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Regioselective synthesis of 3,6-disubstituted-2-aminoimidazo[1,2-*a*]pyridines

Carlos Jaramillo,[a,*] Juan Carlos Carretero,[c] J. Eugenio de Diego,[a] Miriam del Prado,[a] Chafiq Hamdouchi,[b] José Luis Roldán[c] and Concha Sánchez-Martínez[a]

[a]*Centro de Investigación Lilly, Avenida de la Industria, 30, 28108 Alcobendas, Madrid, Spain*
[b]*Lilly Research Laboratories, A Division of Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46385, USA*
[c]*Departamento de Química Orgánica, Facultad de Ciencias, Universidad Autónoma de Madrid, 28049 Madrid, Spain*

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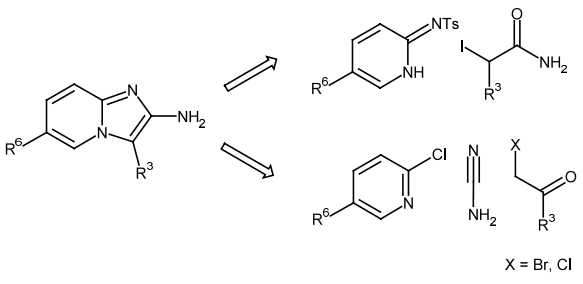
Abstract—A convenient synthesis of 3,6-disubstituted-2-aminoimidazo[1,2-*a*]pyridines **3** is described. A halogen–metal exchange study on building block **1** showed that use of *i*-propyl magnesium chloride is most effective for chemoselective functionalization at position 6. Further regiospecific metalation at position 3, followed by quenching with different electrophiles, afforded target compounds.

Imidazo[1,2-*a*]pyridines have demonstrated significant potential in the search of new drugs.[1] The amine group at position 2 confers special properties to this nucleus, which have been used to prepare 2-aminoimidazo[1,2-*a*]pyridines as antirhinovirus agents.[2] This class of compounds, as well as the related imidazo[1,2-*a*]pyrazines, imidazo[1,2-*a*]pyridazines, and imidazo[1,2-*a*]pyrimidines, are currently object of a renewed interest in the pharmaceutical field.[3] They can be found in pharmacologically active compounds such as benzodiazepine receptor agonists, anti-inflammatory agents, inhibitors of gastric acid secretion, calcium channel blockers and antibacterials.

The main approach for the synthesis of imidazo[1,2-*a*]pyridines is based on the reaction of 2-aminopyridine with α-halocarbonyl compounds.[1h,i,4,5] However, this method is not useful for the corresponding 2-amino analogs. We have recently described (Scheme 1) other approaches for this kind of molecule, from *N*-tosyl-2-aminopyridines[6,7] or 2-chloropyridines.[8,9]

Although these methods afford 3,6-disubstituted-2-aminoimidazo[1,2-*a*]pyridines, their main disadvantage is the use of building blocks (2-iodoacetamides, 2-haloacetophenones) which are usually commercially unavailable, and must therefore be prepared. For this reason, we have developed a new synthesis for this kind of molecules, which has served to perform a broad structure–activity relationship study at positions 3 and 6. In this paper, we describe a convenient method for preparation of 3,6-disubstituted-2-aminoimidazo[1,2-*a*]-pyridines from 6-iodo-2-trifluoroacetamidoimidazo-[1,2-*a*]pyridine **1**, by sequential regioselective introduction of substituents at the desired positions. This convenient starting material can be prepared in four steps from 2-aminopyridine in 40% overall yield.[7]

We envisaged (Scheme 2) the chemoselective introduction of substituents at position 6 by halogen–metal exchange and further addition of electrophiles, which would afford the desired monosubstituted intermediate **2**. Subsequent α-directed metalation at position 3, facilitated by vicinal trifluoroacetamide, followed again by electrophilic quench, would then render target molecule **3**.



Scheme 1. Synthesis of 2-aminoimidazo[1,2-*a*]pyridines.

* Corresponding author.

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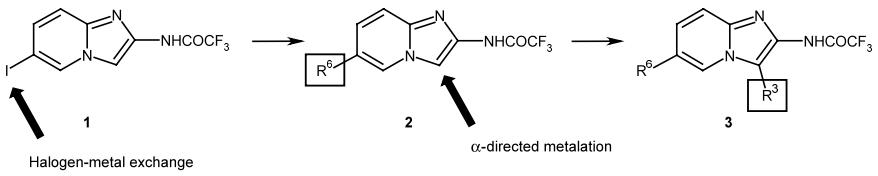
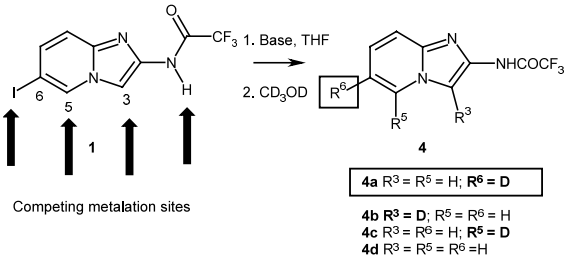


Scheme 2. Synthesis of 3,6-disubstituted-2-aminoimidazo[1,2-*a*]pyridines.

A study on the halogen–metal exchange of **1** followed by deuteration was first performed. The goal was to find out the best conditions for a chemoselective reaction, which would give the corresponding derivative regioselectively deuterated at position 6, **4a**. Acidic amide proton should be abstracted prior to halogen–metal exchange and, even so, metalation at position 3 or 5 could be also a competing process leading to **4b** or **4c**, respectively (Scheme 3).

The results of this study using different bases are summarized in Table 1. The best conditions were obtained by the use of 2 equiv. of *i*-PrMgCl[10] as base (entry 1), affording **4a** as the only deuterated regioisomer. Experiments directed to lower the amount of protonation (which leads to **4d**) were tried (reaction with NaH or LHMDS prior to *i*-PrMgCl addition, with 4 equiv. of base, or with inverse addition of the base), but gave similar results (**4a**:**4d** ratio was 79:21, 80:20 and 74:26, respectively).

Conditions for regioselective deprotonation at other positions of heterocyclic nucleus were also found. PhLi/*t*-BuLi promoted α-lithiation at position 3 (entry 2), leading to **4b** as major product (55%), whereas the use of LDA (entry 3), or more effectively, LiTMP (entry 4) resulted in deprotonation at position 5, affording **4c** selectively (43 and 54%, respectively).



Scheme 3. Chemoselective functionalization on 6-iodo-2-trifluoroacetamidoimidazo[1,2-*a*]pyridine **1** at position 6.

Table 1. Deuteration study of **1**. Relative ratios of **4a**–**d** were calculated from ^{1}H NMR spectra of crude mixtures

Entry	Base 1, Base 2	1	4a	4b	4c	4d
1	*i*-PrMgCl		81			19
2	PhLi, *t*-BuLi			55	32	13
3	LDA	44		13	43	
4	LiTMP	17		28	54	1

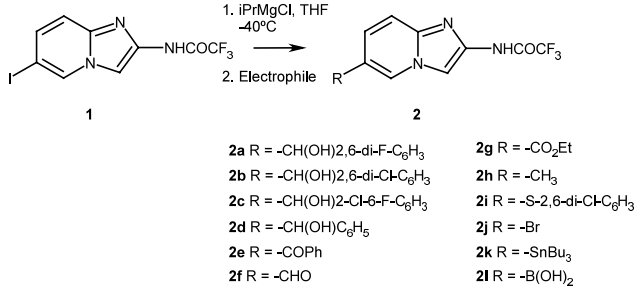
We then turned our attention to the regioselective functionalization of **1** by halogen–metal exchange and further addition of different electrophiles (Scheme 4, Table 2), providing 6-substituted derivatives **2a**–**l**. Trapping of anion was attained in conversions similar to deuteration, except for the less reactive MeI (entry 8). The reaction was optimized[11] with 2,6-dihaloaryl aldehydes (entries 1–3), affording the corresponding carbinols in 76–79% yields.

We were interested in the preparation of 6-benzoyl derivatives such as **2e**. To compare the efficacy of the direct introduction of this kind of substituent with reaction with an aldehyde and subsequent oxidation, we studied the reactivity of the magnesium anion derived from **1** with different benzoyl containing electrophiles. The best results were obtained when benzoyl chloride was used (entry 5), affording desired **2e** in 43% yield.

Introduction of a second substituent at position 3 of the heterocyclic nucleus was next investigated. α-Metalation on **2e** was attempted, but either no reaction, or addition of the base to the carbonyl group, was obtained. However, this intermediate is still useful for the introduction of sulfur containing electrophiles, as we have previously reported.[7]

With these results in hand, we undertook an alternative preparation of 3-substituted-6-benzoyl derivatives by α-metalation of carbinols **2a**–**c**, as exemplified in Scheme 5.[12]

The hydroxyl group was protected as *t*-butyldimethylsilyl ether, and proton at position 3 was abstracted with *n*-BuLi. Reaction of the corresponding carbanion with 2,6-difluorobenzoyl chloride gave **6**. Finally, deprotection of hydroxyl group, oxidation,[13] and nitrogen deprotection, afforded target compound **7** in 56% overall yield from **1**.

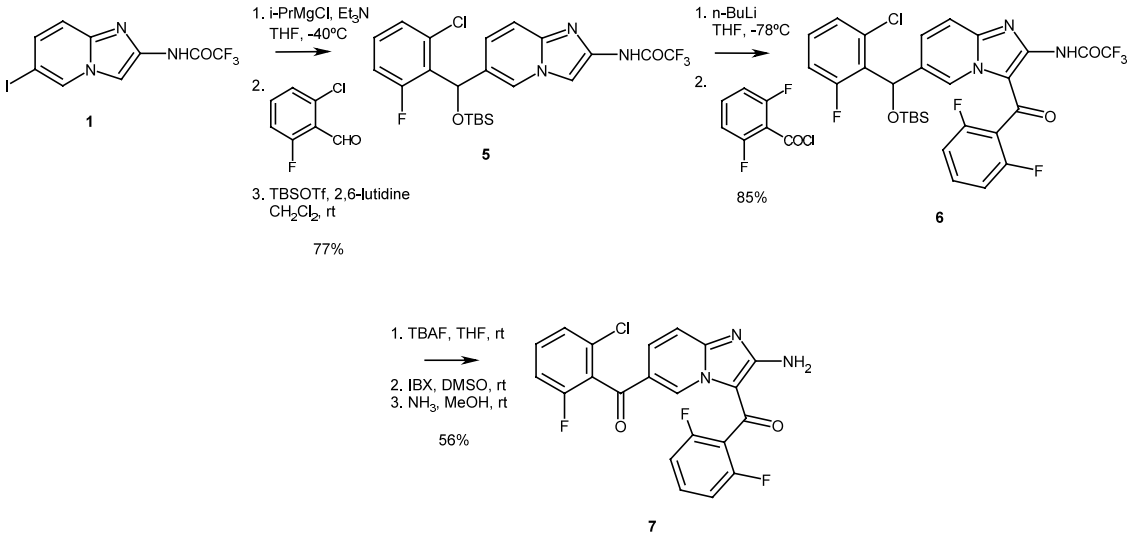


Scheme 4. Regioselective functionalization of 6-iodo-2-trifluoroacetamidoimidazo[1,2-*a*]pyridine **1**.

Table 2. Regioselective functionalization of 6-iodo-2-trifluoroacetamidoimidazo[1,2-*a*]pyridine **1** at position 6. Ratios **2**/**4d** were calculated from ^{1}H NMR spectra of crude mixtures

Entry	Electrophile	Equiv.	Temp. (°C)	Time (min)	**2**, yield (%)	**2**/**4d**
1	2,6-Di-F-C_6H_3CHO	3	−40	45	**2a**, 76	80:20
2	2,6-Di-Cl-C_6H_3CHO	3	−40	5	**2b**, 77	87:13
3	2-Cl-6-F-C_6H_3CHO	3	−40	10	**2c**, 79	80:20
4	C_6H_5CHO	3	−40	45	**2d**, 51	60:40
5	ClCOPh	3	−40	45	**2e**, 43	50:50
6	DMF	3	−40 to 10	300	**2f**, 32	65:35
7	$ClCO_2Et$	3	−40 to 10	300	**2g**, n.i.*	56:44
8	MeI	3	−40 to rt	960	**2h**, n.i.	10:90
9	(2,6-Di-Cl-$C_6H_3S)_2$	2	−40 to rt	180	**2i**, 40	72:18
10	BrCN	1.5	−40 to 0	180	**2j**, 38	83:17
11	Bu_3SnCl	1.5	−40 to rt	120	**2k**, 75	80:20
12	B(O*i*-Pr)$_3$	1.5	−40 to rt	180	**2l**, 32	79:21

* n.i., not isolated.



Scheme 5. Synthesis of 3,6-disubstituted-2-aminoimidazo[1,2-*a*]pyridine.

In summary, we have found a convenient method for the synthesis of 3,6-disubstituted-2-aminoimidazo[1,2-*a*]-pyridines from 6-iodo-2-trifluoroacetamidoimidazo-[1,2-*a*]pyridine **1**, by sequential regioselective introduction of substituents at the desired positions. A variety of functional groups can also be introduced by use of other electrophiles.

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12. All new compounds showed satisfactory physical properties. Selected data: **2a**: ^{1}H NMR (d_6-acetone, 200 MHz): δ 10.89 (bs, 1H), 8.67 (s, 1H), 8.27 (s, 1H), 7.48–7.34 (m, 2H), 7.18 (d, 1H, $J=9.4$ Hz), 7.01 (dd, 2H, $J=8.4$, 8.5 Hz), 6.31 (s, 1H), 5.49 (bs, 1H); Ms (Es+) (M^++H): 372.1. **2e**: ^{1}H NMR (d_6-acetone, 200 MHz): δ 11.25 (bs, 1H), 9.07 (dd, 1H, $J=1.7$, 0.9 Hz), 8.41 (s, 1H), 7.90–7.85 (m, 2H), 7.78–7.54 (m, 5 H); Ms (Es+) (M^++H): 334.1. **2f**: ^{1}H NMR (d_6-acetone, 200 MHz): δ 11.15 (bs, 1H), 10.0 (s, 1H), 9.25 (s, 1H), 8.40 (s, 1H), 7.70 (d, 1H, $J=9.3$ Hz), 7.56 (d, 1H, $J=9.2$ Hz); Ms (Es+) (M^++H): 258.1. **2i**: ^{1}H NMR (d_6-acetone, 200 MHz): δ 8.60 (dd, 1H, $J=1.8$, 1.0 Hz), 8.18 (s, 1H), 7.56–7.40 (m, 4H), 7.16 (dd, 1H, $J=9.5$, 1.8 Hz); Ms (Es+) (M^++H): 406.0. **2j**: ^{1}H NMR (d_6-acetone, 200 MHz): δ 11.76 (bs, 1H), 9.27 (dd, 1H, $J=1.8$, 1.0), 8.72 (s, 1H), 7.91 (dd, 1H, $J=9.5$, 1.0 Hz), 7.84 (dd, 1H, $J=9.5$, 1.8 Hz); Ms (Es+) (M^++H): 308.0. **7**: ^{1}H NMR (d_6-acetone, 300 MHz): δ 10.14 (s, 1H), 8.09 (m, 2H), 7.70–7.00 (m, 6 H), 5.60 (bs, 2H); Ms (Es+) (M^++H): 429.5.
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