Synthetic Methods

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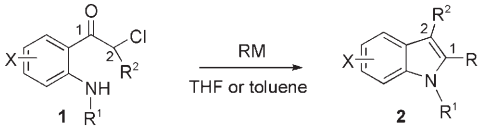
Expanding the [1,2]-Aryl Migration to the Synthesis of Substituted Indoles**

Tao Pei, Cheng-yi Chen,* Peter G. Dormer, and Ian W. Davies*

The indole scaffold is a prevalent substructure of many natural products and biologically active compounds.[1] The need for efficient and practical syntheses of indoles bearing a variety of substitution patterns provides a continual challenge to organic chemists. Despite the many diverse and creative approaches that have been used to assemble the indole nucleus,[2] a general synthesis of indoles with control over the regioselective introduction of substituents at C2 and C3, is of tantamount importance. Herein we report a synthesis of substituted indoles **2** from readily accessible chloroacetophenones **1**,[3] which contain a 1-(2-aminophenyl)-2-chloroethanone core structure, and commercially available organometallic reagents [RM, Eq. (1)]. Of particular significance is the



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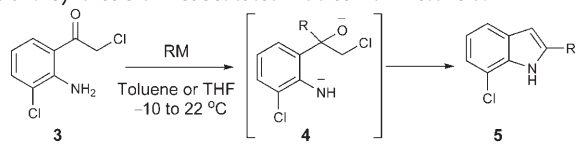
generality of this reaction and the regioselectivity achieved under mild reaction conditions, which makes this transformation viable for the preparation of many structurally diverse indoles. This efficient synthesis of indoles takes advantage of a pivotal [1,2]-aryl rearrangement.

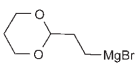
Our initial encounter of the feasibility of using a [1,2]-aryl migration to deliver 2-substituted indoles was observed in the reaction of *n*PrMgCl with 1-(2-amino-3-chlorophenyl)-2-chloroethanone (**3**). Surprisingly, the sole product of the reaction was indole **5a** in 81% yield (Table 1, entry 1). We anticipated that this efficient pathway involving a unique aryl migration would provide the basis for the direct access to 2- and 2,3-substituted indoles upon the appropriate choice of organometallic species as the nucleophile.

To explore the generality of this transformation, the addition of different organometallic compounds to ketone **3** was studied (Table 1). Similar to *n*PrMgCl, other primary alkyl Grignard reagents (RM) reacted with **3** to give C2-substituted indoles in excellent yields (entries 2 and 3).

Table 1: Synthesis of 2-substituted indoles from ketone **3**.[a]



3 **4** **5**

Entry	RM	Product	Yield [%][g]
1[f]		**5a**	81
2[f]		**5b**	89
3[e]		**5c**	86
4[f]		**5d**	45
5[b,e]	*n*HexLi	**5e**	76
6[b,f]	Me_3SiCH_2Li	**5f**	70
7[e]	PhMgCl	**5g**	91
8[c,e]		**5h**	78
9[c,e]		**5i**	76
10[e]		**5j**	72
11[d,e]		**5k**, R = $SiMe_3$	54
12[d,e]		**5l**, R = *n*Bu	55

[a] Reaction conditions: All reactions were carried out without optimization: Ketone **3** (1.0 mmol) in either THF or toluene (2 mL) and nucleophile (2.5 mmol) were stirred at −10 °C for 15 min, then at room temperature for 15 min to 2 h. [b] Addition of nucleophile at −40 °C. [c] The nucleophile was generated in situ from the corresponding aryl iodide and *i*PrMgCl. [d] The nucleophile was generated in situ from the corresponding alkynes and *i*PrMgCl. [e] Solvent = THF. [f] Solvent = toluene. [g] Yields refer to isolated product based on ketone **3**.

[*] Dr. T. Pei, Dr. C.-Y. Chen, Dr. P. G. Dormer, Dr. I. W. Davies
Department of Process Research
Merck Research Laboratories
Rahway, NJ 07065 (USA)
Fax: (+1) 732-594-1499
E-mail: tao_pei@merck.com
cheng_chen@merck.com

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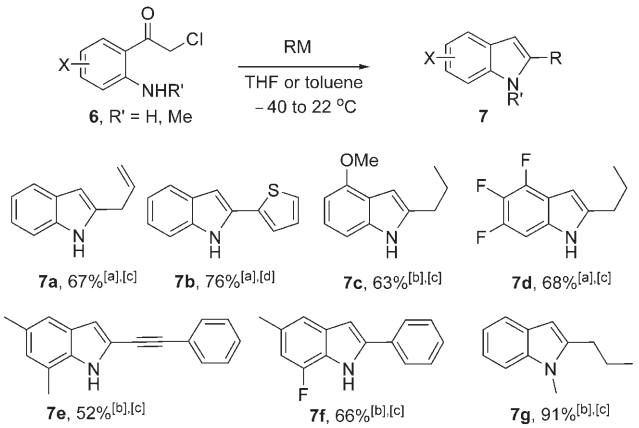
Moreover, the addition of organolithium species such as *n*-hexyllithium and trimethylsilylmethyllithium afforded indole **5e** and **5f**, in yields of 76 and 70%, respectively (entries 5 and 6).

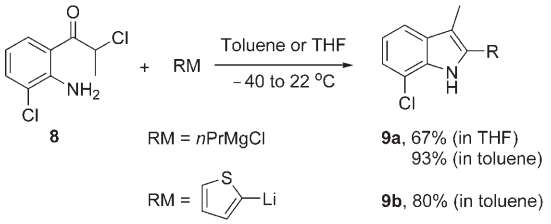
A number of aromatic and heteroaromatic functionalities were readily introduced at the C2-position of the indoles by the addition of aryl and heteroaryl magnesium reagents to ketone **3**. For example, 2-phenyl-7-chloroindole (**5g**) was prepared in excellent yield (91%) using phenylmagnesium chloride (entry 7). Heteroaryl nucleophiles, such as 2- and 3-pyridinylmagnesium chloride, and 2-thienylmagnesium bromide gave the corresponding 2-heteroaryl indoles (**5h–j**) in yields of 78, 76, and 72%, respectively (entries 8–10). Furthermore, 2-alkyn-1-ylindoles were directly synthesized from alkynylmagnesium species (entries 11 and 12).

Having successfully employed various carbon nucleophiles for the preparation of a range of 2-substituted indoles from ketone **3**, we decided to extend our methodology to other substituted ketones (Scheme 1). Not surprisingly, 1-(2-aminophenyl)-2-chloroethanone (**6a**, X, R′ = H) worked well in the reaction, and afforded the 2-allyl- and 2-thien-2-ylindoles (**7a** and **7b**) in yields of 67 and 76%, respectively. The presence of either electron-donating or electron-withdrawing substituents on the phenyl ring had little impact on the transformation. 1-(2-Amino-6-methoxyphenyl)-2-chloroethanone (**6c**, X = 6-MeO, R′ = H) which contains an electron-rich methoxy group was converted into 4-methoxy-2-propylindole (**7c**) in 63% yield, while the substrate containing a trifluoro-substituted phenyl ring reacted with *n*PrMgCl to form 4,5,6-trifluoro-2-propylindole (**7d**) in 68% yield. 5,7-Dimethyl-2-phenylethynylindole (**7e**) and 7-fluoro-5-methyl-2-phenylindole (**7f**) were readily prepared by the addition of either phenylethynyl- or phenylmagnesium chloride, respectively. N Substitution was also tolerated in this reaction, as demonstrated in the reaction of 1-(*N*-methyl-2-aminophenyl)-2-chloroethanone (**6g**, X = H, R′ = Me) with *n*PrMgCl to form *N*-methyl-2-propylindole (**7g**) in very high yield (91%).



Scheme 1. Synthesis of 2-substituted indoles from ketone **6**. All reactions were carried out without optimization. Yields refer to isolated material based on ketone **6**. [a] Solvent = toluene. [b] Solvent = THF. [c] RM = Grignard reagent. [d] RM = Organolithium reagent.

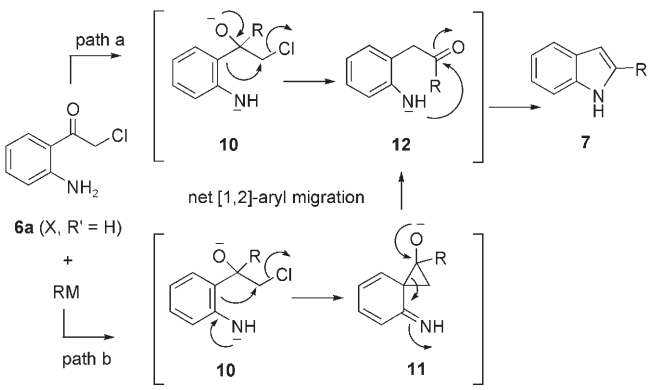
The versatility of this method was further extended to the preparation of 2,3-disubstituted indoles with excellent control over the regioselectivity; these indoles would be difficult to prepare selectively by other means. Hence, treatment of ketone **8** with 2.5 equivalents of *n*PrMgCl at −10 °C→22 °C afforded 7-chloro-3-methyl-2-propylindole (**9a**) in 93% yield. Likewise, 7-chloro-3-methyl-2-thien-2-ylindole (**9b**) was readily obtained in 80% yield by employing 2.0 equivalents of 2-thienyllithium [Eq. (2)]. These particular examples



(2)

clearly highlight the remarkable efficiency of this method, which should be broadly applicable to the regioselective synthesis of 2,3-disubstituted indoles from other substrates.

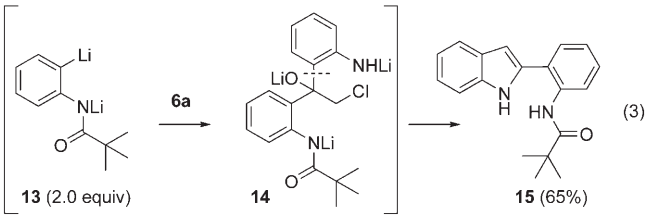
On the basis of the regiochemistry observed in this transformation, we propose the following reaction sequence (Scheme 2): nucleophilic addition of an organometallic reagent to the chloroketone **6a** to form tertiary alkoxide **10**, followed by a facile [1,2]-aryl rearrangement[4] to form ketone **12**, then ring-closure and dehydration to form 2-substituted indole **7**. We believe the aniline moiety serves as a key driver for the success of the reaction, wherein the aniline nitrogen atom promotes the net [1,2]-aryl rearrangement, either through a conventional aryl migration (path a) or the formation of a phenonium ion intermediate, such as **11**, which favors its migration (path b).[5,6] The aniline nitrogen atom could also serve as an effective trap for the ketone in intermediate **12**, thus preventing reaction of the ketone with an additional equivalent of the organometallic reagent.



Scheme 2. Proposed mechanism illustrated with **6a** as the starting material.

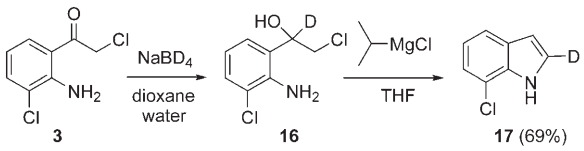
This net [1,2]-aryl migration mechanism is supported by two experiments. When the dianion **13**[7] derived from *N*-2-bromophenylpivaloylamide reacts with ketone **6a**, the only

product observed, **15**, is derived from migration of the unprotected aniline group. Under the assumption that the intermediate **14** forms, there are two possible aniline groups which could participate in this [1,2]-aryl migration. Clearly, the electron-withdrawing effect of the *N*-pivaloyl group disfavors its migration [Eq. (3)].[7] Another experiment



(3)

which supports the proposed rearrangement mechanism involves the reaction of deuterium-labeled alcohol **16** with *i*PrMgCl in THF, which produces [2-D]-7-chloroindole (**17**) in 69% yield [Eq. (4)]. An alternative mechanism involving the



(4)

formation of an epoxide and subsequent rearrangement to form an aldehyde is ruled out since it would lead to a 3-substituted indole after a [1,2]-hydride shift.[8]

In summary, we have discovered a new and efficient method for the regioselective synthesis of substituted indoles. The reaction proceeds from readily available 1-(2-aminophenyl)-2-chloroethanones by a [1,2]-aryl rearrangement followed by intramolecular condensation to form indoles. The method introduces substituents at the C2-position of indoles and tolerates different substitution patterns on α-chloro ketones. This simple and mild procedure renders the method a valuable addition to the arsenal of indole syntheses.

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