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Liquid-phase parallel synthesis of di(aryloxyacetyl)thiosemicarbazides on poly(ethylene glycol)

Junke Wang [a,b,*], Xicun Wang [b], Zheng Li [b], Yingxiao Zong [a]

[a] *Department of Chemistry, Hexi University, 734000 Zhangye, Gansu, PR China*
[b] *Department of Chemistry, Northwest Normal University, 730070 Lanzhou, Gansu, PR China*

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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)thiosemi-carbazides, 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

1. Introduction

Solid-phase synthesis can overcome limitations in the efficiency of classical chemical synthesis [1]. However, solid-phase synthesis suffers from various problems, such as the heterogeneous nature of the reaction condition, reduced rate of reactions, and mass transport of reagents. In recent years, the research efforts, towards the liquid-phase combinatorial synthesis to generate libraries by use of soluble polymer support, has become more popular [2]. The macromolecular carrier used in the liquid-phase synthesis, is soluble in many organic solvents and has a strong tendency to precipitate in ether, hexane and *tert*-butyl methyl ether. After the reactions complete, 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 fungicidal [3], bactericidal [4] and tuberculostatic [5] activities. Meanwhile, aryloxyacetic acid derivatives have also been used as herbicides and plant-growth regulators [6]. These applications promote us to explore more

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[*] Corresponding author. Tel.: +86 9368284286; fax: +86 9368282045.
E-mail address: wangjk@hxu.edu.cn (J. Wang).

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convenient methods to synthesize a new series of compounds bearing both thiosemicarbazide and aryloxyacetyl moieties, with the object of 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.

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. Compound **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 **5a–k**. Compounds **1–3** and **5a–k** were purified by precipitation and washing with diethyl ether. Their purities were monitored by TLC analysis (observation of disappearing material), and the whole course of the reactions were estimated directly by ^{1}H NMR without detaching material from the support. Compounds **5a–k** efficiently cleaved from the support with sodium methoxide in methanol to provide the desired compounds 1-aryloxyacetyl-4-(4′-methoxylcarbonyl-phenyloxyacetyl)thiosemicarbazides (**6a–k**) in 68–90% overall yields. The analytical samples were obtained by recrystallizing the crude products from ethanol and DMF (Table 1).

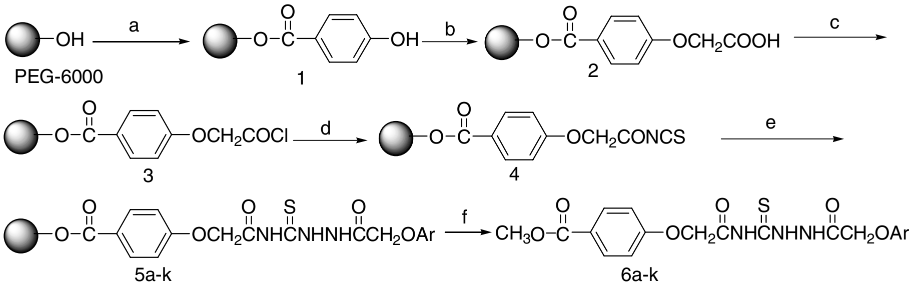
In summary, we have shown soluble polymer supported methodology for the synthesis of di(aryloxyacetyl)thiosemicarbazides. This method reduced the difficulties of established solution protocol to polymer-supported reactions, since reactions can be carried out in homogeneous solution. The final product 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.

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

Entry	Ar	Melting point (°C)	Yield (%)[a]	Purity (%)[b]
6a	C_6H_5	177–178	87	92
6b	2-$CH_3C_6H_4$	184–185	89	91
6c	3-$CH_3C_6H_4$	187–188	88	93
6d	2-$O_2NC_6H_4$	191–192	83	96
6e	3-$O_2NC_6H_4$	181–182	75	92
6f	4-$O_2NC_6H_4$	234–235	73	96
6g	4-ClC_6H_4	166–167	85	91
6h	2,4-$Cl_2C_6H_4$	206–207	72	97
6i	1-Naphthyl	200–201	68	94
6j	2-Naphthyl	205–206	71	91
6k	4-$CH_3OC_6H_4$	147–148	90	95

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

[b] Purity Determined by HPLC analysis (UV detection at $\lambda = 254$ nm , gradient elution acetonitrile (v/v) = 80:20) of crude products.



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) $ArOCH_2CONHNH_2$; and (f) $NaOCH_3$, CH_3OH.