Pergamon

Tetrahedron Letters 40 (1999) 5637–5638

TETRAHEDRON
LETTERS

Solution-phase Parallel Oxazole Synthesis withTosMIC

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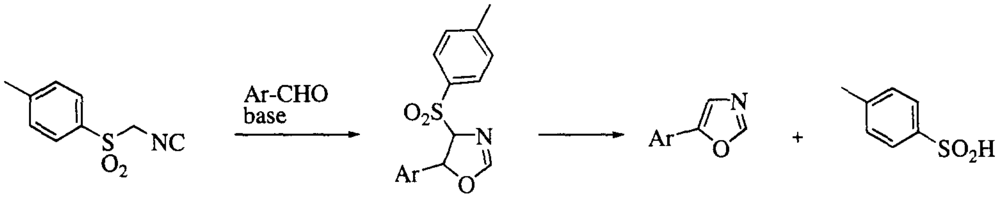
Received 27 April 1999; accepted 25 May 1999

Abstract: A quaternary ammonium hydroxide ion exchange resin catalyzes the reaction of *p*-tolylsulfonylmethyl isocyanide (TosMIC) with aromatic aldehydes to give 5-aryloxazoles. The base and the *p*-tolylsulfinic acid byproduct are removed by simple filtration, resulting in oxazoles in high yield and purity.

Keywords: Supported reagents/reactions; combinatorial chemistry; isocyanides; oxazoles

p-Tolylsulfonylmethyl isocyanide (TosMIC) is a popular synthon for the C-N=C unit developed by van Leusen.[1] The reagent undergoes addition to various unsaturated functional groups, giving rise to azoles such as oxazoles, imidazoles, pyrroles, 1,2,4-triazoles, 1,3-thiazoles, and indoles. We have been exploring the potential of TosMIC for solution and solid-phase combinatorial chemistry. In the preceding communication,[2] we described the synthesis of a TosMIC surrogate suitable for solid-phase organic synthesis. The potential of this resin was illustrated by its base-catalyzed reaction with aldehydes to give 5-substituted oxazoles.

The TosMIC oxazole synthesis (**Scheme 1**) proceeds in two stages via an intermediate oxazoline. The original report[3] employed potassium carbonate as the base, while potassium *tert*-butoxide has also been used.[4] In our solid-phase reactions, tetrabutylammonium hydroxide was a convenient alternative, a result with implications for solution-phase library synthesis as well. For such applications, a limitation of the earlier procedures is that the inorganic base and the *p*-tolylsulfinic acid byproduct remain in the reaction mixture. We anticipated that a quaternary ammonium hydroxide ion exchange resin[5] would circumvent the need for extensive product purification. The heterogeneous base is removed by simple filtration, while the sulfinic acid would exchange with the resin and be tightly bound by noncovalent ionic interactions.



Scheme 1

Indeed, a basic ion exchange resin (OH⁻ form) proved successful in promoting the TosMIC oxazole synthesis. While such reactions can be driven to completion by using a large excess of one of the components, both aldehyde and TosMIC[6] are capable of undergoing other reaction pathways under basic conditions. We find it convenient to run these reactions with a slight excess of TosMIC, and have prepared[7] a broad range of 5-aryloxazoles (examples, **Table 1**). The crude reaction products are sufficiently clean for direct evaluation in biological assays, although we have also quantified the yields of purified material. The commendable features of the resin-catalyzed procedure make it the base of choice for solution-phase oxazole synthesis with TosMIC.

PII: S0040-4039(99)01050-3

Table 1. Synthesis of 5-aryloxazoles using an ion exchange resin as base.

Aldehyde, Ar-CHO	Crude purity (%)[a]	Isolated yield (%)[b]
Ph	87	85
2-MePh	85	64
2,4-Me_2Ph	69	54
2-Naphthyl	70	69
4-(MeO)Ph	82	62
4-(PhO)Ph	90	67
2-Furyl	73	59
3-Cl-Ph	87	72
4-Cl-Ph[c]	57	57
3-(NO_2)-4-Cl-Ph	88	83
4-(NO_2)Ph	94	84
4-(CF_3)Ph[c]	71	70
2-Quinolyl	82	72

[a] Assessed by HPLC with diode array detection at 210 nm.

[b] After preparative TLC. All compounds were characterized by NMR and MS.

[c] These reactions were carried out at rt, as refluxing gave low yields.

Acknowledgments. We are grateful to Professor Albert M. van Leusen (Groningen University) for reprints. Funding from the National Science and Technology Board of Singapore supported this work.

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7. Typical procedure: A solution of aldehyde (0.135 mmol) and TosMIC (1.1 mol equiv) in 1:1 DME/MeOH (4 mL) was refluxed with Ambersep 900 OH^- resin (250 mg, Fluka, exchange capacity 0.95 meq/mL) for 8 h. The reaction mixture was filtered, the resin washed (MeOH, 3 x 10 mL), and the combined filtrates concentrated. The crude products were purified by preparative TLC (10-30 % EtOAc/hexanes eluent).