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Poly(ethylene glycol)-supported Liquid-phase Parallel Synthesis of Di(aryloxyacetyl)thiosemicarbazides

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Abstract: An efficient poly(ethylene glycol) (PEG)-supported liquid-phase parallel approach to di(aryloxyacetyl)thiosemicarbazides is described. PEG-bound phenol reacted with chloroacetic acid to afford PEG-bound phenyloxyacetic acid, which was readily converted into corresponding phenyloxyacetyl chloride. Subsequent nucleophilic substitution with ammonium thiocyanate followed by addition of aryloxyacetic acid hydrazides gave PEG-bound di(aryloxyacetyl)thiosemicarbazides, which were easily cleaved to give the resulting library of 1-aryloxyacetyl-4-(4'-methoxylcarbonylphenyloxyacetyl)thiosemicarbazides in good to high yield and high purity.

Keywords: Liquid-phase synthesis, PEG, di(aryloxyacetyl)thiosemicarbazide.

It is well known that combinatorial chemistry[1] has been widely developed into a potentially powerful tool for the accelerating drug discovery progress. Solid phase synthesis of drug-like molecules offers significant advantages over many conventional solution phase routes. However, such an approach requires a great deal of development time and effort to explore synthetic conditions on solid support. In recent years, the research efforts, toward the liquid-phase combinatorial synthesis to generate libraries by use of soluble polymer support, become more popular[2]. The macromolecular carrier used in the liquid-phase synthesis, in contrast to an insoluble matrix, is soluble in many organic solvents and has a strong tendency to precipitate in ether, hexane and *tert*-butyl methyl ether. After the reactions completing, the products remain covalently bonded to the support, and purification is generally carried out after precipitation simply by filtration and washing away the unwanted materials. Furthermore, this non-destructive method allows routine analytical methodologies (*e.g.* ^{1}H, ^{13}C NMR, IR, TLC) to monitor the reaction transformations and determine the structures of compounds attached to the polymer support.

Thiosemicarbazides have attracted much attention in recent years because of their fungicidal3, bactericidal4 and tuberculostatic5 activities. Meanwhile, aryloxyacetic acid derivatives have also been used as herbicides and plant-growth regulators6. These applications promote us to explore more convenient methods to synthesize a new series of compounds bearing both thiosemicarbazide and aryloxyacetyl moieties, with the object of

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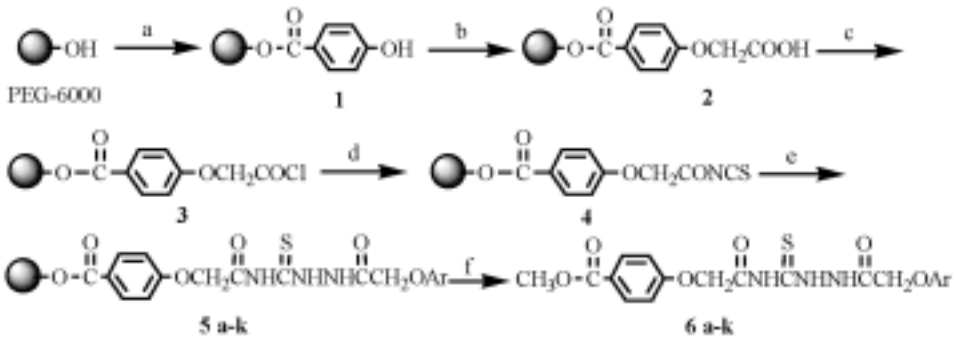
obtaining new biologically active compounds.

Many substituted thiosemicarbazides were synthesized by our research group in recent years[7,8], but separating and purifying problems were often encountered. In this paper, we report an easily handling liquid-phase strategy for the synthesis of the library of 1,4-di(aryloxyacetyl)-thiosemicarbazides, using PEG as soluble polymer support.

Scheme 1



a: 4-hydroxybenzoic acid, DCC, CH_2Cl_2, r.t.; b: $ClCH_2COOH$, K_2CO_3, KI; c: $SOCl_2$; d: NH_4SCN; e: $ArOCH_2CONHNH_2$; f: $NaOCH_3$, CH_3OH

Table 1 The physical and elemental data of **6 a-k**

Compd	Ar	mp (℃)	Yield (%)[a]	Elemental analysis (Calcd.) (%) C	H	N
6a	C_6H_5	177-178	87	54.70 (54.67)	4.66 (4.59)	10.11 (10.07)
6b	2-$CH_3C_6H_4$	184-185	89	55.73 (55.67)	4.86 (4.91)	9.81 (9.74)
6c	3-$CH_3C_6H_4$	187-188	88	55.60 (55.67)	4.88 (4.91)	9.79 (9.74)
6d	2-$O_2NC_6H_4$	191-192	83	49.44 (49.35)	3.87 (3.92)	12.20 (12.12)
6e	3-$O_2NC_6H_4$	181-182	75	49.30 (49.35)	3.89 (3.92)	12.18 (12.12)
6f	4-$O_2NC_6H_4$	234-235	73	49.29 (49.35)	3.98 (3.92)	12.07 (12.12)
6g	4-ClC_6H_4	166-167	85	50.46 (50.50)	4.09 (4.02)	9.25 (9.30)
6h	2,4-$Cl_2C_6H_4$	206-207	72	46.88 (46.92)	3.58 (3.52)	8.72 (8.64)
6i	1-Naphthyl	200-201	68	59.13 (59.09)	4.61 (4.53)	9.02 (8.99)
6j	2-Naphthyl	205-206	71	59.00 (59.09)	4.48 (4.53)	8.94 (8.99)
6k	4-$CH_3OC_6H_4$	147-148	90	53.73 (53.68)	4.79 (4.73)	9.45 (9.39)

[a] The data refer to the overall yield based on PEG-6000.

Table 2 IR and ^{1}H NMR data of compounds **6 a-k**

Compd	IR (cm^{-1})			^{1}H NMR (DMSO-d_6, δ in ppm)
	N-H	C=O	C=S	
6a	3280 3177	1719 1672	1171	3.80 (s,3H,OCH_3), 4.91 (s,2H,CH_2), 4.94 (s,2H,CH_2), 6.98-7.91 (m,9H,Ar-H), 10.97 (s,1H,NH), 11.80 (s,1H,NH), 11.92 (br,1H,NH)
6b	3275 3174	1720 1670	1169	2.29 (s,3H,CH_3), 3.79 (s,3H,OCH_3), 4.90 (s,2H,CH_2), 4.93 (s,2H,CH_2), 6.97-7.90 (m,8H,Ar-H), 10.96 (s,1H,NH), 11.79 (s,1H,NH), 11.91 (br,1H,NH)
6c	3277 3175	1721 1678	1168	2.30 (s,3H,CH_3), 3.79 (s,3H,OCH_3), 4.90 (s,2H,CH_2), 4.92 (s,2H,CH_2), 6.98-7.91 (m,8H,Ar-H), 10.95 (s,1H,NH), 11.78 (s,1H,NH), 11.92 (br,1H,NH)
6d	3286 3181	1715 1675	1173	3.81 (s,3H,OCH_3), 4.92 (s,2H,CH_2), 4.96 (s,2H,CH_2), 7.01-7.94 (m,8H,Ar-H), 10.99 (s,1H,NH), 11.82 (s,1H,NH), 11.94 (br,1H,NH)
6e	3289 3178	1716 1677	1175	3.81 (s,3H,OCH_3), 4.91 (s,2H,CH_2), 4.97 (s,2H,CH_2), 7.03-7.97 (m,8H,Ar-H), 10.98 (s,1H,NH), 11.81 (s,1H,NH), 11.93 (br,1H,NH)
6f	3282 3186	1718 1670	1176	3.81 (s,3H,OCH_3), 4.90 (s,2H,CH_2), 4.96 (s,2H,CH_2), 6.98-7.92 (m,8H,Ar-H), 11.00 (s,1H,NH), 11.83 (s,1H,NH), 11.96 (br,1H,NH)
6g	3279 3181	1720 1677	1170	3.80 (s,3H,OCH_3), 4.89 (s,2H,CH_2), 4.94 (s,2H,CH_2), 6.96-7.90 (m,8H,Ar-H), 10.99 (s,1H,NH), 11.81 (s,1H,NH), 11.93 (br,1H,NH)
6h	3287 3183	1718 1679	1179	3.81 (s,3H,OCH_3), 4.93 (s,2H,CH_2), 4.97 (s,2H,CH_2), 7.03-7.98 (m,7H,Ar-H), 11.01 (s,1H,NH), 11.84 (s,1H,NH), 11.96 (br,1H,NH)
6i	3321 3143	1715 1674	1167	3.80 (s,3H,OCH_3), 4.92 (s,2H,CH_2), 4.95 (s,2H,CH_2), 6.97-7.93 (m,11H,Ar-H), 10.98 (s,1H,NH), 11.82 (s,1H,NH), 11.94 (br,1H,NH)
6j	3324 3146	1717 1676	1168	3.80 (s,3H,OCH_3), 4.93 (s,2H,CH_2), 4.96 (s,2H,CH_2), 7.00-7.92 (m,11H,Ar-H), 10.96 (s,1H,NH), 11.81 (s,1H,NH), 11.94 (br,1H,NH)
6k	3271 3185	1721 1673	1172	3.42 (s,3H,OCH_3), 3.80 (s,3H,OCH_3), 4.88 (s,2H,CH_2), 4.93 (s,2H,CH_2), 6.98-7.91 (m,8H,Ar-H), 10.98 (s,1H,NH), 11.82 (s,1H,NH), 11.94 (br,1H,NH)

The synthetic route described in **Scheme 1** is utilized for the synthesis of the representative library. PEG-6000 was modified with the commercially available 4-hydroxybenzoic acid through dicyclohexylcarbodiimide (DCC) activation to afford the immobilized **1** in high yield. **1** was refluxed with chloroacetic acid in the presence of potassium carbonate, catalyzed by potassium iodide, to give PEG-bound phenyloxyacetic acid **2**. Reaction proceeded efficiently without cleavage of the O-C=O bond at the polymer attached site. After refluxing with thionyl chloride, compound **2** was converted into corresponding PEG-bound phenyloxyacetyl chloride **3**. Compound **3** on treatment with ammonium thiocyanate at ambient temperature gave PEG-bound isocyanate **4** as an intermediate, which *in situ* reacted with aryloxyacetic acid hydrazides to afford PEG-bound di(aryloxyacetyl)thiosemicarbazides **5 a-k**. Compounds **1-3** and **5a-k** were purified by precipitation and washing with diethyl ether. The whole course of the reactions was monitored by TLC analysis (observation of disappearing acid hydrazides) and estimated directly by ^{1}H NMR without detaching material from the support. **5 a-k** efficiently cleaved from the support with sodium methoxide in methanol to provide the desired compounds 1-aryloxyacetyl-4-(4'-methoxylcarbonylphenyloxyacetyl)-thiosemi-

carbazides (**6 a-k)** in 68-90% overall yields. The analytical samples were obtained by recrystallizing the crude products from ethanol and DMF (**Table 1-2**).

In summary, we have shown soluble polymer supported methodology for the synthesis of di(aryloxyacetyl)thiosemicarbazides. This method reduced the difficulties of established solution protocol to polymer-supported reactions, since reactions can be carried out in homogeneous solution. The final product contains a methyl ester group, which can be further transformed into other useful functional groups and is a possible site for another point of molecular diversity. Reactions involved here are highly efficient for the synthesis of the desired compounds in high yields and purity. The method of purification is simple just to need precipitation and washing. This method is versatile and adaptable for the parallel synthesis of the targeted structures on the soluble polymer support.

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