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Synthesis and purification of 3-*N*-acylaminopyrazolinones using a sequence of functionalized polymers

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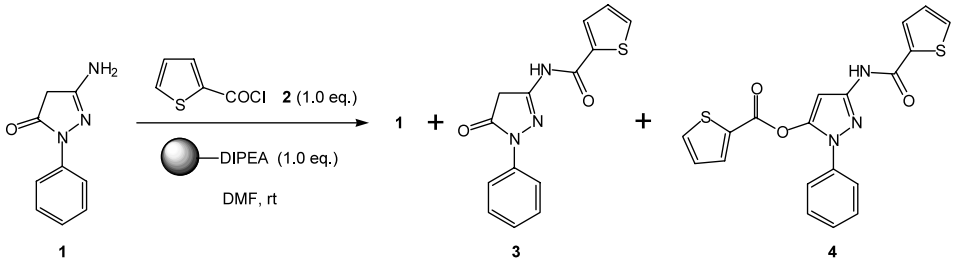
Abstract—A parallel synthesis route to 3-acylaminopyrazolinones using a sequence of functionalized polymers has been developed. The polymers were utilized as both stoichiometric reagents and purification agents to allow for the clean formation of the desired target compounds.

The chemistry of 3-aminopyrazolinones was studied extensively over a 20 year period beginning in the 1940s.[1] However, aside from a small number reports disclosing the uses of 1-phenyl-3-aminopyrazolinones as building blocks in the construction of 6,5-fused heterocyclic systems,[2–4] these interesting heterocycles have attracted scarce literature attention over recent years.

Our initial investigations into the chemistry of 3-aminopyrazolinones focused on developing conditions for *N*-acylation.[5,6] This simple reaction proved to be extremely capricious, however, and presented several synthetic challenges. Our first experiment involved treating 1-phenyl-3-aminopyrazolinone with 2-thiophenecarbonyl chloride in *N*,*N*-dimethylformamide in the presence of polymer-supported Hünig's base (Scheme 1). After 10 min at room temperature, LCMS analysis of the reaction mixture indicated the presence of starting amine **1** and acid chloride **2**, the desired 3-*N*-acylpyrazolinone **3**, and a bis-acylated product **4**; this observation was consistent with established—though limited—literature precendent.[1] We subsequently conducted a statistically-designed series of experiments in an attempt to attenuate the reactivity of the substrate **1** and to cleanly isolate the desired 3-acylaminopyrazolinone product **3**. A range of alternative solvents was examined, including dichloromethane, dichloroethane, chloroform, acetonitrile, 1,4-dioxane and tetrahydrofuran. Additionally, we varied the reaction temperature from –20 to 50°C, and a variety of substrate/reactant ratios were examined. Further, activated carboxylic acid esters were studied as alternative substrates to acid chlorides, and the reaction was conducted in the presence and absence of a range of organic bases, including *N*-methylmorpholine, Hünig's base, 4-dimethylaminopyridine and their polymer-supported counterparts.[7] In all cases, however, we routinely observed the mixture of components outlined above.

In light of these results, we chose to develop a synthetic route to 3-*N*-acylaminopyrazoliones utilizing a sequence of functionalized polymers serving as both stoichiometric reagents and purification media. Based



1 3 4

Scheme 1.

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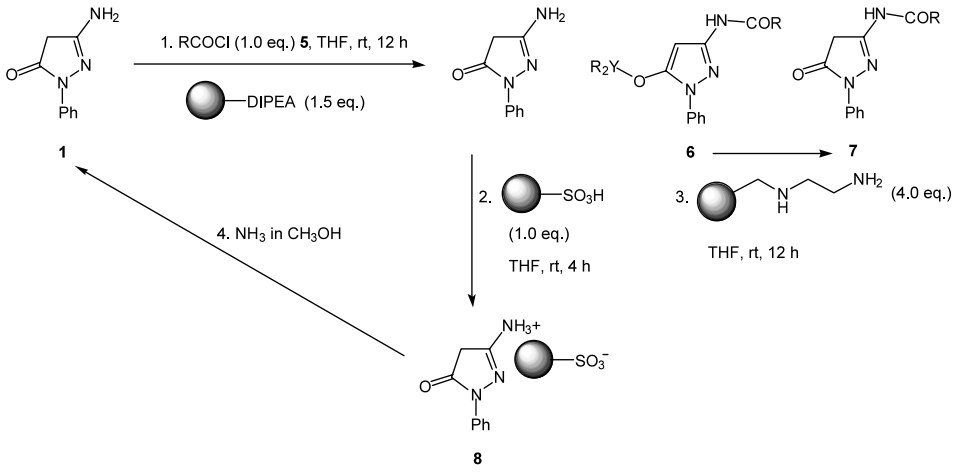
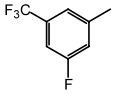
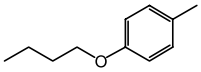
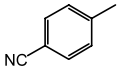
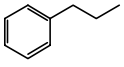
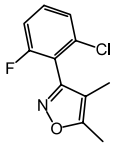
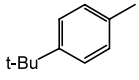


Scheme 2.

upon our initial findings, we anticipated that isolated yields of products might be disappointing, but nonetheless aimed to develop an approach that could not only allow for the clean isolation of the desired 3-acylaminopyrazolinones but which could also be applied to the rapid parallel synthesis of targeted compound libraries. The synthetic route we developed is outlined in Scheme 2.

Following extensive method development, we concluded that the optimum procedure involved initially treating 3-aminopyrazolinone **1** (1 weight) with acid chloride **5** (1 equiv.) in tetrahydrofuran in the presence of polymer-supported Hünig's base (1.5 equiv.). The reaction mixture was agitated for 12 h at room temperature and was then filtered, and the resin was washed with tetrahydrofuran. The filtrate, containing a mixture of amine **1**, acid chloride **5**, bis-acylated derivative **6** and the desired product **7**, was subsequently treated with polymer-supported sulfonic acid resin (1 equiv.),[8] and the suspension was agitated for 4 h at room temperature before being filtered under reduced pres-

Table 1.

Entry	R (from 5)	Isolated yield of 7 (%)	Purity determined at 220 nm (%)[10]	Purity determined at 254 nm (%)[10]
1	CH_3	81	98	98
2	Ph	36	93	92
3		40	95	98
4		44	92	81
5		34	80	84
6		28	73	72
7		25	78	87
8		27	81	87
9		25	96	97

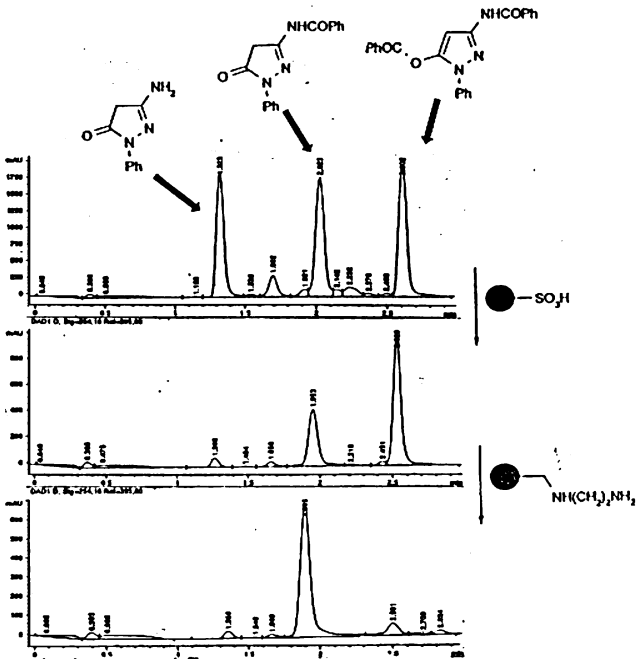


Figure 1.

sure. Analysis of the filtrate indicated that the supported acid had effectively scavenged the excess starting material **1** from the reaction mixture to furnish the resin-bound amine **8**. Finally, the filtrate was treated with *N*-(2-aminoethyl)aminomethylpolystyrene (4 equiv.),[9] which efficiently reacted with the bis-acylated derivative **6** to liberate the desired product **7** in high levels of purity; this supported amine also served to sequester any remaining acid chloride present in the reaction mixture. All of the reactions in this exercise were conducted on a scale of 1.14 mmol of substrate amine using 6 mL of solvent, and a representative selection of results obtained for the reactions involving 1-phenyl-3-aminopyrazolinone is summarized in Table 1.

Whilst the isolated yields of products were variable, we were able to recycle the starting material **1** for further use by treating the resin-bound amine **8** with a solution of 2 M ammonia in methanol.[11] Additionally, the products were isolated with high purities in all cases. To illustrate the effectiveness of the functionalized polymers used in this synthetic process, LCMS traces from the reaction involving 1-phenyl-3-aminopyrazolinone with benzoyl chloride (Table 1, entry 2) are depicted in Figure 1.

In summary, a convenient method for the *N*-acylation of 3-aminopyrazolinones has been successfully developed and applied to parallel synthesis. The method utilizes a sequence of functionalized polymers to promote *N*-acylation, recycle unreacted starting material, and circumvent a troublesome bis-acylation reaction allowing for the desired products to be cleanly isolated. By using this approach we were able to prepare a library of 400 diverse analogues; we believe this procedure to be the optimum method disclosed to date for the rapid preparation of 3-*N*-acylaminopyrazolinone derivatives.

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7. Polymer-supported Hünig's base was purchased from Polymer Laboratories Ltd., catalogue # 3413-4679. Polymer-supported *N*-methylmorpholine and 4-dimethylaminopyridine were both purchased from Argonaut Technologies Inc., catalogue # 800282 and # 800288, respectively.
8. Polymer-supported sulfonic acid is commercially-available from Polymer Laboratories Ltd., catalogue # 3404-4679.
9. *N*-(2-Aminoethyl)aminomethylpolystyrene is commercially available from Novabiochem Inc., catalogue # 01-64-0178.
10. Purity of products was determined using an Agilent 1100 LC/MSD VL ESI system. Representative analytical data for Table 1, entry 1, consistent with the enol form of 1-phenyl-3-*N*-acetylaminopyrazolinone: δ_H (400 MHz, DMSO-d_6) 10.40 (1H, s), 7.70 (2H, d), 7.50–7.40 (2H, d), 6.20 (1H, t), 5.95 (1H, s), 2.00 (3H, s). δ_c (400 MHz, DMSO-d_6) 167.69, 152.36, 147.17, 138.79, 129.06, 124.94, 124.19, 120.35, 117.81, 80.68, 23.23. M+1 found 218; $C_{11}H_{11}N_3O_2$ requires 217.23.
11. As a typical example, for Table 1, entry 2, treatment of **8** with methanolic ammonia enabled 27% of amine **1** to be recycled, corresponding to a 63% overall account of mass balance; the loss of material in this experiment is attributed to sub-optimal resin washing in step 3.