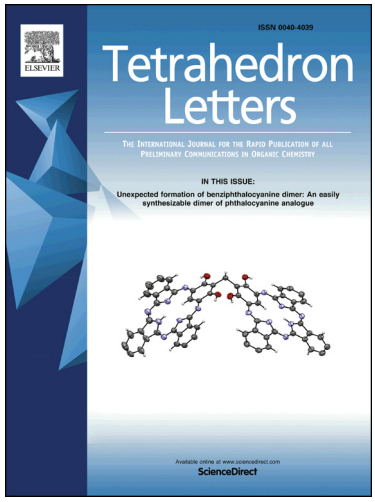

Direct C-H substitution reaction of anilides using hypervalent iodine and their regioselective issues

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Direct C-H substitution reaction of anilides using hypervalent iodine and their regioselective issues

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Abstract: The direct C-H substitution reactions of anilides using hypervalent iodine proceeded to afford azide, chloro, bromo, and fluoro derivatives, and their regioselectivity were described. In the specific reaction conditions, the unique regioisomers were obtained.

Keywords: Hypervalent iodine, Anilide substitution, Regioselective reaction

There are great number of nitrogen-containing compounds in our society, and among them, aniline derivatives are an important family in various fields, such as pharmaceuticals, functional molecules, and bioactive molecules. Therefore, further modification would provide more useful compounds. In the last decades, the late-stage functionalization through the direct cleavage of C-H bond has arisen in the synthetic chemistry, and recently its significance has been recognized.[1] For the efficient late-stage functionalization, C-H activation using hypervalent iodine is a powerful method, which is nonmetal, safe and easy to handle under mild conditions.[2] A lot of transformations of phenol derivatives with hypervalent iodine have been reported,[2,3] and the same strategies have also been applied to aniline derivatives, affording acetoxy,[4] alkoxy,[5] fluoro,[6] hydroxy,[7] and tosyloxy[8] anilides. Moreover, aryl-aryl coupling reactions of anilides with other aromatic compounds affording biaryl or annulated compounds have been reported.[9] However, there was little inclusive discussion about the regioselectivity in these reactions. In the course of our research projects, we investigated the same kinds of reaction to prepare the other derivatives of anilides, and found unique regioselectivity to be presented here.

According to the reaction conditions in the above precedent papers, at first, we tried to introduce an azide group to *tert*-Butoxycarbonyl (Boc) protected aniline using $TMSN_3$, $PhI(OAc)_2$ (PIDA) in hexafluoroisopropanol (HFIP).[3b] However, the desired reaction did not proceed, and the starting material decomposed (Table 1, entry 1). Because the Boc group was removed in some of the decomposed products, the Ms-protected aniline derivative was reacted under the same conditions,[9d-e,10] however, the starting material was recovered (entry 2). Whereas Boc-protected *p*-toluidine derivative showed almost the same results as entry 1 (entry 3), the introduction of the azide group was successful for the Ms-protected *p*-toluidine, and the corresponding 2-N_3 derivative was obtained in 35% yield with 37% of recovered starting material (entry 4). Other protecting groups were examined for the amine moiety; the Ac-protected *p*-toluidine did not brought the introduction of azide group (entry 5), and the *N*-methyl *p*-toluidine gave the decomposed products accompanied with a trace amount of an azide derivative and 19% of the starting material (entry 6). For other toluidine derivatives, i.e., Ms-protected *o*- and *m*-toluidine, the desired products were not

Table 1

Modification of anilides with hypervalent iodine and TMSX

entry	R	P	X	yield (%) (position)	Rsm (%)
1	H	Boc	N_3	0	26
2	H	Ms	N_3	0	93
3	4-CH_3	Boc	N_3	0	10
4	4-CH_3	Ms	N_3	35 (2)	37
5	4-CH_3	Ac	N_3	0	89
6	4-CH_3	Me	N_3	trace (-)	19
7	2-CH_3	Ms	N_3	0	56
8	3-CH_3	Ms	N_3	0	62
9	H	Ms	Cl	35 (4)	0
10	4-CH_3	Ms	Cl	64 (2) / 26 (3)	0
11	2-CH_3	Ms	Cl	78 (4)	0
12	3-CH_3	Ms	Cl	77 (4)	0
13	4-CH_3	Ts	Cl	59 (2)	0
14	4-CH_3	Ns	Cl	34 (2)	68
15	4-CH_3	Ac	Cl	66 (2)	28
16	4-CH_3	Me	Cl	0	0
17 [a]	4-CH_3	Ms	Cl	61 (2)	8
18 [b]	4-CH_3	Ms	Cl	56 (2)	0
19 [c]	4-CH_3	Ms	Cl	48 (2)	5
20 [d]	4-CH_3	Ms	Cl	58 (2)	0
21 [e]	4-CH_3	Ms	F	27 (4) [f]	0
22	4-CH_3	Ms	Br	86 (2)	12
23	4-CH_3	Ms	I	0	93
24	4-CH_3	Ms	CN	0	12
25	4-CH_3	Ms	CF_3	0	9
26	4-CH_3	Ms	OAc	0	0

[a] TFE was used as a solvent.

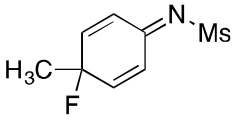
[b] CH_2Cl_2 was used as a solvent.

[c] MeCN was used as a solvent.

[d] Toluene was used as a solvent.

[e] KF was used instead of TMSF.

[f] The structure is shown in the right.

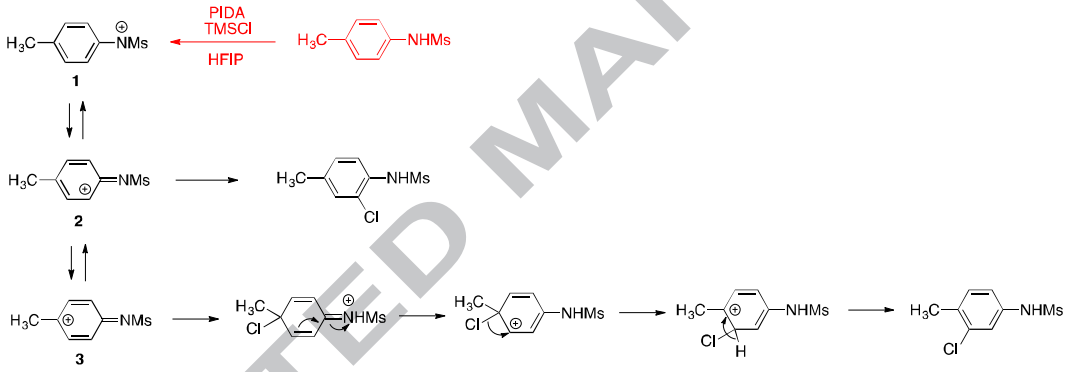


obtained, and a part of the starting material decomposed (entries 7 and 8), and we do not have a reasonable explanation for these results. Following the azidation reaction, we investigated the introduction of a chloro group. The Ms-protected aniline was reacted with TMSCl under the same reaction conditions, to give the 4-chloro derivative in moderate yield (entry 9).[11] However, the Ms-protected *p*-toluidine provided some interesting results, and this reaction afforded two derivatives. We carefully confirmed their structure, which were turned out to be 2- and 3-chloro *p*-toluidine derivatives in 64% and 26% yields, respectively (entry 10).[12] In contrast, for the Ms-protected *o*- and *m*-toluidine, the 4-chloro derivatives were obtained as a single product in good yields (entries 11 and 12). Additionally, Ts- and *o*-nitrobenzenesulfonyl (Ns)-, and Ac-protected compounds afforded only 2-chloro derivatives (entries 13,[13] 14, and 15[14]), and the decomposition of the starting material was observed with methyl compounds (entry 15).

Concerning the regioselectivity in entry 10 in Table 1, we further investigated the reaction conditions. No solvents other than HFIP afforded the regioisomers; only the 2-substituted derivatives were obtained in 2,2,2-trifluoroethanol (TFE), CH_2Cl_2, CH_3CN, and toluene (entries 17 ~ 20).[15] In terms of substituents, we next intended to prepare other anilide derivatives. In entries 21 ~ 26, several reagents were used, and a fluorine atom was introduced at the 4-position using KF as reported previously,[6] whereas a bromine atom was introduced at the 2-position using TMSBr. Other reagents such as TMSI, TMSCN, $TMSCF_3$, and TMSOAc[16] did not provide the desired products, and the starting material was partially decomposed in entries 23 ~ 26.

The two regioisomers obtained in entry 10, Table 1, especially the 3-chloro derivative are noteworthy, and we speculate the reaction mechanism. As shown in Scheme 1, we assume that this reaction proceeds through the nitrenium ion **1**,[4,9d] and the sulfonyl protecting groups for the amine moiety contribute to the formation of arenium ions **2** and **3**, derived from the nitrenium ion **1**.[9d] They also probably prevent the overoxidation of the substrates. Under specific reaction conditions, those were the reaction of Ms-protected *p*-toluidine with TMSCl in HFIP, two products were acquired, which were 2- and 3-chloro derivatives. While the arenium ion **2** was reacted with TMSCl to form the 2-chloro derivative, no

direct arenium ion was available to prepare the 3-chloro derivative. After the reaction of arenium ion **3** with TMSCl, however, it was assumed that the migration of the chloride and rearomatization would proceed to afford the 3-chloro compound.[4a] The methyl substituent on the benzene ring would contribute to the stabilization of arenium ion **3**, and HFIP might play some role in maintaining the arenium ions. The reason why Ts- and Ns-protected compounds provided only the 2-Cl derivative was not clear, however, these protecting groups might stabilize the arenium ion **2** more than Ms-protected compound (entries 13 and 14).[9d] Regarding the other substituents, the regioselectivity of the products could depend on the nucleophilicity of the reagents, and we assumed that a hard nucleophile (TMSF) would attack the tertiary carbocation (**3**), whereas a soft nucleophile (TMSBr) would attack the sterically unhindered carbocation (**2**).



Scheme 1. Proposed mechanism to produce the 2- and 3-chloro derivatives in entry 10.

In summary, we presented the information about the direct C-H substitution reactions of anilide derivatives with Cl, N_3, F, and Br using a hypervalent iodine reagent. Also, we found unique regioselectivity in these reactions, which we believe would be helpful for late-stage functionalization of biologically active compounds.

Acknowledgments

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Supplementary data

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12. The structures of the products were determined by 2D-NMR analysis, and moreover confirmed by comparison with the products of *N*-methanesulfonylation of 2-chloro-4-methylaniline and *N*-methanesulfonylation of 3-chloro-4-methylaniline. The structures of the other products were determined by 2D-NMR analysis (supporting information).
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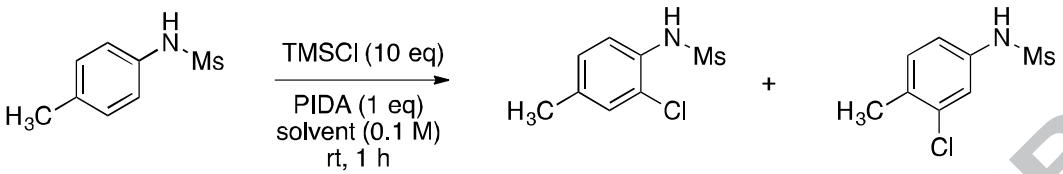
15. Using HFIP/DCM as reference 9d (for entry 10 in Table 1), the yields were slightly lower than those of entry 10.
16. The reaction could cause the *N*-acetoxylation of the starting material.

Legends

Table 1. Modification of anilides with hypervalent iodine and TMSX.

Scheme 1. Proposed mechanism to produce the 2- and 3-chloro derivatives in entry 10.

Graphical Abstract



unique regioselectivity

Highlights

The direct C-H substitution reactions of anilides proceeded using hypervalent iodine.

Azide-, chloro-, bromo-, and fluoro-substituted derivatives were obtained.

The unique regioisomers were obtained in the specific reaction conditions.