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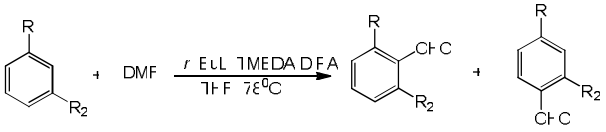

R = F, Cl, CF_3
R_2= CF_3, NC_2, F, Cl, CH_3, MOM, CCH_3, $N(CH_3)_2$

1-16a **1-16b** **1-16c**

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Regioselective formylation of 1, 3-disubstituted benzenes through *in situ* Lithiation

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ABSTRACT

A facile method of regioselective formylation of disubstituted benzene via *in situ* deprotonation/metalation using *n*-BuLi/TMEDA/DIPA has been developed. Effect of different electron withdrawing and electron donating substituents in 1,3-interrelated aromatic system was studied; the metalation mostly occurred at the 2-position to afford the desired products in high yields.

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Introduction

Benzene was first discovered over a century ago by Kekule.[1] Since then, the generation, structure, and reactivity of benzene and related aromatics have been studied in both industrial and academic laboratory.[2] Regiocontrolled introduction of different groups into benzene and benzene-like substrates bearing multiple active sites that can lead to structural fragments of modem drugs and pesticides has gained enormous significance.[3]

A number of studies dealing with lithiations of 1,2- and 1,4-disubstututed arenes have been conducted.[4] However, literature furnishes much less information regarding lithiations of 1,3-interrelated systems, which offer selection of either of the three possible ortho substitutions (C-2, C-4, and C-6).[5] (**Fig.1**) Because of harsh conditions and possibility of formation of mixtures of positional isomers, these reactions are hard to control in synthetic protocol. Herein, we performed a few of systematic regioselective formylation of 1,3-disubstituted benzene bearing different electron withdrawing or donating groups via *in situ* deprotonation/metalation using *n*-BuLi/TMEDA/DIPA.

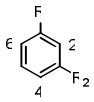


Fig.1 The structure of 1,3-interrelated system

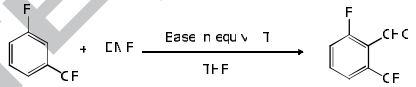
Results &Discussion

Since fluorine is a known ortho-directing group in aromatic metalation and exhibits excellent physical, chemical and biological properties[6], 1,3-disubstituted fluorinated benzene is widely studied for regioselective substitution through ortho-lithiation . Of these various electrophilic reagents such as *N,N*-dimethyl formamide (DMF), D_2O or carbon dioxide which are employed for aromatic electrophilic substitution, DMF appears to be the most convenient electrophile. At the outset, we optimized the reaction conditions for regioselective formylation taking 1-fluoro-3-(trifluromethyl)benzene (**Scheme 1**) as the model compound. The course of formation of the target product **1b** was followed by ^{19}F NMR spectroscopy. Different parameters such as type of base employed for lithiation, molar equivalent of the reacting components and formylating agent DMF, reaction time and temperature were studied in THF to obtain the best selectivity and yield of **1b**.

It is evident from the data presented in Table **1** that under similar reaction conditions (entries 1-6), *n*-BuLi and lithium diisopropylamide (LDA) afforded much higher yield compared to other bases e.g. lithium bis(trimethylsilyl) amide (LiHMDS) and lithium 2,2,6,6-tetramethyl piperidide (LTMP). The selectivity of the product **1b** in relation to other regioisomers was however slightly superior with *n*-BuLi.

Having identified *n*-BuLi as the most suitable base for formylation of **1a**, we tried to enhance the selectivity for the formation of regioisomer **1b** in the presence of ligands *N,N,N′,N′*-tetramethyl-1,2-ethylenediamine(TMEDA)[7]and diiso-propylamine (DIPA)[8]. The results are depicted in entries 7-9 of **Table 1**. While TMEDA in conjunction with *n*-BuLi helped to improve the selectivity of the product significantly, the use of 5% DIPA with TMEDA (1 eq.) further increased the isomeric purity of the product (entry 9). The selectivity or yield could not be improved significantly by altering the molar eq. of the base and reaction time while a lower temperature was desirable for obtaining optimal results. (entries 9-14).

Under optimal conditions [9], the regioselective formylation of disubstituted benzene was conduced with 1 eq. of substrate, 1.1 eq. each of *n*-BuLi and TMEDA, and 5 mol% of DIPA at -78^{o}C for 1.5 h..(**Table 2**.) For fluorinated products, the progress of the reaction and regiomeric distributions were studied by ^{19}F NMR spectroscopy while non-fluorinated products were analyzed by GC/MS.



1a **1b**

Scheme 1. Regioselective formylation of 1-fluoro-3-(trifluromethyl) benzene

Table 1. Optimization of reaction conditions via Scheme 1 [a]

Entry	Base	n[b](mole)	T(^{o}C)	t(h)	Isomer selectivity [c] (%)	Yield [d] (%)
1	LDA	1.1	-78	1.5	65	69
2	LiHMDS	1.1	-78	1.5	nd[e]	<10%
3	LiHMDS	2.2	0	1.5	nd[e]	<20%
4	LTMP	1.1	-78	1.5	nd[e]	<10%
5	LTMP	4.4	-78	3.5	nd[e]	<20%
6	*n*-BuLi	1.1	-78	1.5	71	75
7	*n*-BuLi/TMEDA	1.1/1.1	-78	1.5	90	85
8	*n*-BuLi/ DIPA	1.1/1.1	-78	1.5	78	77
9	*n*-BuLi/TMEDA/DIPA	1.1/1.1/5%	-78	1.5	97	90
10	*n*-BuLi/TMEDA/DIPA	1.1/1.1/5%	0	1.5	<30%	nd[e]
11	*n*-BuLi/TMEDA/DIPA	1.1/1.1/5%	-50	1.5	70	81
12	*n*-BuLi/TMEDA/DIPA	1.5/1.1/5%	-78	0.5	85	70
13	*n*-BuLi/TMEDA/DIPA	1.1/1.1/5%	-78	1	87	79
14	*n*-BuLi/TMEDA/DIPA	1.1/1.1/5%	-78	2.5	83	90

[a] General procedure. To a stirred solution of base (n equiv) in anhydrous THF was added dropwise under argon substrate 1-fluoro-3-(trifluromethyl) benzene (3 mmol) dissolved in dry THF (10 mL) at the temperature mentioned. After adding DMF (4.5 mmol, 1.5 equiv), the reaction mixture was worked up in the usual manner (see the supporting information).[b] w.r.t. the starting material.[c] The isomeric ratio of *m*-1-fluoro-3-(trifluromethyl)benzaldehyde was determined by ^{19}F NMR. [d] overall crude yield [e] Not determined.

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As may be observed from the data presented in **Table 2** that in general (entries 3,4,7 and 9-12) formylation of 1,3-disubstituted benzenes afforded the desired product with very high crude yields and very good regioselectivities. With the exception of 3-nitro fluorobenzene and 3-methyl fluorobenzene (entries 2 and 5), both electron donating and electron withdrawing groups such as fluoro, chloro, trifluoromethyl, methoxy and methoxymethyl exert an activating effect for in situ lithiation and subsequent formylation (entries 3-12). In most cases very high ortho-selectivity of 1,3-disubstituted benzene at the position flanked by two substituents was observed (entries3-4,6,9-12).The relatively bulky CF_3 group not only imposes steric restrictions to the incoming electrophile adjacent to it but also reveals a powerful π-polarization at the *ortho*, *meta* and *para* positions.[10]Therefore, metalation of 3-substituted trifluoromethyl benzene occurs preferentially at the methoxy or methoxymethyl neighboring position (entries13-15). At the same time, fluorobenzene also was studied as a control (entry 16) which mainly afforded formylated product at the 2-position.

Given the normal electrophilic substitution rules, the preparation of regio-controlled 2/4-formylated 1,3-disubstituted benzene can become a challenge. Regioselective formylation was achieved using directed metalation groups such as F, Cl, CF_3 ,OCH_3 ,OMOM and some excellent results were obtained with some selected substrates. Interpretation of regioselectivities at the the 2 or 4-position for 1,3-disubstituted systems must take into account coordination, steric and inductive effects as well as formation of the ortho-lithiated species. The directed ortho metalation (DOM) reaction mechanism[2] was preliminary proposed (**Fig.2**), and the further research is in progress.

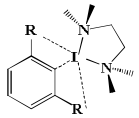
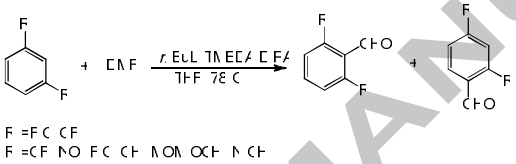


Fig.2 The proposed mechanism of 1,3-interrelated system

In summary, A facile method of regioselective formylation of disubstituted benzene via *in situ* deprotonation/metalation using *n*-BuLi/TMEDA/DIPA was reported. Different combinations of directed metalation groups for 1,3-interrelated system have been discussed and most of them showed metalation at the 2-position. Studies on functionalization of *in situ* generated lithiated benzene to generate more useful products are currently underway.



1-16a **1-16b** **1-16c**

Table 2 Regioselective formylation of 1,3-disubstituted substrate under optimal conditions[a]

Entry	Substrate	Yield[b] (%)	Regioisomer distribution b or c (%)	Others	Entry	Substrate	Yield[b] (%)	Regioisomer distribution b or c (%)	Others
1		85	97 (**1b**)	3	9		85	90(**9b**)	10
2		nd[c]	0	nd[c]	10		94	99(**10b**)	1
3		90	99 (**3b**)	1	11		91	99(**11b**)	1
4		91	94(**4b**)	6	12		90	99(**12b**)	1
5		nd[c]	< 5(**5b**)	nd[c]	13		60	75(**13c**)	25
6		90	88(**6b**)	12	14		86	94(**14c**)	6
7		92	95(**7b**)	5	15		66	70(**15c**)	20
8		30	88(**8b**)	12	16		64	-[d]	-[d]

[a] Under optimal conditions, the reaction was conduced with 1 eq of substrate, 1.1 eq each of *n*-BuLi and TMEDA, and 5 mol% of DIPA at -78^{0}C for 1.5 h.
[b] Overall crude yield. [c] Not determined. [d] The isomeric ratio of *o*-fluorobenzaldehyde was 72% .

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9. General synthetic method: To a flame dried 100 mL flask was added 1,3-disustituted benzene (3.0 mmol), TMEDA (1.1 equiv., 3.3 mmol), DIPA (5% equiv., 0.16 mmol) and THF (10.0 mL). The solution was cooled to – 78 ^{o}C for 10 min and then *n*-BuLi (1.1 equiv., 3.3mmol) was added dropwise. Thee mixture was kept at this temperature for 1 hour; DMF (1.5 equiv., 4.5 mmol) was added and the mixture was further stirred for another half an hour at -78 ^{o}C. The mixture was allowed to warm up to room temperature and quenched by the addition of saturated NH_4Cl-H_2O solution (5 mL); extracted three times with ethyl acetate (10 mL×3). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The regioselectivity of the crude product was ascertained by ^{19}F NMR (for fluorinated products) or by GC/MS (for non-fluorinated ones) and then subjected to flash chromatography to obtain the desired products which were characterized by ^{1}H NMR, ^{19}F NMR ,^{13}C NMR spectral dada and GC-MS analyses..
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