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An improved synthesis of solid-supported reagents (SSRs) for selective acylation of amines by microwave irradiation

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Abstract—Microwave-assisted acylation of a solid-supported pyrimidine linker with different acyl chlorides gave polymer-bound 4-acyloxypyrimidines, which in turn were used as SSRs for rapid and selective acylation of amines under microwave irradiation.

Recent reports indicate increasing efforts toward high throughput solution synthesis using solid-supported reagents (SSRs).[1–5] Used since 1960, SSRs have been the subject of several review articles.[6–10] After the development of combinatorial synthesis, the use of SSRs became attractive and suitable for parallel synthesis because of the possibility of having very clean, high-yielding, and easily monitorable reactions. Moreover, isolation of the reaction product simply involves filtration of the resin and evaporation of the solvent.

During our studies on the synthesis of pyrimidinones as antiviral compounds,[11–18] 4-*O*-acylated pyrimidines were found to be able to acylate amines, phenols and thiophenols in high yields and good chemoselectivity.[16] In a recent communication[11] we have described the synthesis on a solid support of 4-*O*-acylated pyrimidines which can be used as solid-supported reagents (SSRs) for selective and high yielding acylation of amines. Considering the long reaction times (48–72 h) required for both the preparation of our SSRs and the subsequent amine acylation, the use of microwave irradiation as a means to enhance the rate of solid-phase reactions was investigated. In fact, microwave activation as a non-conventional energy source is becoming a very popular and useful technique in organic chemistry, as demonstrated by the rapidly growing number of annual publications on microwave-assisted organic synthesis,[19–24] including microwave-assisted SSR strategies.[25,26] The combination of solvent-free reaction conditions and microwave irradiation leads to a remarkable reduction in reaction time, enhancement in conversion and, sometimes, in selectivity with several advantages for the eco-friendly approach, termed green chemistry.[27]

In a typical experiment, the solid-supported pyrimidinone derivative **1** (0.50 mmol), prepared in a few, high yielding, steps from commercially available compounds,[11] the appropriate acyl chloride **2a–h** (2 mmol) and pyridine (3 mmol) were mixed in CH_2Cl_2 (1 mL) and irradiated by microwaves for 3 min at 200 watts[28] to give regioselectively the polymer-bound 4-acyloxypyrimidines **3a–h**.[29] The resin was filtered and washed successively with CH_2Cl_2, toluene and Et_2O. The acylation reaction was repeated twice under the same experimental conditions. The SSRs **3a–h** (0.50 mmol) so prepared and amines **4a,b** (0.50 mmol) were mixed in CH_2Cl_2 (1 mL) and irradiated by microwaves for 3 min at 200 watts. After filtration and evaporation of the solvent, amides **5a–i** were obtained as pure crystalline solids[30] in acceptable to excellent yield (40–100%) (Scheme 1).

Resin **1**, regenerated from the acylation reaction, could be recycled and transformed again into the acylating SSRs **3a–h** at least twice with no decrease in the reaction yield. The attempt to acylate **1** using acetic anhydride in DMF under microwave irradiation for 1 min at 650 watts[38] and to use it as acylating agent for **4a** resulted in only 20% yield of the amide **5a**.

With the aim of exploring the dependence of the acylating ability of these SSRs on their electronic properties, two new reagents **6** and **7**, characterized by the presence of a methyl group at both C-5 and C-6 positions or the absence of the C-6 substituent, respec-

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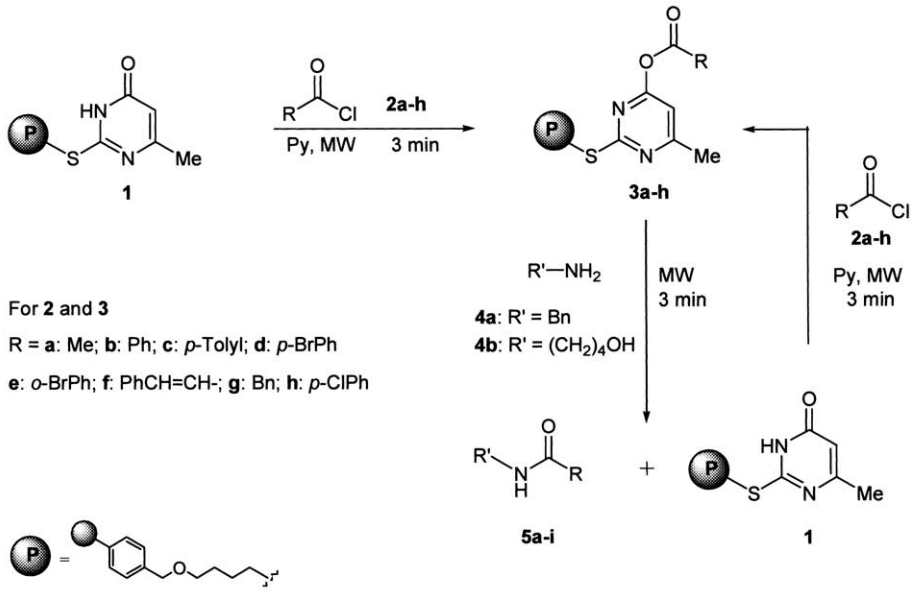

Compd	R	R'	Yield (%)[a]	m.p. °C (lit)
5a	Me	Bn	47	99-101 (100-102)[31]
5b	Ph	"	75	112-114 (115)[32]
5c	*p*-Tolyl	"	45	133-136 (138-139)[33]
5d	*p*-BrPh	"	100	160-163 (—)
5e	*o*-BrPh	"	40	112-115 (115-117)[34]
5f	PhCH=CH–	"	50	106-109 (107-110)[35]
5g	Bn	"	42	112-115 (112-114)[31]
5h	Ph	$-(CH_2)_4OH$	70	71-73 (74.5)[36]
5i	*p*-ClPh	Bn	85	163-166 (164-165)[37]

Scheme 1.

tively, were synthesized starting from the polymer-bound pyrimidinones **8** and **9**[11] (Scheme 2). Rather surprisingly, neither **6** nor **7** showed better acylating properties than **3b**: in fact, when reacted with benzylamine, they afforded the corresponding amide **5b** in only 35 and 70% yield, respectively. On the other hand, the most electrophilic SSRs **3d** and **3h** proved to be the most effective acylating agents, giving amides **5d** and **5i** in 100 and 85% yield, respectively. In this regard, the scarce efficiency of **3e** might be due to the steric hindrance exerted by the *ortho*-bromo substituent. In agreement with previous findings,[11] when 4-aminobutanol was used as nucleophile no *O*-acylated product was detected, thus showing the complete chemoselectivity of the acylation reaction.

In conclusion, solid-supported reagents **3a**–**h** have been cheaply, rapidly and easily prepared by microwave-assisted solid-phase synthesis. **3a**–**h** proved to be efficient and selective acylating reagents for amines when used under microwave irradiation, affording the corresponding amides in a few minutes and high purity. Quite interestingly, the by-product of the acylation reaction, i.e. the polymer-bound pyrimidinone **1**, can be recycled for several reaction runs. In addition, the microwave-assisted acylating method we have described compares favourably with those developed so far,[7] giving in most cases better results in terms of yield and reaction times.

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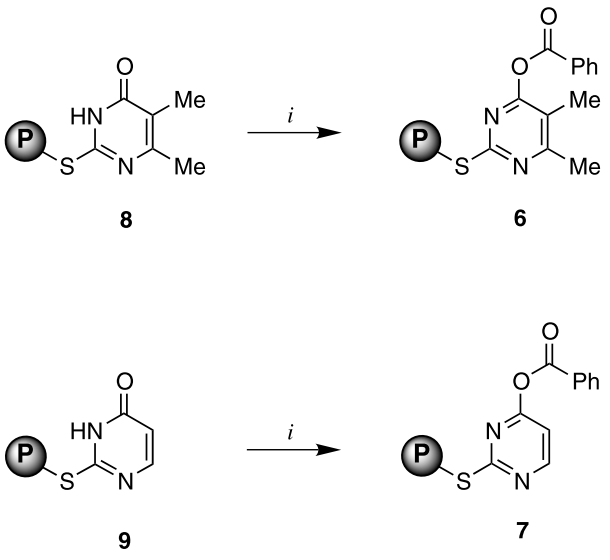

i. PhCOCl, Py, MW, 3 min

Scheme 2.

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29. The loading of the resin **3** was determined to be 68% through the same experimental procedure described in Ref. 11.
30. Spectroscopic and analytical data for compounds **5** are in agreement with the assigned structure.
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