



## Solid phase-mediated synthesis of isonitriles

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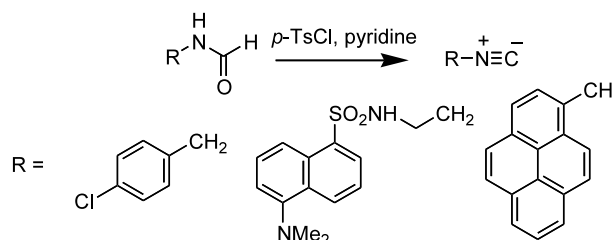
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**Abstract**—Supported sulfonyl chlorides and microwave irradiation are an efficient combination for isonitrile synthesis. © 2002 Elsevier Science Ltd. All rights reserved.

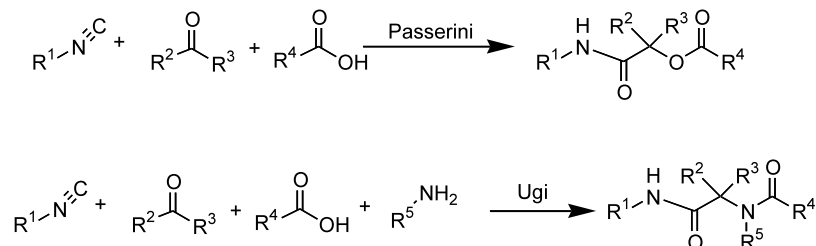
Multi-component reactions (MCRs) have become an important constituent of the combinatorial chemist's arsenal, allowing large numbers of compounds to be produced in a rapid parallel synthesis programme. Thus, the Passerini<sup>1</sup> and Ugi<sup>2</sup> reactions, to name but two, have become well established in library synthesis programmes (Scheme 1).<sup>3</sup>

One of the most important components of these reactions, and one that is very limited in accessibility, is the isonitrile. Isonitriles are especially important due to their unusual bifunctional reactivity, acting as both a nucleophile and an electrophile during the reaction. There are numerous methods reported for isonitrile synthesis,<sup>4</sup> however, during the synthesis of a series of isonitrile tags we became aware of the limited utility and applicability of many current methods. Eventually the synthetically most useful conditions, the treatment of formamides with *p*-toluene sulfonyl chloride, were identified<sup>5</sup> and this led to the synthesis of a number of isonitriles in reasonable yield and purity (Scheme 2).



**Scheme 2.** Solution synthesis of isonitriles.

Work-up and purification of this reaction was problematic due to the reactivity of the isonitriles. The use of a polymer supported sulfonyl chloride therefore appeared to offer a fast and efficient method of isonitrile generation, with just a simple filtration and acidic work-up (to remove the pyridine) being involved. A number of reactions were therefore investigated using a range of formamides, as shown in Table 1 and Scheme 3.



**Scheme 1.** (a) Passerini and (b) Ugi reaction.

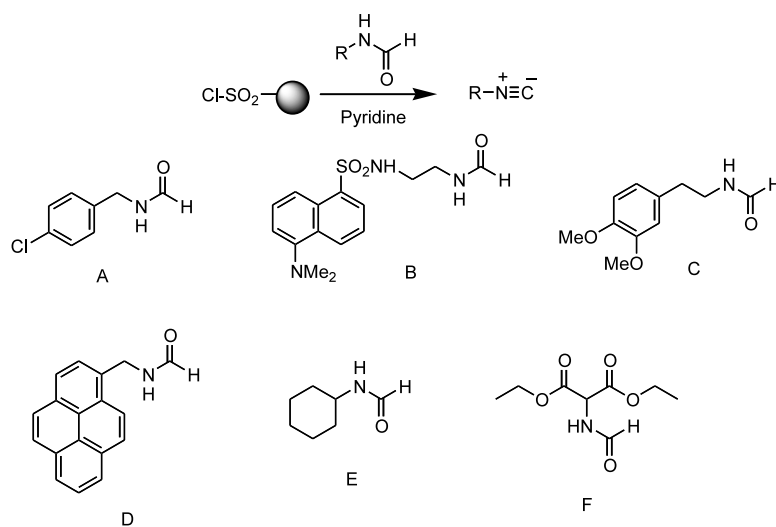
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Table 1.

Entry no.	Sulfonyl chloride resin (Novabiochem) (equiv.)	Pyridine (equiv. in DCM)	Formamide	Isonitrile <sup>b</sup> (% purity)
1	3	Neat pyridine	B	11
2	3	Neat pyridine	A	49
3	9	Neat pyridine	A	50
4	3	10	A	66
5	3	50	A	74
6	6	50	A	100
7	6	100	A	100
8	6	50	B	27
9 <sup>a</sup>	3	50	A	100
10 <sup>a</sup>	3	50	B	81
11 <sup>a</sup>	3	50	C	100
12 <sup>a</sup>	3	50	D	100
13 <sup>a</sup>	3	50	E	95
14 <sup>a</sup>	3	50	F	18

<sup>a</sup> Using the Smith Synthesiser, 100°C, 10 min.

<sup>b</sup> Determined by RP-HPLC.



Scheme 3. Solid phase-mediated synthesis of isonitriles.

The reaction was successfully optimised with formamide A using a gel based sulfonyl chloride resin from Novabiochem<sup>6</sup> (see entries 6 and 7 in Table 1) and a limited quantity of pyridine, to give the isonitriles in exceptional purity. Using microwave irradiation and 3 equiv. of sulfonyl chloride resin the method became very reproducible and gave the desired product in good to excellent purities for five out of the six substrates investigated (see entries 9–14 in Table 1).<sup>7</sup> Only reaction with the formamide F gave poor conversion, presumably because the formamide here was more heavily substituted and less benign than the other formamides investigated.

The sulfonyl chloride resin was also quantitatively regenerated (according to the results from microanalysis) from the sulfonic acid resin by treatment with 5 equiv. of  $\text{PCl}_5$  in DMF at room temperature.

A solid phase-mediated synthesis of isonitriles using a resin supported sulfonyl chloride has proven to be a

highly efficient and clean technique of synthesis for this important class of compounds. Interestingly we observed that the use of a Smith Synthesiser<sup>TM</sup> and microwave irradiation gave much faster reactions, while maintaining product purity and in many cases improved yields, thereby allowing rapid access to this class of compounds for subsequent incorporation into a range of compounds, including the synthesis of isonitrile tags, useful probes for a range of biological processes.

#### Acknowledgements

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6. From Novabiochem. Sulfonyl chloride polystyrene resin 100–200 mesh. The polymer matrix is copoly(styrene–1% DVB). Substitution: 2.9 mmol/g.
7. Typical experimental procedure for the solution phase synthesis. To a cooled and stirred solution of the formamide **B** (0.31 mmol) in pyridine (3 mL) was added *p*-toluenesulfonyl chloride (0.77 mmol). After 5 min the ice bath was removed and the mixture was stirred at room temperature for 6 h. The yellow solution became slowly brown. The solution was quenched with water (10 mL) and extracted with DCM (3×15 mL). The organic layer was washed with a saturated aqueous solution of  $\text{KH}_2\text{SO}_4$  (2×15 mL), the extracts were dried ( $\text{MgSO}_4$ ), filtered, concentrated and chromatographed on silica gel (hexane/ethyl acetate, 9/1 then 8/2 and 7/3), to give 74 mg of a yellow oil (yield = 79%).  
Typical solid-supported synthesis procedure. To polystyrene sulfonyl chloride resin (414 mg, 1.2 mmol) in dichloromethane (2.4 mL) were added 4-chlorobenzylformamide (68 mg, 0.40 mmol) and pyridine (1.58 mL, 20 mmol) in a sealed reaction vial. The reaction was performed for 10 min at 100°C in the microwave reactor Smith Synthesizer. The crude mixture was filtered with dichloromethane (15 mL). The filtrate was poured into water (15 mL) and extracted with dichloromethane (2×20 mL). After washings with an aqueous solution of potassium hydrogensulfate (3×15 mL), the organic layer was dried over  $\text{MgSO}_4$  and concentrated to afford 40 mg of the expected compound, in 70% yield and 98% purity.