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Deprotonation of chloropyridines using lithium magnesates

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Abstract—4-Chloropyridine was deprotonated on treatment with 1/3 equiv of the highly coordinated magnesate $Bu_3(TMP)MgLi_2$ in THF at −10 °C, as evidenced by trapping with I_2. The use of $Bu(TMP)_2MgLi$ in Et_2O allowed the reaction of 2-chloropyridine, giving the 3-functionalized derivative as the main product. Mixtures of 3- and 4-functionalized derivatives were obtained when 2,6-dichloropyridine was involved in the reaction. Performing the reaction on 3-chloropyridine with lithium magnesates in THF, either the 4,4′-dimer or the 4-iodo derivative was formed after quenching by I_2, the former using 1/3 equiv of $Bu_2(TMP)MgLi$ and the latter using 1 equiv of $(TMP)_3MgLi$. Similar results were observed with 3,5-dichloropyridine, 2,5-dichloropyridine and 3-chloro-2-fluoropyridine. 1,2-Migration of the lithium arylmagnesate formed by deprotonation was proposed to justify the dimers formation.
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We describe the first deprotonation/electrophilic trapping and deprotonation/1,2-migration sequences with chloropyridines using magnesates.

The preparation of functional heterocycles is an important synthetic goal because of the multiple applications of these molecules.[1] Among the methods developed, lithiation is convenient to allow a number of polyfunctional azine (pyridines, quinolines, etc.) and diazine syntheses since lithiated derivatives display a high reactivity towards many electrophilic functions.[2] Nevertheless, this methodology often requires low temperatures, which can be difficult to realize on an industrial scale.

Some substituted azines can be deprotonated at higher temperatures using the Hauser base TMPMgCl (TMP = 2,2,6,6-tetramethylpiperidino);[3] because of its weak reactivity when compared to alkylmagnesium halides, a large excess (6–8 equiv) has in general to be used to ensure good yields, and the scope of the reaction is rather narrow until now. Alkylmagnesium halides and dialkylmagnesiums rarely deprotonate such substrates because 1,4-addition reactions occur more easily.[4]

More recently, deprotonations of pyridine, quinoline and isoquinoline rings have been accomplished at room temperature through the formation of an arylzincate using lithium di-*t*-butyl(2,2,6,6-tetramethylpiperidino)zincate or lithium di-*t*-butyl(diisopropylamino)-zincate as a base.[5]

The arylmagnesates reacting with a wider range of electrophiles than arylzincates, we have been interested in deprotonation reactions of aromatics using lithium magnesates.

Since a magnesium ate complex (R_3MgLi) was first published in 1951,[6] several investigations on its structure have been reported.[7] However, the synthetic applications of magnesate reagents remained unexplored until very recently.[8] While halogen–magnesium exchanges using organomagnesium ate complexes were described in the benzene, thiophene, pyridine, quinoline and diazine series,[8i,l,m,p–r,u] few studies have been devoted to aromatic deprotonation. Mulvey and co-workers documented in 1999 the preparation of a mixed-metal sodium–magnesium macrocyclic amide, which behaves like a template for the site selective dideprotonation of benzene and toluene.[9] This process cannot be used as it is for synthetic purposes because it involves a large excess of arene (5 mmol out of the 5 mL used are consumed in the reaction). Richey and co-workers observed in 2004 that treating benzene halides with magnesates

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partially results in benzyne formation.[8s] Very recently, we documented the deprotonation of fluoro aromatics using lithium magnesates, the generated arylmagnesates being either intercepted with electrophiles or involved in a palladium-catalyzed cross-coupling reaction.[10]

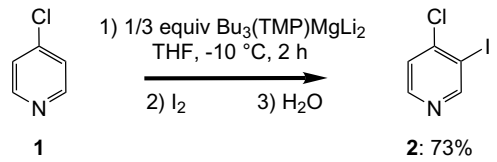
Herein, we describe the synthesis through deprotonation and the reactivity of lithium (chloropyridyl)magnesates.

The first experiments were conducted on 4-chloropyridine (**1**). It is known that a solution of LDA in THF at −75 °C promotes a clean hydrogen/metal exchange (metallation) at the 3-position adjacent to the halogen.[2a,11] No reaction was noted when 4-chloropyridine (**1**) was exposed to lithium tributylmagnesate (Bu_3MgLi) in THF at −10 °C. Considering the migratory aptitude of TMP over alkyl groups,[5] lithium dibutyl(2,2,6,6-tetramethylpiperidino)magnesate ($Bu_2(TMP)MgLi$)[12] was tested, but without success. We decided to turn to highly coordinated magnesates and chose dilithium tributyl(2,2,6,6-tetramethylpiperidino)magnesate ($Bu_3(TMP)MgLi_2$),[13] which was convenient for the deprotonation of 2-fluoropyridine.[10] When 4-chloropyridine (**1**) was successively treated with 1/3 equiv of $Bu_3(TMP)MgLi_2$ in THF at −10 °C for 2 h and iodine, the iodide **2**[14] was produced in a good yield (Scheme 1).

The deprotonation of the 2-chloropyridines **3** and **4** was next studied. Concerning 2-chloropyridine (**3**), it occurs regioselectively at C3 using LDA[2a] or a mixture of phenyllithium and 5 mol% diisopropylamine.[2b] Using Bu_3MgLi, the substrate either remained unchanged or underwent addition reactions of the base. Consequently, we turned to the amido-magnesates $Bu_2(TMP)MgLi$ and $Bu(TMP)_2MgLi$. When the reaction was effected in THF at −10 °C, a complex mixture containing the iodide **5a** as the main compound was obtained after quenching with iodine. Replacing THF with diethyl ether reduced the competitive reactions and afforded the iodide **5a**[15] in 46% or 67% yields, using 1 equiv of $Bu_2(TMP)MgLi$ (entry 1) or $Bu(TMP)_2MgLi$ (entry 2), respectively. While the formation of the iodinated isomer **5b**[16] was not avoided using these bases, the latter was discarded using 1 equiv of the lithium-magnesium-dialkylamide $(TMP)_3MgLi$;[17] the iodide **5a** was nevertheless isolated in a low yield of 32%, probably due to the size of the base (entry 3).

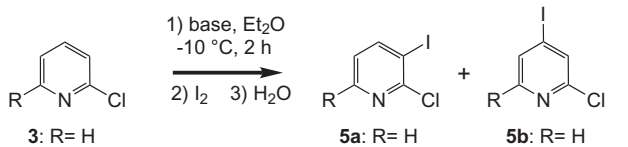
We then studied the effect of a second chlorine atom at C6. 2,6-Dichloropyridine (**4**) tends to form mixtures of 3- and 4-isomers, for example, in the ratios of 2:1 and 1:3 after treatment with LDA or BuLi, respectively, for 30 min in THF at −80 °C, followed by trapping with benzaldehyde.[2b] However, prolongation of the interaction with LDA,[2b] or the use of a combination of phenyllithium and diisopropylamine,[2b] gives rise to relatively pure 3-isomer; these results suggest a thermodynamic control at C3, the lithio derivative being stabilized by the neighbouring chlorine. Using 1 equiv of $Bu_2(TMP)MgLi$ (entry 4) or $Bu(TMP)_2MgLi$ (entry 5) in diethyl ether at −10 °C, mixtures of 3-iodo **6a**[18] and 4-iodo **6b**[18] were obtained after quenching with iodine in 1:2 or 1:1 ratio, respectively. The base containing the most butyl groups deprotonating more easily at C4, we therefore attempted the use of $(TMP)_3MgLi$ in order to favour the proton abstraction at C3. The result was disappointing: the derivatives **6a** and **6b** were obtained in a 55:45 ratio (Table 1, entry 6). Due to the long range effect of chlorine,[19] both H_3 and H_4 are acidified and it seems that the bulky base can abstract equally a more acidic but less accessible hydrogen at C3 and a less acidic but easily accessible hydrogen at C4. That such bases (diisopropylamino instead of TMP) have been regarded as sources of hyperbasic 'R_2N^-' anions, which separate from the cations '$LiMg[NR_2]_2^+$' in hydrocarbon solutions provides one complication.[17]

The behaviour of the arylmagnesates coming from 3-chloropyridines **7** and **8** were next investigated. It is known that LDA in THF at −75 °C allows the regioselective lithiation of 3-chloropyridine (**7**) at the 4-position.[2a] Since the substrate either remained unchanged or underwent addition reactions of the base using Bu_3MgLi, we turned to $Bu_2(TMP)MgLi$. Interestingly, when 3-chloropyridine (**7**) was successively treated with 1/3 equiv of $Bu_2(TMP)MgLi$ in THF at −10 °C for 2 h and iodine, the 4,4′-dimer **9a**[20] was isolated in a very good yield (entry 1). The same result was noticed employing the less hindered $Bu_2(DA)MgLi$ (DA = diisopropylamino, entry 2). In order to understand how the compound **9a** was formed, the reaction was carried out using 1 equiv of $Bu_2(TMP)MgLi$. Curiously, only traces of the 4,4′-dimer **9a** were obtained, the main product being the iodide **9b**[21] (entry 3). This result suggests the 4,4′-dimer **9a** is formed through an intramolecular way. We turned to the less nucleophilic lithium-magnesium-dialkylamide $(TMP)_3MgLi$ to eliminate addition reactions giving butylated compounds. Using 1 equiv of $(TMP)_3MgLi$ in THF at −10 °C, the 4,4′-dimer was discarded and the iodide **9b** was given in 45% (entry 4). This result could be attributed to



Scheme 1.

Table 1. Deprotonation of **3** and **4** using lithium magnesates



3: R= H
4: R= Cl

5a: R= H
6a: R= Cl

5b: R= H
6b: R= Cl

Entry	Substrate	Base (1 equiv)	Products (yields)
1	**3**	$Bu_2(TMP)MgLi$	**5a** (46%), **5b** (5%)
2	**3**	$Bu(TMP)_2MgLi$	**5a** (67%), **5b** (10%)
3	**3**	$(TMP)_3MgLi$	**5a** (32%), **5b** not detected
4	**4**	$Bu_2(TMP)MgLi$	**6a** (20%), **6b** (40%)
5	**4**	$Bu(TMP)_2MgLi$	**6a** (35%), **6b** (35%)
6	**4**	$(TMP)_3MgLi$	**6a** (45%), **6b** (37%)

a majority formation of $(TMP)_2$(3-chloro-4-pyridyl)-MgLi, avoiding the formation of dimers.

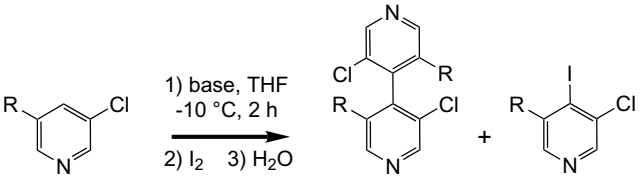
In order to gain an insight into this possibility, 3,5-dichloropyridine (**8**) was involved in the reaction. In this case, there is no need to replace a butyl group of the base with TMP: when 3,5-chloropyridine (**8**) was successively submitted to 1/3 equiv of Bu_3MgLi in THF at −10 °C for 2 h and iodine, the 4,4′-dimer **10a**[22] was furnished in a very good yield (entry 5). The latter was lowered by reducing the amount of Bu_3MgLi to 1/2 equiv (entry 6). As for 3-chloropyridine (**7**), the reaction was effected using 1 equiv of $Bu_2(TMP)MgLi$ (entry 7) or $Bu(TMP)_2MgLi$ (entry 8). This led to the iodide **10b**,[23] but in low yields of 6% and 35%, respectively, due to the competitive formation of **10a** (Table 2).

In view of the results, and since the deuterated compound **11**[24] was identified by NMR using D_2O, the formation of the 4,4′-dimer **10a** could be explained by a deprotonation at C4, followed by the 1,2-migration of the 4-pyridyl group,[8k] as depicted in Scheme 2.

A similar dimerization, but under the action of LDA at −70 or −100 °C, is documented in the pyridine, quinoline, isoquinoline and pyrimidine series.[2a] In every case, 2,2′- or 4,4′-dimers are produced in good yields when the reaction is conducted in Et_2O in the presence of hexamethylphosphoramide (HMPA). The coupling reaction was rationalized by a SET route between LDA and the substrate, giving a radical anion, which can add to a neutral molecule.[25] Since various phenyllithiums have been shown to form triple ions (lithium ate complexes $[Ph_2Li]^-Li^+$) in the presence of HMPA,[26] a 1,2-migration/nucleophilic addition of these species could be advanced as an alternative mechanism to rationalize the dimers formation.

The reaction was next extended to the substituted 3-chloropyridines **12** and **13**. Treatment of 2,5-dichloropyridine (**12**) with 1/3 equiv of $Bu_2(DA)MgLi$ in THF at

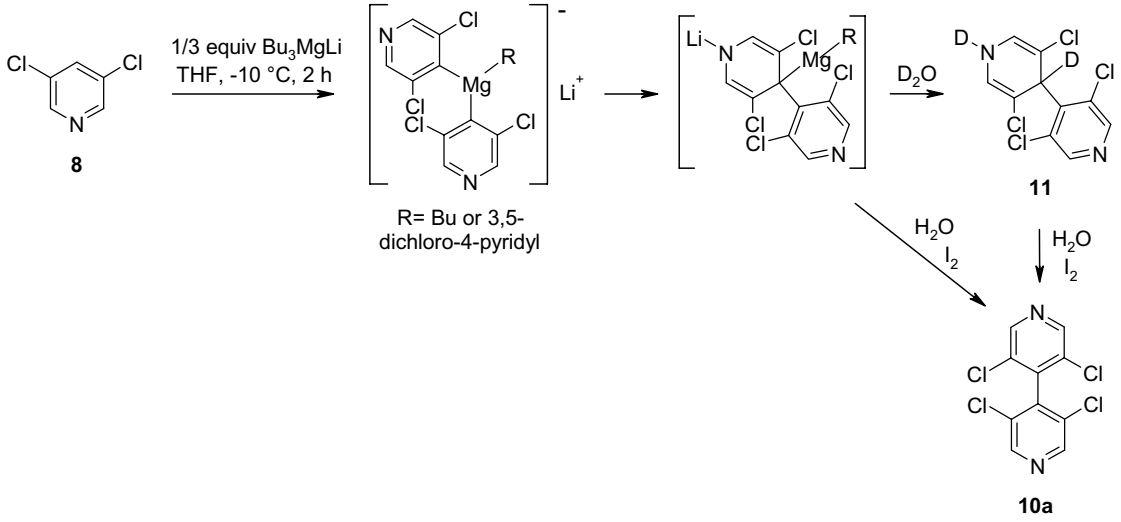
Table 2. Deprotonation of **7** and **8** using lithium magnesates



Entry	Substrate	Base	Products (yields)
1	**7**	1/3 equiv $Bu_2(TMP)MgLi$	**9a** (86%), **9b** not detected
2	**7**	1/3 equiv $Bu_2(DA)MgLi$	**9a** (88%), **9b** not detected
3	**7**	1 equiv $Bu_2(TMP)MgLi$	**9a** (traces), **9b** (32%)
4	**7**	1 equiv $(TMP)_3MgLi$	**9a** not detected, **9b** (45%)
5	**8**	1/3 equiv Bu_3MgLi	**10a** (88%), **10b** not detected
6	**8**	1/2 equiv Bu_3MgLi	**10a** (61%), **10b** (traces)
7	**8**	1 equiv $Bu_2(TMP)MgLi$	**10a** (30%), **10b** (6%)
8	**8**	1 equiv $Bu(TMP)_2MgLi$	**10a** not determined, **10b** (35%)

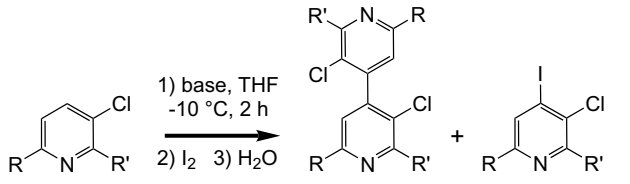
−10 °C for 2 h followed by iodine led to the 4,4′-dimer **14a**[27] (entry 1). The use of 1 equiv of $Bu_2(TMP)MgLi$, $Bu(TMP)_2MgLi$ or $(TMP)_3MgLi$ reduced the formation of **14a** and afforded the iodide **14b**[28] in 41%, 60% and 51%, respectively (entries 2–4). Similar results were obtained with 3-chloro-2-fluoropyridine (**13**), giving either the 4,4′-dimer **15a**[29] using 1/3 or 1/2 equiv of $Bu_2(TMP)MgLi$ (entries 5 and 6) or the iodide **15b**[30] using 1 equiv of $Bu_2(TMP)MgLi$ (entry 7) or $(TMP)_3MgLi$ (entry 8, Table 3).

In summary, 4-chloropyridine was deprotonated using 1/3 equiv of the highly coordinated magnesate



Scheme 2.

Table 3. Deprotonation of **12** and **13** using lithium magnesates



12: R= Cl, R'= H
13: R= H, R'= F

14a: R= Cl, R'= H **14b**: R= Cl, R'= H
15a: R= H, R'= F **15b**: R= H, R'= F

Entry	Substrate	Base	Products (yields)
1	**12**	1/3 equiv $Bu_2(DA)MgLi$	**14a** (64%), **14b** not detected
2	**12**	1 equiv $Bu_2(TMP)MgLi$	**14a** (traces), **14b** (41%)
3	**12**	1 equiv $Bu(TMP)_2MgLi$	**14a** not detected, **14b** (60%)
4	**12**	1 equiv $(TMP)_3MgLi$	**14a** not determined, **14b** (51%)
5	**13**	1/3 equiv $Bu_2(TMP)MgLi$	**15a** (42%), **15b** (traces)
6	**13**	1/2 equiv $Bu(TMP)_2MgLi$	**15a** (27%), **15b** (traces)
7	**13**	1 equiv $Bu_2(TMP)MgLi$	**15a** (traces), **15b** (44%)
8	**13**	1 equiv $(TMP)_3MgLi$	**15a** (traces), **15b** (56%)

$Bu_3(TMP)MgLi_2$ in THF at −10 °C, as evidenced by trapping with I_2. The use of $Bu(TMP)_2MgLi$ in Et_2O allowed the reaction of 2-chloropyridine, giving the 3-functionalized derivative as the main product. Mixtures of 3- and 4-functionalized derivatives were obtained when 2,6-dichloropyridine was involved in the reaction. Surprisingly, by performing the reaction on 3-chloropyridine with lithium magnesates in THF, either the 4,4′-dimer or the 4-iodo derivative was formed after quenching by I_2, the former using 1/3 equiv of $Bu_2(TMP)MgLi$ and the latter 1 equiv of $(TMP)_3MgLi$. Intramolecular 1,2-migration of the sterically congested lithium arylmagnesate formed by deprotonation was proposed to justify the dimer formation. Similar results were observed with 3,5-dichloropyridine, 2,5-dichloropyridine and 3-chloro-2-fluoropyridine.

Deprotonation using Bu_3MgLi, typical procedure. BuLi (6.0 mmol) was added to a solution of $MgBr_2$ (2.0 mmol) in THF (3 mL) at −10 °C. After stirring for 1 h at −10 °C, 3,5-dichloropyridine (0.88 g, 6.0 mmol) was introduced at −30 °C. After 2 h at −10 °C, a solution of I_2 (1.5 g, 6.0 mmol) in THF (3 mL) was added and the mixture was stirred for 18 h at rt. Addition of water (0.5 mL) and $Na_2S_2O_3$ (until bleaching), dilution with CH_2Cl_2 (50 mL), drying over $MgSO_4$ and column chromatography using CH_2Cl_2 as an eluent afforded compound **10a** (88% yield).

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12. $Bu_2(TMP)MgLi$ is a medium structure: by mixing Bu_3MgLi (2 mmol) and 2,2,6,6-tetramethylpiperidine (2 mmol), it is statistically the main product formed but Bu_3MgLi, $Bu(TMP)_2MgLi$ and $(TMP)_3MgLi$ can also be present.
13. $Bu_3(TMP)MgLi_2$ is a medium structure: by mixing Bu_4MgLi_2 (2 mmol) and 2,2,6,6-tetramethylpiperidine (2 mmol), it is statistically the main product formed but Bu_4MgLi_2, $Bu_2(TMP)_2MgLi_2$, $Bu(TMP)_3MgLi_2$ and $(TMP)_4MgLi_2$ can also be present.
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18. The ^1H and ^{13}C NMR data of compound **6a** and compound **6b** were found identical to those previously described: Marzi, E.; Bigi, A.; Schlosser, M. *Eur. J. Org. Chem.* **2001**, 1371–1376.
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20. Compound **9a**: mp 117–118 °C; ^1H NMR ($CDCl_3$): 8.74 (s, 1H), 8.61 (d, 1H, $J = 4.9$), 7.21 (d, 1H, $J = 4.9$); ^{13}C NMR ($CDCl_3$): 149.5, 147.4, 142.5, 129.9, 124.1; IR (KBr): 3400, 2924, 1575, 1462, 1398, 1118, 1104, 1022, 838, 733, 618, 587 cm^{-1}. Anal. Calcd for $C_{10}H_6Cl_2N_2$ (225.08): C, 53.36; H, 2.69; N, 12.45. Found: C, 53.02; H, 3.08; N, 12.25. See also: Laye, R. H.; Couchman, S. M.; Ward, M. D. *Inorg. Chem.* **2001**, *40*, 4089–4092.
21. (a) Compound **9b**: mp 106 °C. The physical and spectral data were found identical to those previously described: Talik, T. *Rocz. Chem.* **1962**, *36*, 1049–1056; (b) Gribble, G. W.; Saulnier, M. G. *Heterocycles* **1993**, *35*, 151–169.
22. Compound **10a**: mp 102–103 °C; ^1H NMR ($CDCl_3$): 8.67 (s, 4H); ^{13}C NMR ($CDCl_3$): 147.6 (4C), 139.6 (2C), 130.8 (4C); IR (KBr): 3066, 1823, 1525, 1423, 1388, 1212, 1198, 1109, 1027, 1010, 889, 821, 750, 733, 654, 595 cm^{-1}. Anal. Calcd for $C_{10}H_4Cl_4N_2$ (293.97): C, 40.86; H, 1.37; N, 9.53. Found: C, 40.92; H, 1.32; N, 9.72.
23. (a) Compound **10b**: mp 183–184 °C; IR (KBr): 1537, 1398, 1384, 1221, 1196, 1116, 1030, 882, 812, 702, 524 cm^{-1}. The physical and spectral data were found identical to those previously described: Marzi, E.; Bigi, A.; Schlosser, M. *Eur. J. Org. Chem.* **2001**, 1371–1376; (b) Graf, R. *J. Prakt. Chem.* **1937**, *148*, 13–23.
24. Compound **11**: ^1H NMR ($CDCl_3$): 8.51 (s, 1H), 8.50 (s, 1H), 6.34 (d, 1H, $J = 0.75$), 6.32 (s, 1H).
25. Newkome, G. R.; Hager, D. C. *J. Org. Chem.* **1982**, *47*, 599–601.
26. Reich, H. J.; Sikorski, W. H.; Gudmundsson, B. Ö.; Dykstra, R. R. *J. Am. Chem. Soc.* **1998**, *120*, 4035–4036.
27. Compound **14a**: mp 117–119 °C; ^1H NMR ($CDCl_3$): 8.53 (s, 1H), 7.26 (s, 1H); ^{13}C NMR ($CDCl_3$): 149.3, 149.0, 144.0, 128.8, 124.5; IR (KBr): 3072, 3053, 1566, 1437, 1349, 1311, 1122, 1018, 898, 778, 647, 626, 559, 546 cm^{-1}. Anal. Calcd for $C_{10}H_4Cl_4N_2$ (293.97): C, 40.86; H, 1.37; N, 9.53. Found: C, 40.94; H, 1.40; N, 9.78.
28. Compound **14b**: mp 140 °C; ^1H NMR ($CDCl_3$): 8.34 (s, 1H), 7.85 (s, 1H); ^{13}C NMR ($CDCl_3$): 148.9, 147.2, 136.0, 134.5, 111.0; IR (KBr): 3394, 2926, 1542, 1514, 1438, 1417, 1302, 1271, 1119, 1022, 798, 664, 561 cm^{-1}. Anal. Calcd for $C_5H_2Cl_2IN$ (273.89): C, 21.93; H, 0.74; N, 5.11. Found: C, 22.14; H, 0.72; N, 5.13.
29. Compound **15a**: mp 140–141 °C; ^1H NMR ($CDCl_3$): 8.23 (d, 1H, $J = 4.9$), 7.14 (d, 1H, $J = 4.9$); ^{13}C NMR ($CDCl_3$): 159.7 (d, $J = 239$), 147.5, 145.5 (d, $J = 14$), 123.0 (d, $J = 4.9$), 116.7 (d, $J = 35$); IR (KBr): 1583, 1528, 1452, 1392, 1282, 1228, 1171, 1142, 1121, 1048, 862, 850, 694 cm^{-1}. Anal. Calcd for $C_{10}H_4Cl_2F_2N_2$ (261.06): C, 46.01; H, 1.54; N, 10.73. Found: C, 45.84; H, 1.56; N, 10.71.
30. Compound **15b**: mp 98–99 °C; ^1H NMR ($CDCl_3$): 7.75 (dd, 1H, $J = 5.3$, 0.75), 7.65 (d, 1H, $J = 5.3$); ^{13}C NMR ($CDCl_3$): 157.7 (d, $J = 241$), 144.7 (d, $J = 15$), 132.7 (d, $J = 4.8$), 123.0 (d, $J = 35$), 112.8; IR (KBr): 1914, 1571, 1537, 1439, 1388, 1280, 1234, 1054, 884, 825, 732, 591, 568, 509 cm^{-1}. Anal. Calcd for C_5H_2ClFIN (257.43): C, 23.33; H, 0.78; N, 5.44. Found: C, 23.38; H, 0.77; N, 5.42.