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Microwave-assisted synthesis of imidazoles: Reaction of *p*-toluenesulfonylmethyl isocyanide and polymer-bound imines

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Abstract—A convenient method for the synthesis of 1,5-disubstituted imidazoles has been developed on a polymeric support using base-promoted 1,3-dipolar cycloaddition reaction of *p*-toluenesulfonylmethyl isocyanide (TOSMIC) with immobilized imines under microwave irradiation. The immobilized imines were synthesized by the reaction of various primary benzyl amines with 4-formyl-3-methoxyphenoxymethyl polystyrene in the presence of trimethyl orthoformate at room temperature. Cleavage from the polymeric support using trifluoroacetic acid gave the desired 1,5-disubstituted imidazoles with excellent yield and high purity.

Several biologically active synthetic compounds possess five-membered nitrogen-containing heterocycles in their structures.[1] The imidazole core is a common moiety in a large number of natural products and pharmacologically active compounds.[2] Recently, there has been considerable amount of progress in imidazole chemistry due to the recognition of the importance of the imidazole structure in biological processes and the increasing application of imidazole-containing compounds, such as etomidate, cimetidine, omeprazole and lansoprazole, in drug therapy.[3] On the other hand, microwave-assisted solid-phase organic synthesis is a relatively new technique that has shown significant improvement in the generation of combinatorial libraries of small molecules.[4] Various types of thermally conducted organic reactions have been accelerated by the use of microwave irradiation. Microwave irradiation has not only been demonstrated to dramatically accelerate many organic reactions, but also to improve the yields and selectivity. These advantages offer an opportunity for a convenient and rapid library synthesis of substituted imidazoles.

So far, there are only a few published studies about the solid-phase synthesis of substituted imidazoles. Ranganathan and Rathi have synthesized imidazoles by using polymer-supported 4-carboxamido-5-aminoimidazole and hypoxanthine.[5] Synthesis of substituted imidazole libraries on the Wang resin has been reported by Mjalli and co-workers.[6] The imidazoles were obtained in very good yield and purity by means of a condensation reaction between primary amines, aldehydes and 1,2-diones in the presence of NH_4OH. Moreover, Bilodeau and Cunningham have synthesized 2,4,5-triaryl imidazoles through the [3 + 2] cycloaddition reaction.[7] They allowed aryltosyl imines to react with the polymer-supported 1,3-oxazolium-5-olates (münchnones) in the presence of EDC. As a result, the 2,4,5-trisubstituted imidazoles were obtained after cleavage with refluxing acetic acid in moderate to good yield and purity. The van Leusen group was the first to report on the preparation of 1,5-disubstituted imidazoles from *p*-tosylmethyl isocyanide (TOSMIC) and aldimines in solution.[8] We have successfully translated this 1,3-dipolar cycloaddition reaction to the polymer-bound 3-methoxy-4-hydroxybenzaldehyde, as shown in Scheme 1.

Commercially available 4-formyl-3-methoxyphenoxymethyl polystyrene (Ameba resin,[9] 1% DVB, 100–200 mesh, 1.0–1.5 mmol/g) **1** was treated with trimethyl orthoformate (4 equiv) and substituted benzylamine (4 equiv) in a parallel synthesizer under an inert atmosphere at room temperature to yield the immobilized imines[10] (**2a**–**i**). The imine formation was followed until the aldehyde functionality was fully consumed, and the progress of the reaction was monitored by means of FT-IR spectroscopy and a qualitative 2,4-dinitrophenylhydrazide test.[11] After the

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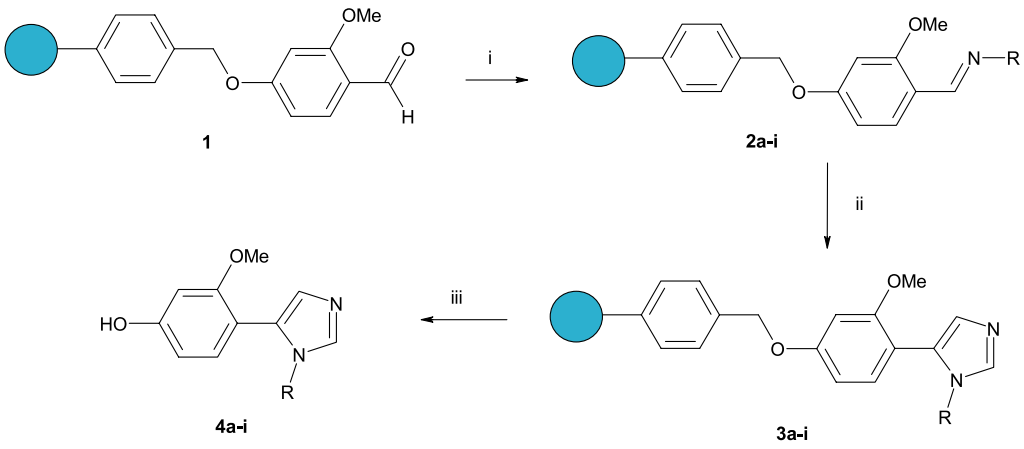


Scheme 1. Reagents and conditions: (i) $CH(OMe)_3$ (4 equiv), substituted benzylamine (4 equiv), DMF, rt, 12 h; (ii) 4-$CH_3C_6H_4SO_2CH_2NC$ (2.4 equiv), DMF, 130 °C, 20 min; (iii) 50% TFA/CH_2Cl_2, rt, 1.5 h.

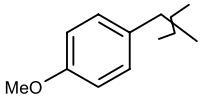
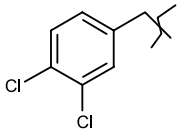
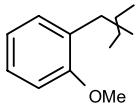
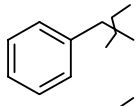
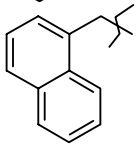
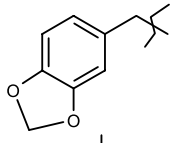
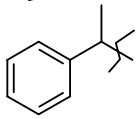
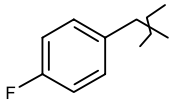
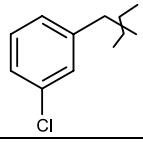
completion of the reaction, the resin was filtered and washed successively with DMF, MeOH and CH_2Cl_2 and dried in vacuo for 3 h. A small portion of the resin was then checked by means of the 2,4-dinitrophenylhydrazide test for the presence of any remaining aldehydic groups. The absence of a red colour indicated that the reaction was completed. The yield of the imine formation was quantitative, and the polymer-bound products **2a**–**i** were light yellow in colour.

In a typical reaction, the polymer-bound imine **2a** (500.0 mg, 0.625 mmol) was placed into the 2–5 mL reaction vial, swollen in 2.5 mL DMF and treated with TOSMIC (300 mg, 1.53 mmol, 2.4 equiv) in the presence of *N*,*N*-diisopropylethylamine (2.00 mL, 11.5 mmol, 18 equiv). The vial was sealed and heated by the microwave reactor at 130 °C for 20 min.[12] The product resin was washed successively with DMF, CH_2Cl_2, MeOH, and finally with CH_2Cl_2 and dried in vacuo for 3 h to yield the polymer-bound imidazole **3a**, which was weighed to obtain the mass of the resin before the cleavage step. All other polymer-bound imidazoles **3b**–**i** were synthesized in a similar fashion.[13]

Finally, the 1,5-disubstituted imidazoles **4a**–**i** were cleaved from the resin very efficiently and cleanly by treatment with 50% TFA/CH_2Cl_2 at room temperature for 1.5 h. The cleavage process was repeated two or three times. Products were recovered in excellent yield (70–85%, calculated on the basis of the original loading of the resin, 1.25 mmol/g) after cleavage and purification with SiO_2 column chromatography using 5% MeOH/EtOAc as an eluent (see Table 1). All the product imidazoles **4a**–**i** were characterized[13] by means of ^1H and ^{13}C NMR, FT-IR and LC–MS.

For comparison to the conventional reaction conditions, these 1,3-dipolar cycloaddition reactions were also carried out at room temperature and at 130 °C for 1 h, using the same stoichiometry. No formation of the 1,5-disubstituted imidazoles was observed after cleavage from the polymeric support. This reaction sequence also failed when we used α-aryl substituted TOSMIC.[14] This may be due to the fact that the aryl substituent

Table 1. Preparation of the 1,5-disubstituted imidazoles (**4**)

Entry	Imidazole	R	Yield[a] (%)	Purity[b] (%)
1	**4a**		82	92
2	**4b**		70	82
3	**4c**		85	88
4	**4d**		75	85
5	**4e**		80	89
6	**4f**		81	90
7	**4g**		76	86
8	**4h**		81	84
9	**4i**		85	86

[a] The yields are based on the original loading of the resin (1.25 mmol/g).
[b] Purities were determined by ^1H NMR and LC–MS (280 nm).

(*p*-chlorophenyl) prevents the favourable approach of the α-substituted dipolar *p*-tosylmethyl isocyanide dipole and the polymer-bound imine dipolarophile in the transition state leading to the formation of an imidazole ring. Despite excellent purities and yields of the 1,5-disubstituted imidazoles, our method still suffers from the limitation that the imidazole 5-substituent (4-hydroxy-2-methoxyphenyl) remains constant, while only the 1-substituent can be varied. The traceless removal of the resin appendage at the 5-position might be achieved by using a 3-methoxy-4-(2-oxoethyl)phenoxymethyl polystyrene as a resin for the formation of the polymer-bound imines. The benzylic substituent might be removed by means of DDQ oxidation.[15]

In conclusion, we have developed an expedient synthesis sequence for the preparation of 1,5-disubstituted imidazoles. The method utilizes a 1,3-dipolar cycloaddition reaction between the polymer-supported imine and *p*-tosylmethyl isocyanide. This three-step procedure offers an efficient synthesis of 1,5-disubstituted imidazoles, complementing the known methods that provide other substituted imidazoles on solid support. Further studies on improvement and extension of this strategy for the synthesis of 1,5-disubstituted imidazoles in a traceless manner are now underway in our laboratory and will be reported in due course.

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12. The microwave reactor used in our experiments is the Initiator^{TM} EXP from Biotage. Reactions were carried out in their proprietary 2–5 mL sealed vials. **Caution!** Certain isonitriles are unstable at temperatures above 80 °C. Therefore, care should be taken when using these compounds as reagents at higher reaction temperatures.
13. *Compound* ***4a****:* Yield 82%; yellow solid, mp: 145–147 °C; R_f: 0.23 (5% MeOH/EtOAc); ^{1}H NMR (CD_3OD): δ 3.70 (3H, s), 3.77 (3H, s), 4.88 (2H, s), 6.47–6.53 (2H, m), 6.78–6.81 (2H, d, J = 9 Hz), 6.95–7.00 (4H, m), 7.50 (1H, s); ^{13}C NMR (CD_3OD): δ 51.90, 55.90, 56.16, 100.4, 106.2, 109.0, 115.5, 119.7, 127.3, 131.0, 134.3, 134.4, 136.1, 160.6, 161.7, 163.2; MS: *m*/*z* [M^+ + H] 311.
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