **4** are obtained in 75% and 68% yield, respectively. Treatment of these allylated products **3** and **4** with HCl in THF/H_2O (25 °C, 30 min) produces the polyfunctional indoles **5** and **6** in 90% and 71% yield, respectively (Scheme 1).

Scheme 1



Remarkably, the diiodoaniline derivatives of type **1** are selectively converted to the monomagnesium reagent, since the increased electron density of the aromatic ring of the magnesiated intermediate prohibits a further iodine−magnesium exchange. However, once this magnesium reagent has reacted with an electrophile to give product **3**, a second iodine−magnesium exchange can now be readily achieved (*i*-PrMgCl, −20 °C, 0.5 h), furnishing the polyfunctional arylmagnesium reagent **7** (Scheme 2). After

Scheme 2



transmetalation into the copper reagent using CuCN·2LiCl, reaction with allyl bromide leads after cyclization under acidic conditions to the indole **10** in 88% yield. Alternatively, alkylation with ethyl 4-iodobutyrate[3d] followed by successive treatment with HCl (rt, 5 min) and $ZnCl_2$ in EtOH (80 °C, 16 h) produces the indole **11** in 53% yield. Finally, transmetalation of the aryl iodide **3** to the corresponding arylzinc reagent by reaction with $ZnBr_2$ followed by Negishi cross-coupling[11] with ethyl *p*-iodobenzoate, using tri-*o*-furylphosphine[12] (tpf, 10 mol %) and $Pd(dba)_2$ (5 mol %) leads, after acidic workup, to the functionalized indole **12** in 72% yield (Scheme 2).

Functionalized aminated aryl iodides can also be used for the preparation of quinolines. Thus, the conversion of the

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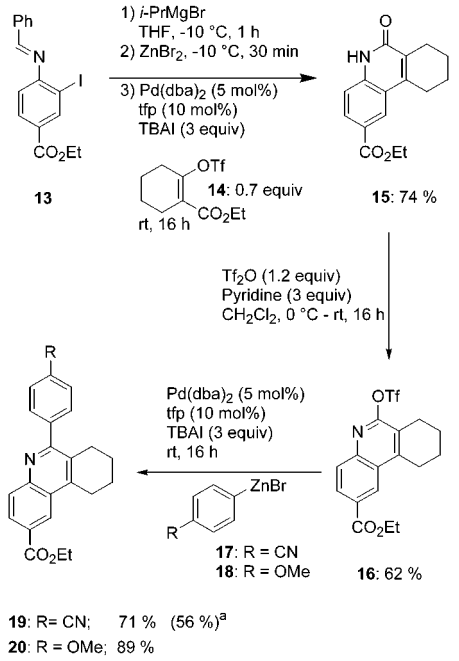
iodoaniline derivative **13** to the corresponding zinc reagent is performed by a sequential iodine−magnesium exchange reaction, followed by a transmetalation with zinc bromide (Scheme 3). Subsequent Negishi cross-coupling with ethyl

Scheme 3

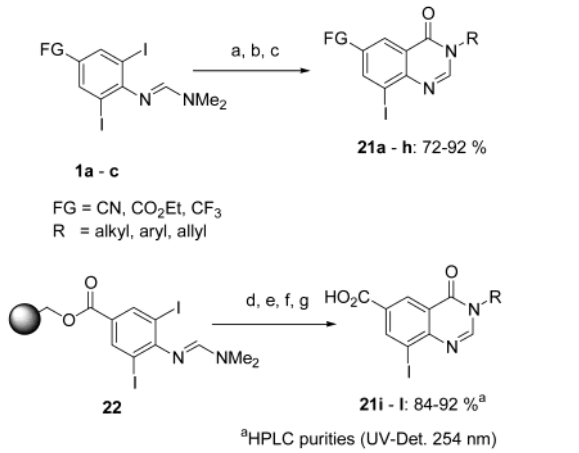


[a] Yield in the absence of TBAI.

2-trifluorosulfonyloxy-1-cyclohexenylcarboxylate **14** (0.7 equiv)[13] leads to the heterocycle **15** in 74% yield ($Pd(dba)_2$ (5 mol %); tfp (10 mol %), 25 °C, 16 h). The amide function of **15** can then be converted to the enol triflate (**16**) by reaction with Tf_2O and pyridine in CH_2Cl_2 (0−25 °C, 16 h; 62% yield).[14] Palladium(0)-catalyzed cross-coupling of **16** with functionalized arylzinc bromides, such as **17** and **18**, leads to the polyfunctional quinolines **19** and **20** in 71% and 89% yield, respectively (Scheme 3). Interestingly, the yield of this cross-coupling can be greatly improved by the addition of tetrabutylammonium iodide (TBAI, 3 equiv).[15] This enhanced reactivity is proposed[16] to be due to activation of the palladium catalyst by the formation of a palladate species,[16] thereby facilitating the oxidative addition to the carbon-triflate bond.

Finally, by exploiting the electrophilic carbon and dimethylamino leaving group of the amidine unit, several diversely functionalized diiodoamidines of type **1** have been converted, in a one-pot procedure, to quinazolinones of type **21**. Thus, formation of the corresponding Grignard reagents (THF, *i*-PrMgCl (1.1 equiv), −20 °C, 5−30 min) followed

Scheme 4



[a] a: *i*-PrMgBr (1.1 equiv), THF, −20 °C, 30 min; b: R−N=C=O (1.2−1.4 equiv), 0 °C, 3−6 h, then MeOH; c: HCl (1 equiv), silica gel, THF, rt, 16 h; d: *i*-PrMgBr (5 equiv), THF, −20 °C, 5 min; e: R−N=C=O (15 equiv), −20 °C to 0 °C, 2−3 h; f: $ZnCl_2$ (15 equiv), THF, 60 °C, 16 h; g: TFA/CH_2Cl_2/H; 9:1:1, 15 min.

by reaction with a range of isocycanates furnishes, after workup and treatment with silica gel (rt, 16 h), the desired quinazolinones **21a**−**h** in 72−92% yield (Scheme 4 and Table 1). The same synthetic sequence has also been

Table 1. Functionalized Quinazolinones of Type **21** Prepared in Solution Starting from **1a**−**c** or on Solid Phase Starting from **22** via Intermediate Functionalized Magnesium Reagents

entry	FG	R	product of type **21**	yield (%)[a]
1	CO_2Et	*p*-ClC_6H_4	**21a**	88
2	CO_2Et	*m*-$CF_3C_6H_4$	**21b**	90
3	CO_2Et	*n*-$C_{14}H_{29}$	**21c**	72
4	CO_2Et	$CH_2CH{=}CH_2$	**21d**	75
5	CN	*m*-$CF_3C_6H_4$	**21e**	92
6	CN	*p*-ClC_6H_4	**21f**	91
7	CN	*p*-$MeOC_6H_4$	**21g**	86
8	CF_3	2,4-MeC_6H_3	**21h**	84
9	CO_2H	2,4-MeC_6H_3	**21i**	90[b,c]
10	CO_2H	*m*-CNC_6H_4	**21j**	89[b,c]
11	CO_2H	*p*-$MeOC_6H_4$	**21k**	84[b,c]
12	CO_2H	*p*-ClC_6H_4	**21l**	92[b,c]

[a] Isolated yield of analytically pure product. [b] HPLC purity (254 nm). [c] Solid-phase reaction.

performed successfully on solid phase. Thus, Wang resin attached ester **22**[17] was treated with *i*-PrMgBr (5 equiv, 5 min, −20 °C) and various functionalized isocyanates (15 equiv, 0 °C, 2−3 h). After washing the resin, functionalized quinazolinones **21i**−**l** can be formed either by direct cleavage

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and cyclization reaction with TFA/CH_2Cl_2/H_2O 9:1:1 (15−30 min) or prior use of $ZnCl_2$ (15 equiv, 60 °C, 0.6 M in THF) in order to form the heterocycle on solid phase without cleaving it. Further diversity might be introduced in the resin-attached molecule, by applying one of the two strategies described above.

In conclusion, we have shown that the Grignard reagents derived from readily available *o*-iodoaniline derivatives can be used to prepare a wide range of polyfunctional indoles, quinolines, and quinazolinones, which may be of great interest for their potential pharmaceutical properties. Extensions of this method for the preparation of more complex heterocycles is currently underway in our laboratories.[18]

Acknowledgment. We thank the DFG (Leibniz-Program) and the Fonds der chemischen Industrie for financial support. W.D. thanks the BASF AG for a fellowship. A.E.J. thanks L'Oréal (Aubervilliers) for a fellowship. D.M.L. thanks the Alexander von Humboldt Foundation for a fellowship. We thank Chemetall GmbH (Frankfurt), the BASF AG (Ludwigshafen), OMG (Hanau-Wolfgang), and Degussa AG (Hanau) for generous gifts of chemicals.

Supporting Information Available: Experimental procedures and full characterization of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL025597X

(18) **Typical Experimental Procedure. Preparation of the Iodoaryl Amidine (3).** A dry and argon-flushed 50-mL Schlenk flask, equipped with a septum and a magnetic stirrer, was charged with the diiodoarylamidine **1a** (3.81 g, 8.08 mmol) in dry THF (25 mL). The solution was cooled to −25 °C, and *i*-PrMgCl (4.1 mL, 2.1 M in Et_2O, 8.6 mmol) was added slowly, keeping the temperature below −20 °C. After 10 min the exchange was complete (checked by TLC analysis), a solution of CuCN·2LiCl (8.8 mL, 1 M in THF, 8.8 mmol) was added at −20 °C, and the reaction mixture was stirred for 30 min at this temperature. Then 2-methoxyallyl bromide (4.04 g, 45%, 12.0 mmol)[10] was added, keeping the temperature below −15 °C. The reaction mixture was stirred then for 1 h at −20 °C, after which TLC analysis indicated complete conversion. Then the reaction mixture was quenched by the addition of a 9:1 mixture of saturated $NH_4Cl_{(aq)}$ and 25% $NH_{3(aq)}$ (5 mL) and poured into a separatory funnel containing saturated $NH_4Cl_{(aq)}$ (40 mL). The aqueous phase was extracted with ethyl acetate (3 × 40 mL), and the combined organic phases were washed with water (50 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (19:5:1 pentane/ether/triethylamine) yielding **3** as a pale yellow oil (2.52 g, 75% yield). **Preparation of the Polyfunctional Indole (11).** A dry and argon-flushed 10-mL Schlenk flask, equipped with a septum and a magnetic stirrer, was charged with the iodoaryl amidine **3** (545 mg, 1.3 mmol) in dry THF (2 mL). The solution was cooled to −25 °C, and *i*-PrMgBr (1.2 mL, 1.3 M in THF, 1.6 mmol) was added slowly, keeping the temperature below −20 °C. After 1 h at −20 °C the exchange was complete (checked by TLC analysis), and a solution of CuCN·2LiCl (1.6 mL, 1 M in THF, 1.6 mmol) was added slowly at −20 °C and stirred for 30 min at this temperature. Ethyl 4-iodobutyrate (578 mg, 2.4 mmol) was added, and the reaction mixture was allowed to warm to room temperature and stirred then for 16 h. After this time, TLC analysis indicated complete conversion, and the reaction mixture was quenched and worked up as described for **3**. The residue was purified by flash chromatography (67:33:1 ether/pentane/triethylamine) to give 318 mg of a pale yellow oil. This oil was then dissolved in THF (4 mL) and water (4 mL), and concentrated HCl (0.4 mL) was added. After 5 min of stirring at room temperature, TLC analysis indicated complete conversion. The reaction mixture was poured into a separatory funnel containing saturated $NaHCO_{3(aq)}$ solution (10 mL). The aqueous phase was extracted with ethyl acetate (4 × 10 mL), and the organic phases were washed with water (20 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was redissolved in ethanol (5 mL), and dry zinc chloride (325 mg, 2.4 mmol) was added. The reaction mixture was heated to reflux for 16 h and then cooled to room temperature, and ethanol was removed in vacuo. The residue was dissolved in ethyl acetate (10 mL) and poured into water (10 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (4 × 10 mL). The combined organic phase was washed with water (30 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was then titurated with a few mL of 1:1 pentane/ether to give **11** as a white powder (224 mg, 53% yield).