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# A Solid-phase Equivalent of van Leusen's TosMIC, and its Application in Oxazole Synthesis

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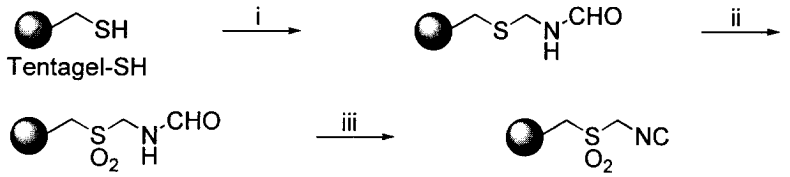
**Abstract**: Polystyrene-SH resin, prepared from Merrifield resin in two steps, was converted to polystyrene-$SO_2$-$CH_2$-NC in three steps. This resin functions as a solid-phase equivalent of *p*-tolylsulfonylmethyl isocyanide (TosMIC). Thus, reaction with aromatic aldehydes and tetrabutylammonium hydroxide as base yields 5-aryloxazoles. 

**Keywords**: Solid-phase synthesis; combinatorial chemistry; isocyanides; oxazoles

The synthesis and screening of combinatorial compound libraries has become a powerful problem-solving approach in chemistry, particularly for drug discovery.[1] These advances have rejuvenated the field of solid-phase organic synthesis,[2] previously largely limited to oligomeric peptides and nucleotides, resulting in a need for the successful translation of organic reactions traditionally performed in solution-phase to solid-phase conditions. Here, we report a solid-phase version of *p*-tolylsulfonylmethyl isocyanide (TosMIC). This reagent, developed by van Leusen,[3] is widely used in a number of synthetic applications including the assembly of azoles such as oxazoles, imidazoles, pyrroles, and indoles.

We used Tentagel-SH resin (Rapp Polymere) as a starting point for the synthesis of an immobilized sulfonylmethyl isocyanide (**Scheme 1**). The route is similar to the solution-phase[4] preparation of TosMIC or related analogues, except that we found $Ph_3P/CCl_4$ to be more convenient than $POCl_3$ for dehydration of the formamide.[5] The solid-phase reactions were monitored by gel-phase $^1H$ NMR and IR. For example, isonitrile formation was accompanied by the appearance of a new absorption in the IR spectrum (2129 $cm^{-1}$) and the disappearance of the formamide proton (δ 7.8) in the NMR.




**Scheme 1.** Reagents: i) KO*t*Bu (12 equiv), *p*-$CH_3$-$C_6H_4$-$SO_2CH_2NHCHO$ (10 equiv), 1:2 DMSO/THF, 0° C to rt, 18 h; ii) *m*-CPBA (10 equiv), $CH_2Cl_2$, rt, 16 h; iii) $POCl_3$ (5 equiv), $Et_3N$ (26 equiv), THF, -30° C to 0° C, 3 h or $Ph_3P$ (4 equiv), $CCl_4$ (4 equiv), $Et_3N$ (10 equiv), $CH_2Cl_2$, rt, 16 h.

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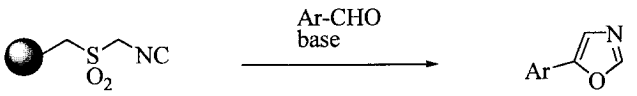
As an illustration of the isocyanide resin's potential, we investigated the TosMIC reaction with aldehydes to give oxazoles (**Scheme 2**).[6,7] The resin was reacted with excess benzaldehyde and $K_2CO_3$ as base in refluxing methanol (6 h). Chromatographic purification of the supernatant afforded 5-phenyloxazole in 49 % isolated yield, based on the manufacturer's loading of Tentagel-SH. However, upon extension to other aldehydes, we observed contamination by a number of non-UV active impurities. The $^1$H NMR of the crude product revealed singlets in the region 3.5-5.0 ppm, suggesting breakdown of the PEG linker. Indeed, treatment of unloaded Tentagel-SH resin with $K_2CO_3$ in refluxing methanol also produced similar impurities.




**Scheme 2**

Because of Tentagel's instability to our basic conditions, we repeated the resin synthesis (**Scheme 1**) starting with polystyrene-SH, prepared from Merrifield resin (Advanced ChemTech) according to the method[8] of Kobayashi. This resin ("PS-TosMIC")[9] also performed satisfactorily in the reaction with aldehydes, without the impurities seen with Tentagel. We then evaluated the efficiency of 5-phenyloxazole formation with benzaldehyde using various bases (**Table 1**).

**Table 1.** Effect of base on the reaction of PS-TosMIC with benzaldehyde.

| Base[a] | Yield of 5-phenyloxazole (%)[b] |
|---|---|
| $K_2CO_3$ | 44 |
| $Bu_4N^+OH^-$ | 50 |
| $Bu_4N^+F^-$ | 37 |
| NaOEt | 0 |

[a]The reaction with $K_2CO_3$ was performed in refluxing 1:1 MeOH/DME for 6 hours, others in neat DME at room temperature for 24 hours. All reactions were carried out with 3 equivalents of benzaldehyde and 3.5 equivalents of base.
[b]Yields of chromatographically purified material, based on the manufacturer's loading of Merrifield resin.

The results indicate that a quaternary ammonium hydroxide base is quite efficient in promoting this reaction. Compared to the original protocol[6] employing $K_2CO_3$ or KOH, the elimination of sulfinic acid from the intermediate oxazoline takes place at room temperature. With these conditions, we have successfully prepared[10] a series of 5-aryloxazoles from PS-TosMIC and various aromatic aldehydes (**Table 2**). Although we have only examined oxazole synthesis in our exploratory study, we anticipate that PS-TosMIC will be a

suitable solid-phase replacement for other applications of TosMIC. In the following communication, we also report the extension of these results to a streamlined protocol for solution-phase oxazole synthesis.

**Table 2.** Synthesis of 5-aryloxazoles using PS-TosMIC and aromatic aldehydes.

| Aldehyde, Ar-CHO | Yield of 5-aryloxazole (%)[a] |
|---|---|
| Ph | 50 |
| 4-*t*BuPh | 33 |
| 2-MePh | 43 |
| 2,4-$Me_2$Ph | 42 |
| 4-(Ph)Ph | 45 |
| 4-(CN)Ph | 40 |
| 4-($NO_2$)Ph | 44 |
| 2-($NO_2$)Ph | 42 |
| 3-(Br)Ph | 25 |
| 3-(F)Ph | 32 |

[a]Yields of chromatographically purified material, based on the manufacturer's loading of Merrifield resin.

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**References and Notes**

1. For monographs, see: (a) *Combinatorial Chemistry: Synthesis and Application*; Wilson, S. R.; Czarnik, A. W., Eds.; Wiley: New York 1997. (b) Terrett, N. K. *Combinatorial Chemistry*; Oxford University: Oxford, 1998. (c) *Combinatorial Chemistry and Molecular Diversity in Drug Discovery*; Gordon, E. M.; Kerwin, J. F. Jr., Eds.; Wiley: New York, 1998.
2. For reviews, see: (a) Bunin, B. A. *The Combinatorial Index*; Academic: San Diego, 1998. (b) Brown, R. C. D. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3293-3320. (c) Booth, S.; Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. C. *Tetrahedron* **1998**, *54*, 15385-15443.
3. For reviews, see: (a) Lamberth, C. *J. Praktische Chem.* **1998**, *340*, 483-485. (b) van Leusen, A. M.; van Leusen, D. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; Wiley: New York, 1995; Vol. 7, pp 4973-4979. (c) van Leusen, A. M. In *Perspectives in the Organic Chemistry of Sulfur*; Zwanenburg, B.; Klunder, A. J. H., Eds.; Elsevier: Amsterdam, 1987; pp 119-143. (d) van Leusen, A. M. *Lect. Heterocycl. Chem.* **1980**, *5*, S-111-S122.

4. (a) Hoogenboom, B. E.; Oldenziel, O. H.; van Leusen, A. M. *Org. Synth.* **1977**, *57*, 102-106. (b) van Leusen, D.; Rouwette, P. H. F. M.; van Leusen, A. M. *J. Org. Chem.* **1981**, *46*, 5159-5163. (c) Hundscheid, F. J. A.; Tandon, V. K.; Rouwette, P. H. F. M.; van Leusen, A. M. *Tetrahedron* **1987**, *43*, 5073-5088.

5. For an example of solid-phase formamide dehydration to isonitriles, see: Zhang, C.; Moran, E. J.; Woiwode, T. F.; Short, K. M.; Mjalli, A. M. M. *Tetrahedron Lett.* **1996**, *37*, 751-754.

6. van Leusen, A. M.; Hoogenboom, B. E.; Siderius, H. *Tetrahedron Lett.* **1972**, 2369-2372.

7. For reviews on oxazoles, see: (a) Boyd, G. V. In *Comprehensive Heterocyclic Chemistry*; Potts, K. T., Ed.; Pergamon: Oxford, 1984; Vol 6, pp 177-233. (b) Hartner, F. W. Jr. In *Comprehensive Heterocyclic Chemistry-II*; Shinkai, I., Ed.; Elsevier: Oxford, 1996; Vol 3, pp 261-318.

8. Kobayashi, S.; Hachiya, I.; Suzuki, S.; Moriwaki, M. *Tetrahedron Lett.* **1996**, *37*, 2809-2812.

9. Preparation of PS-TosMIC: Merrifield resin (1.5 g, 1.5 mmol/g loading) was suspended in dry DMF (20 mL), followed by the addition of potassium thioacetate (2.6 g, 15 equiv). The resin was agitated for 16 h, filtered, and washed (DMF, MeOH, $CH_2Cl_2$, 3x25 mL). The thioacetate resin (1.5 g) was suspended in THF (10 mL) and reduced with $NaBH_4$ (0.85 g, 15 equiv) while agitated for 16 h. Filtration and washing of the resin (DMF, MeOH, $CH_2Cl_2$, 3x25 mL) yielded polystyrene-SH resin (1.5 g).

   Polystyrene-SH resin (1.5 g) was suspended in THF (30 mL) and DMSO (15 mL), followed by the addition of KO*t*Bu (2.0 g, 12 equiv). After stirring at room temperature (1 h), the reaction mixture was cooled to 0° C, followed by addition of *N*-(*p*-tosylsulfonylmethyl)formamide (3.2 g, 10 equiv) in two portions. After agitation (18 h, rt), the resin was filtered, washed (DMF, MeOH, $CH_2Cl_2$, 3x25 mL), and dried. The formamide resin was then suspended in $CH_2Cl_2$ (25 mL), followed by addition of 3-chloroperoxybenzoic acid (2.6 g, 10 equiv). After agitation (16 h), the resin was filtered, washed (DMF, MeOH, $CH_2Cl_2$, 3x25 mL), and dried. Formamide dehydration was accomplished by suspending the resin in $CH_2Cl_2$ (15 mL), followed by addition of triphenylphosphine (1.6 g, 4 equiv), carbon tetrachloride (0.58 mL, 4 equiv), and triethylamine (2.1 mL, 10 equiv). After agitation (16 h), the resin was filtered, washed (DMF, MeOH, $CH_2Cl_2$, 3x25 mL), and dried to yield PS-TosMIC resin.

10. Typical procedure: PS-TosMIC resin (75 mg) was suspended in DME (3 mL) followed by the addition of benzaldehyde (23 μL, 3 equiv) and 1 M tetrabutylammonium hydroxide solution in methanol (263 μL, 3.5 equiv). After agitation (24 h), the resin was filtered and rinsed ($CH_2Cl_2$, 3x10 mL). The combined organic filtrates were concentrated and purified by preparative TLC (7 % EtOAc/hexanes eluent) to yield 5-phenyloxazole (5.4 mg, 50 %). $^1$H NMR (400 MHz, $CDCl_3$) δ 7.34-7.37 (m, 2H), 7.44 (t, $J$ = 7.4 Hz, 1H), 7.67 (d, $J$ = 7.5 Hz, 2H), 7.93 (s, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 121.5, 124.4, 127.8, 128.7, 128.9, 150.5, 151.6. MS (electrospray) *m/z* 146 $(M+1)^+$.