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Novel Quenchers for Solution Phase Parallel Synthesis

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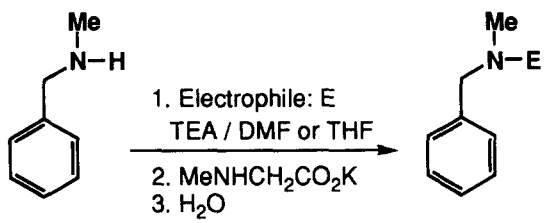
Abstract: The bifunctionality of amino acids can be exploited by utilizing them as quenchers in rapid solution phase parallel synthesis. The amino group was used to covalently trap the excess electrophiles, whereas the carboxylic acid moiety was used to solubilize the derivatized amino acid in water. As a prototype we used potassium sarcosinate as a quencher for excess electrophiles in the acylation or sulfonation of N-methyl-benzylamine. Various electrophilic reagents such as acid chlorides, isocyanates and sulfonyl chlorides were quenched successfully to give pure products in excellent yields.

Solution-phase parallel synthesis is an excellent way to form large libraries of small molecules. This is a logical extension of solid phase organic synthesis (SPOS) which has a few limitations in terms of selection of resins and an appropriate handle to hook up the resin on the substrate.[1] Additionally SPOS may not be compatible with a variety of reagent types and in the future will need other complementary solution phase methods to give pure compounds in multi-gram quantities in good yields. Earlier, a few reports have appeared where solid phase quenchers in the form of reagents on the solid-phase[2] or ion exchange resins[3] have been used for quenching reactions to eliminate the reactive components in the reaction. Boger and his coworkers[4] have also reported an excellent protocol for multiple step solution phase parallel synthesis to synthesize final compounds in good purity and quantities. We wish to report here our use of potassium sarcosinate as a novel solid-phase quencher in solution phase parallel synthesis.

Scheme 1



In one of our projects we needed a rapid synthesis of various acylated and sulfonated derivatives of secondary aralkyl amines. As a prototype we chose N-benzylmethylamine as our substrate (Scheme 1). Thus, in a typical reaction 1 eq. of the amine was treated with an excess (>1.5 eq.) of electrophile such as acid chloride, isocyanate or sulfonyl chloride in the presence of triethylamine in DMF or THF. After stirring or shaking for 4 h, potassium sarcosinate 1eq. was added to the reaction and the reaction mixture was stirred for an additional 0.5 h. Water was then added to the reaction mixture under stirring and the product was filtered or extracted in EtOAc. The reaction and the purity of the product were monitored by ^{1}H-NMR, which indicated pure product with no evidence of the starting electrophile. The products were

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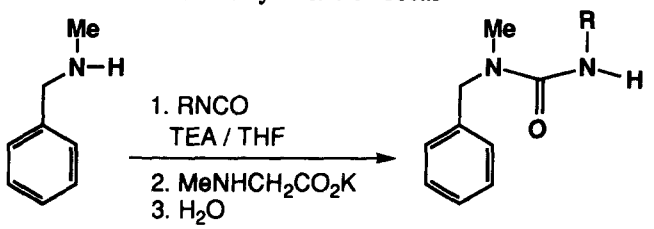
isolated in excellent yields with very good purities. The reactions involving isocyanates were monitored rather closely as the products are generally contaminated by symmetrical ureas. it was important to

Table 1. Synthesis of Ureas

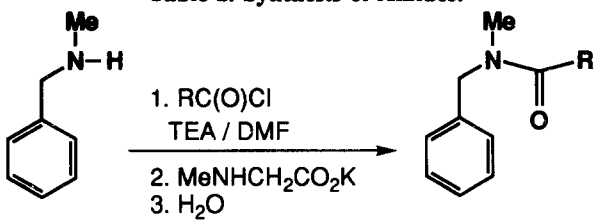


Entry #	R	Yield (%)[a, 5]	MS m/z[b]
1	Et	>99	193
2	n-Butyl	>99	221
3	i-Propyl	>99	207
4	t-Butyl	>99	221
5	Benzyl	>99	255
6	Cyclohexyl	>99	247
7	Phenyl	>99	241
8	2-Et-Phenyl	98	269
9	2,6-dimethyl-Phenyl	96	269
10	2-i-Pr-Phenyl	>99	283
11	2,6-diisopropyl-Phenyl	98	193
12	4-Chloro-Phenyl	93	275
13	4-Trifluoro-Phenyl	87	221
14	2-Nitro-Phenyl	>99	286
15	4-Nitro-Phenyl	>99	286
16	4-Carbethoxy-Phenyl	>99	313
17	2-Methoxy-Phenyl	>99	271
18	CH_2CO_2Et	97	251

a. Purity of the compounds checked by 1H-NMR and elemental analysis. All compounds gave satisfactory elemental analysis except: Entries #2, (Calcd C, 62.38; H, 7.25; N, 11.19. Found: C, 69.88; H, 9.4; N, 12.71), #14 (Calcd C, 76.09; H, 7.51; N, 10.44. Found: C, 61.97; H, 7.51; N, 15.26) and #17 (Calcd C, 63.15; H, 5.3; N, 14.73. Found: C, 61.63; H, 7.64; N, 11.11). b. MS (APCI, M+1).

start with pure isocyanates for these reactions. The ureas isolated were very pure in most cases and gave satisfactory elemental analysis (Table 1). On similar lines, other electrophiles such as acid chlorides (Table 2) and sulfonyl chlorides (Table 3) were reacted with N-benzylmethylamine to give the corresponding amides and sulfonamides in excellent purity and isolated yields (Table 2).

Table 2. Synthesis of Amides.



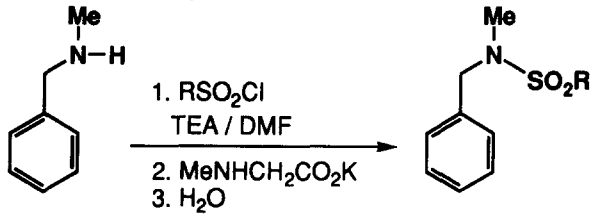
Entry #	R	Yield (%)[a, 6]	MS m/z[b]
1	CH_3	>99	164
2	Benzyl	98	240
3	Cyclohexyl	98	232
4	Diphenylmethyl	72	316
5	CH_2CH_2Ph	92	254
6	Phenyl	>99	226
7	Piperonal	85	270
8	3,4-Dichloro-phenyl	>99	294
9	4-NO_2-Ph	81	271

a. Purity of the compounds checked by 1H-NMR and elemental analysis. All compounds gave satisfactory elemental analysis except: Entries #1, (Calcd C, 73.59; H, 8.03; N, 8.58. Found: C, 72.03; H, 7.86; N, 8.37), 8% starting amine in ^{1}H-NMR, #4 (Calcd C, 83.78; H, 6.71; N, 4.44. Found: C, 82.85; H, 6.71; N, 4.47) and #5 (Calcd C, 80.63; H, 7.51; N, 4.25. Found: C, 78.59; H, 7.97; N, 4.25). b. MS (APCI, M+1).

The choice of potassium sarcosinate as the quenching agent was made to exploit the bifunctional nature of the amino acid. The amine end of the amino acid was important for quenching the excess electrophile and the carboxylic acid end for solubilizing the impurity bound aminoacid in aqueous medium. This protocol can be done with most amino acids. However, we chose sarcosine because of the higher nucleophilicity and basicity of the amine functionality (pKa: sarcosine: 10.01, Gly: 7.73). Sarcosine as a free acid could not be used due to poor soubility in DMF or THF. Hence, the potassium salt was used, which was prepared by mixing equimolar quantities of sarcosine and methanolic KOH. The solvent was evaporated and the white solid was dried under vacuum (0.02 mm). After the aqueous quench no sarcosine or its derivatives were seen in ^{1}H-NMR of the products. In an independent reaction we observed that the derivatized sarcosine potassium salt, phenyl urea for example, was very soluble in water. This methodology worked with a larger excess of electrophiles in the reaction, which needed to be quenched with excess amounts of potassium sarcosinate. This is especially important when the amine or nucleophile is to be conserved. Similarly, acid chlorides and sulfonyl chlorides were completely consumed after potassium sarconiate quench. Triethylamine was used as a homogenous base for acid chloride and sulfonyl chloride reactions and was found to be useful in the isocyanate reactions to solubilize all the components of the reaction mixture.

This methodology can be easily automated on a synthesizer for synthesizing an array of compounds and several gram quantities of the desired acylated compounds can be obtained expeditiously.

Table 3. Synthesis of Sulfonamides



Entry #	R	Yield[a, 6]	MS m/z[b]
1	Benzyl	91	276
2	p-Tolyl	79	276
3	p-Methoxyphenyl	>99	296
4	p-Chlorophenyl	>99	292
5	3,4-Difluorophenyl	>99	254
6	2,4,6-triisopropyl phenyl	75	388
7	1-Naphthyl	>99	312

a. Purity of the compounds was monitored by ^{1}H-NMR and Elemental anal. All products gave satisfactory analysis. b. MS (APC M+1)

In summary, we have developed a simple solution-phase parallel synthesis using a novel quencher of excess electrophiles. The quencher, potassium sarcosinate, is readily available and was found to be very efficient in trapping excess isocyanates, acid chlorides and sulfonyl chlorides to give water soluble by-products which could be removed by an aqueous quench.

References and Notes:

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4. Cheng, S.; Comer, D.D.; Williams, J.P.; Myers, P.L.; Boger, D.L. *J. Am. Chem. Soc.* **1996**, *118*, 2567.
5. The ureas were synthesized by treating N-methylbenzylamine (0.302 g , 2.5 mmol) with isocyanate (3.5 mmol) in THF (5 mL) / triethylamine (0.695 g, 5 mmol) and quenching with K sarcosinate (0.19 g, 1.5 mmol) followed by aqueous quench.
6. The amides and sulfonamides were synthesized by treating N-benzylmethylamine (0.302 g, 2.5 mmol) with an acid chloride or sulfonyl chloride (3.5 mmol) in DMF (2 mL) and triethylamine (0.695 g, 5 mmol). Reaction was quenched with K sarcosinate (0.127 g, 1 mmol) and water (6 mL). The product was isolated by filtration in the case of solids and extracted in ETOAc (10 mL) in the case of oils. EtOAc extract was pipetted out and evaporated to give the product.