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Solid-Phase Synthesis of 4-Substituted Imidazoles Using a Scaffold Approach

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Abstract—Immobilized 4-iodoimidazole **2** was used in a metal/halogen exchange reaction followed by treatment with electrophiles and subsequent cleavage from the resin to yield 4-substituted imidazoles **8**–**11**. Grignard reaction with the resin-bound ketones **5** yielded the corresponding alcohols **11**. This approach was used for a library synthesis of 35 imidazoles.

The imidazole moiety is an important structural element in ligands that aim at biological targets.[1,2] For example, several compounds with affinity for histamine receptors contain an imidazole moiety.[3,4]

Although some imidazole containing compounds have been synthesized on solid supports,[5–7] none of the published methods provide a large diversity among the substituents or are suitable to prepare the mono substituted compounds. For example, the preparation of imidazoles carrying three aryl substituents has been reported,[6] but the presence of these aryl substituents was a prerequisite to obtain reasonable yields. In another approach, a library of imidazole compounds has been reported that still carried the remainder of the linker to the solid support.[7] This remainder could not be removed.

In our search for novel, imidazole-based ligands we are interested in the stepwise preparation of mono-, di- and trisubstituted imidazoles on a solid support using a scaffold approach. Instead of building up the imidazole nucleus during synthesis, imidazole or halogenated imidazoles are used as a starting point. The introduction of substituents is achieved by proton abstraction or by a metal/halogen exchange reaction followed by the addition of an electrophile. Successful examples of this approach are known from solution phase chemistry.[8,9]

Here we present our first results in the solid-phase synthesis of 4-monosubstituted imidazoles **8**–**11** via a metal/halogen exchange reaction of polymer-bound 4-iodoimidazole (**2**) and subsequent treatment with different electrophiles (Scheme 1). This sequence of reactions can be performed using readily available starting materials at room temperature in dichloromethane, which ensures good swelling of the resin.

Commercially available 2-chlorotrityl chloride resin was used to immobilize 4-iodoimidazole (**1**).[10,11] This was our resin of choice, because of its high loading capacity and its similarity to the well known trityl protection group, which has been used in metal/halogen exchange reactions in solution.[8] Immobilization of **1** onto the resin proceeded very smoothly using triethylamine as a base and dichloromethane (DCM)/*N*-methylpyrrolidinone (NMP) as the solvent mixture. The degree of coupling was determined by weighing of the resin and by cleavage of the resin bound 4-iodoimidazole.

In order to determine the viability of the route, we started with benzaldehyde (entry 1, Table 1) as the electrophile. The reactions were performed in single vials in the fume cupboard. Treatment of **2** with EtMgBr gave the resin-bound magnesio compound **3**, which was subsequently treated with benzaldehyde for 20 h. However, after TFA cleavage ketone **9a** (R^1 = phenyl) instead of the expected alcohol **8a** (R^1 = phenyl) was obtained. A similar oxidation also occurred with butyraldehyde (Table 1, entries 4–6 and Table 2, entry 2) The alcohol/

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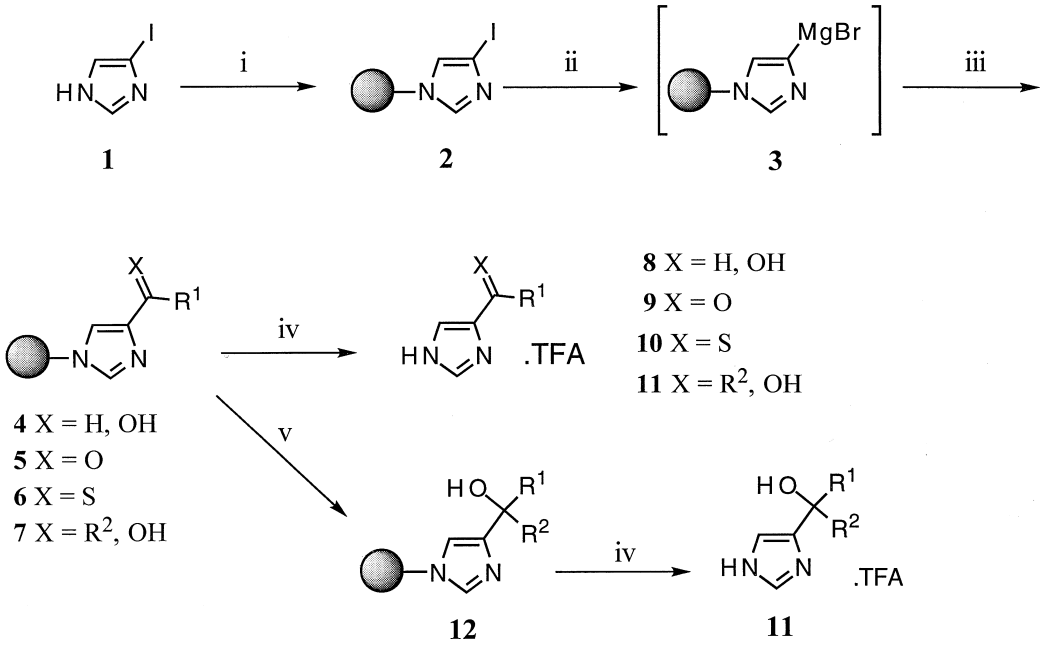


Scheme 1. (i) 2-Chlorotrityl chloride resin, Et_3N, DCM, NMP; (ii) EtMgBr; (iii) Electrophile (see text); (iv) TFA; (v) R^2MgBr.

Table 1. Reaction of **3** with aldehyde

Entry	Reaction time	Aldehyde (equiv)	Compound[a]
1	20 h	Benzaldehyde (100)	**9a**
2	20 h	Benzaldehyde (50)	**8a:9a** (1:4)
3	1 h	Benzaldehyde (50)	**8a**
4	2 h	Butyraldehyde (50)	**9b**
5	15 min	Butyraldehyde (10)	**8b:9b** (3:2)
6	2 min	Butyraldehyde (10)	**8b:9b** (9:1)

[a]a, R^1 = Phenyl; b, R^1 = Propyl.

ketone ratio found depended on the reaction time and the amount and type of aldehyde used (Table 1). IR spectra of the resin-bound imidazoles clearly showed absorptions in the carbonyl region, indicating that the oxidation of the alcohol takes place before cleavage from the resin. This oxidation is probably due to an Oppenauer reaction rather than air oxidation as proposed by other groups for related reactions.[9,11,12] In general, the oxidation can easily be controlled, giving either alcohol **8** or ketone **9** in good to high yields.

Next, we studied the reaction of the resin-bound magnesio compound **3** with a selection of electrophiles (Table 2, entries 7, 9, 12, 15–17, 25 and 29–31). These reactions were also carried out in single vials in the fume cupboard. They proceeded in reasonable to good yields and purity.

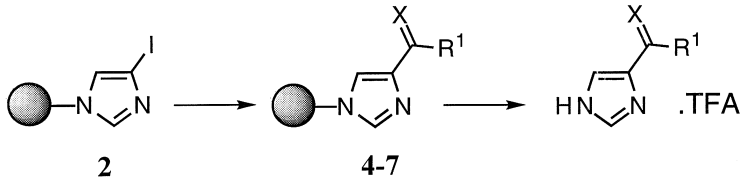
An alternative route to **11** (Scheme 1) would be via alkylation of the resin-bound ketoimidazoles **5**. Reaction of the resin-bound ketoimidazoles **5** (R^1 = phenyl or isopropyl) with methyl-, vinyl- or allyl magnesium bromide gave indeed — via **12** — the desired imidazoles **11 a**, **e**, **h**, **g**, **i** and **k** in 30–80% purity after TFA cleavage (Table 3, entries 1, 3, 5, 6, 7 and 9). When the resins were washed and dried after the first addition and then treated with a second aliquot of alkyl Grignard, the purities could be increased to 80–85%. This way, a sublibrary of imidazoles **11** could be synthesized, which is not limited by the availability of ketones.

After these successful trial experiments a library synthesis was conducted using a MultiSynTech stand-alone apparatus. For this purpose a series of electrophiles, as shown in Table 2, was selected to react with **3**. TFA cleavage of the resin-bound compounds **4**–**7** resulted in imidazoles **8**–**11** in reasonable yields and purities. The only side product that could be detected was 4-iodoimidazole. However, the conversion degrees of these reactions were significantly lower than the ones performed in single vials. A selection of resin-bound keto-imidazoles **5** (R^1 = phenyl, propyl, cyclohexyl, isopropyl and thienyl) were subsequently reacted with methyl-, vinyl- or allyl magnesium bromide to yield the corresponding imidazoles **11** (Table 3, entries 1, 2, 4 and 8). In these cases the purities dropped to ca. 35% or even lower (purities lower than 10% were omitted from Table 3). Most likely, the purities of the addition reactions performed in the stand-alone are low due to difficulties in maintaining a sufficiently dry blanket of nitrogen throughout the reactions. Nevertheless, the imidazoles **8**–**11** can easily be purified by HPLC,[13] resulting in 4-monosubstituted imidazoles in >95% purity.

Conclusions

We have developed a new method to simultaneously synthesize a large variety of 4-monosubstituted imidazoles on a solid support. Lower conversions were achieved using a stand-alone apparatus compared to the same reactions in the fume cupboard. Purification of the reaction products was achieved by preparative HPLC to obtain 4-substituted imidazoles in >95% purity.

Table 2. Mono-substituted imidazoles obtained via a metal/halogen exchange reaction



Entry	Electrophile	R^1	Results in fume cupboard: product (%yield[a]/%purity[b])	Results with stand-alone: product (%yield[a]/ %purity[b])
1	Aldehyde	Phenyl	**8a** (50/95)	**8a** (46/65)
2	(R^1CHO)	Propyl	**9b** (89/95)[c]	**9b** (61/65)[c]
3		Cyclohexyl		**8c** (34/30)
4		Pentyl		**8d** (34/55)
5		2-Pyridyl		**8e** (>100[d]/10)
6		3-Pyridyl		**8f** (31/50)
7		4-Pyridyl	**8g** (82/90)	**8g** (21/50)
8		*p*-Cl-phenyl	**9b** (89/95)[c]	**8h** (56/40)
9	Acid chloride	Phenyl	**9a** (50/70)	**9a** (52/30)
10	(R^1COCl)	Propyl		**9b** (67/73)
11		Cyclohexyl		**9c** (63/85)
12		Isopropyl	**9d** (66/ >95)	**9d** (73/86)
13		Thiënyl		**9e** (45/50)
14		Oxyethyl		**9f** (34/70)
15	Nitrile	Phenyl	**9a** (50/70)	**9a** (78/30)
16	(R^1CN)	Ethyl	**9g** (45/75)	**9g** (70/80)
17	Isocyanate	NH-*t*-butyl	**9h** (60/ >95)	**9h** (100/45)
18	(R^1NCO)	NH-ethyl		**9i** (59/40)
19		NH-cyclohexyl		**9j** (100/64)
20		NH-allyl		**9k** (99/65)
21		NH-phenyl		**9l** (99/45)
22		NH-benzyl		**9m** (55/55)
23		NH-*p*-Cl-phenyl		**9n** (86/55)
24	Isothiocyanate	NH-methyl	**10b** (54/65)	**10a** (76/20)
25	(R^1NCS)	NH-cyclohexyl		**10b** (33/20)
26		NH-allyl		**10c** (51/50)
27		NH-benzyl		**10d** (50/85)
28		NH-pyrroyl		**10e** (100/45)
29	Ketone	Methyl/phenyl[e]	**11a** (60/70)	**11a** (35/40)
30	(R^1COR^2)	Phenyl/phenyl	**11b** (74/90)	**11b** (66/20)
31		Ethyl/ethyl	**11c** (49/50)	**11c** (37/60)

[a]Unpurified cleavage product.
[b]Purity was determined by ^{1}H NMR, remainder is 4-iodomidazole unless stated otherwise.
[c]Oxidation product only.
[d]Due to remaining solvent.
[e]Dehydration product only.

Further studies on reactions other than metal/halogen exchange reactions to substitute the imidazole nucleus are underway and will be reported in due course.

Experimental

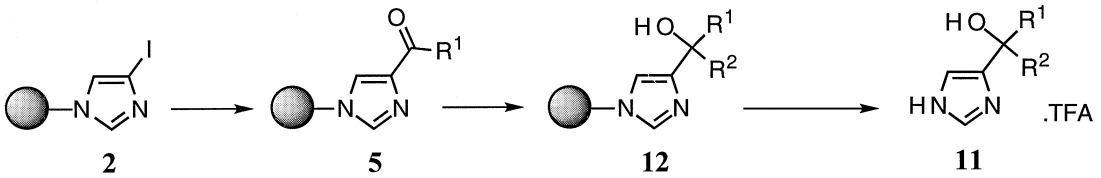
2-Chlorotrityl chloride resin was purchased from Novabiochem®. The library synthesis was performed on MultiSynTech standalone apparatus using teflon reaction vessels (5 mL). The electrophiles were used as purchased. ^{1}H NMR analysis was performed on a Brüker 400 MHz. HPLC analysis was performed using a Gilson apparatus.[13] Mass spectra were determined on a Perkin Elmer series 200 autosampler.

Preparation of the functionalized resin (2). 2-Chlorotrityl chloride resin (1.09 mmol/g, 2.5 g) was swollen in freshly destilled DCM (5 mL). A solution of 4-iodoimidazole (3 g) in NMP (3 mL), triethylamine (3 mL) and DCM (4 mL) was added dropwise to the suspension and stirred overnight at room temperature. The derivatized resin was filtered and washed with NMP, MeOH, 3×DCM:MeOH (3:1), MeOH, 3×DCM:MeOH (3:1), MeOH, 3×DCM and dried overnight.

Preparation of resin coupled products (4–7). The teflon reaction vessels were charged with 50 mg of **2**, placed in the standalone apparatus and filled with DCM (2.5 mL). Then 200 μL of ethylmagnesium bromide solution (3M in ether) was added. The suspensions were left for 3 h under a nitrogen atmosphere and stirred every 30 min for several seconds. Next, the electrophiles (50 μL) were added and the mixtures were stirred for several seconds. The reactions with the acyl chlorides were stopped after 5 min. The other reactions were stopped after 2 h. The resins were filtered and washed with saturated ammonium chloride solution, MeOH, 2×DCM, MeOH, 2×DCM and 2×ether and dried at 40 °C under vacuum overnight.

Preparation of resin coupled products 12. The resins **5** were swollen in THF and the temperature of the standalone apparatus was lowered to 0 °C before the

Table 3. Mono-substituted imidazoles **11** obtained via intermediates **5** and **12**



2 **5** **12** **11**

Entry	R^1	R^2	Results in fume cupboard: product (%yield[a]/%purity[b])	Results with stand-alone: product (%yield[a]/ %purity[b])
1	Phenyl	Methyl[c]	**11a** (61/75)	**11a** (70/30)
2	Propyl	Methyl		**11d** (73/20)
3	Isopropyl	Methyl[d]	**11e** (65/80)	
4	Thienyl	Methyl		**11f** (55/30)
5	Phenyl	Vinyl	**11g** (45/60)	
6	Isopropyl	Vinyl[d]	**11h** (54/50)	
7	Phenyl	Allyl	**11i** (40/30)	
8	Propyl	Allyl		**11j** (51/40)
9	Isopropyl	Allyl[d]	**11k** (49/50)	**11d** (73/20)

[a]Unpurified cleavage product.
[b]Purity was determined by ^{1}H NMR.
[c]Complete dehydration.
[d]Partial dehydration.

Grignard reagents (30 equiv) were added. The resulting concentration of the Grignard reagent in each reaction vessel was 0.1 M. After 20 h the resins were filtered and washed with methanol, 2×DCM, MeOH, 2×DCM and ether. The resins were dried under vacuum at 40 °C for 5 h and the reaction and washing sequence was repeated twice. Finally the resins were dried at 40 °C under vacuum overnight.

Preparation of imidazole products 8–11. cleavage protocol. The reaction vessels containing the resin-bound imidazoles were mounted on a VacMaster® and 1.5 mL 10% TFA in DCM was added. After 2 h the filtrates were collected in 10 mL preweighted tubes. The filtrates were concentrated in a TurboVap® apparatus and the yield of product was determined. The composition of the product was analysed by NMR spectroscopy, mass spectroscopy and HPLC.

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