

# A new approach for the synthesis of *N,N'*-bis(phenoxyacetyl)hydrazines

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## ABSTRACT

This report is about an unexpected formation of *N,N'*-bis(substituted phenoxyacetyl) hydrazine derivatives. The reaction between *N'*-(4-ethylcyclohexylidene)phenoxyacetohydrazide with sulfanyl acids to obtain 4-thiazolidinones, gave an unexpected product, *N,N'*-bis(phenoxyacetyl)hydrazine, with high purity instead of the expected cyclocondensation product. When repeating the reaction with *p*-toluenesulfonic acid under the same conditions, the reaction resulted in the same compound. This indicates that two molecules of *N'*-(4-ethylcyclohexylidene)phenoxyacetohydrazide were involved in the reaction. The reaction can be applied as a different and new procedure for the synthesis of several *N,N'*-bis(substituted phenoxyacetyl) hydrazine derivatives.

**Keywords:** Diacylhydrazines, sulfanyl acid, reaction mechanism

## INTRODUCTION

Diacylhydrazines have attracted considerable attention recently due to their simple structure, low toxicity, and high insecticidal selectivity. Their synthesis can be achieved by the reaction of hydrazine with acyl chlorides or anhydrides of carboxylic acids (Patai 1970; Wang et al. 2011; Sun and Zhou 2015). When the operation is applied by the reaction of esters of carboxylic acids, monoacyl hydrazine derivatives are generally obtained and subsequent insertion of a second acyl moiety is very difficult.

During our studies on the synthesis of 4-thiazolidinone derivatives, we obtained an incidental product, *N,N'*-bis(phenoxyacetyl) hydrazine with high purity and yield. The reaction of phenoxyacetohydrazide hydrazones with sulfanyl acids resulted in the same product.

In this paper will examine the interconversion of phenoxyacetohydrazide hydrazones, mainly *N'*-(4-ethylcyclohexylidene)phenoxyacetohydrazide, into *N,N'*-bis(phenoxyacetyl)hydrazine, through a new synthetic route for *N,N'*-bis(phenoxyacetyl)hydrazine derivatives.

## MATERIALS AND METHODS

For our study the chemicals were obtained from Merck and Aldrich. Melting points (mp) were determined on a Buchi 530 melting point apparatus in open capillaries and are uncorrected. Microanalysis and mass spectrum of *N,N'*-bis(phenoxyacetyl)hydrazine was performed on a Thermo Finnigan Flash EA 1112 elemental analyzer and Agilent 6460 TripQuad LC-MS/MS mass spectrometer. IR spectra were recorded in KBr discs ( $\nu_{\max}$  in  $\text{cm}^{-1}$ ) on a Shimadzu IR Affinity-1 FTIR spectrophotometer.  $^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ ) spectra were obtained on a Varian Mercury-400 MHz and PULSAR NMR Spectrometer-60 MHz instruments. (*E,Z*)-*N'*-(4-ethylcyclohexylidene)

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phenoxyacetohydrazide was recorded in SciFinder Scholar database but no analytic or spectral data have been given.

### Synthesis of (*E,Z*)-*N'*-(4-ethylcyclohexylidene)phenoxyacetohydrazide

A solution of 2-phenoxyacetohydrazide and 4-ethylcyclohexanone (0.01 mol) in 20 mL of ethanol (96%) was refluxed for 1 hour and then the solution was allowed to cool. The solid thus formed was filtered off, dried and directly used in the next step.

White powder (Yield 72%); mp: 113-115°C; IR (KBr):  $\nu$  max 3327, 3180 (N-H), 3072 (Ar-H), 1683 (C=O). <sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>/60 MHz): 0.81-3.07 (m, cyclohexane C<sub>2,6</sub>-H, C<sub>3,5</sub>-H, C<sub>2</sub>-H<sub>5</sub> and DMSO), 4.66, 5.00 (2H, 2s, OCH<sub>2</sub>), 6.65-7.80 (5H, m, phenyl C<sub>2,6</sub>-H), 10.38, 10.51 (1H, 2 broad s, NH).

### *N,N*-bis(phenoxyacetyl)hydrazine as a by-product during the synthesis of 4-thiazolidinones

0.005 mol (1.37 g) *N'*-(4-ethylcyclohexylidene) substituted phenoxyacetohydrazide and (0.005 mol) sulfanyl acids (sulfanylacetic acid or 2-sulfanylpropanoic acid) or p-toluenesulfonic acid was refluxed in 30 mL of dried toluene for 4-6 hours using a Dean-Stark water separator. Excess toluene was evaporated *in vacuo*. The resulting mixture was treated with saturated sodium bicarbonate solution to remove the excess acid. The solid thus obtained was filtered, washed with water, dried and recrystallized from ethanol.

White powder (Yield 56%); mp: 168-170°C; IR (KBr):  $\nu$  max 3450 (O-H), 3228 (N-H), 1703, 1660 (C=O). <sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>/400 MHz): 4.60 (4H, s, OCH<sub>2</sub>), 6.95-7.00 (6H, m, phenyl C<sub>2,4,6</sub>-H), 7.28-7.32 (4H, m, phenyl C<sub>3,5</sub>-H), 10.18 (2H, s, NH). MS (ESI-) *m/z* (%): 299 [M-H]<sup>-</sup> (100). Anal. calcd. for C<sub>16</sub>H<sub>16</sub>N<sub>2</sub>O<sub>4</sub>·H<sub>2</sub>O: C: 60.37, H: 5.70, N: 8.80. Found: C: 59.82, H: 5.72, N: 8.80 (mp 164°C; Baltazzi and Delavigne 1955).

## RESULTS AND DISCUSSION

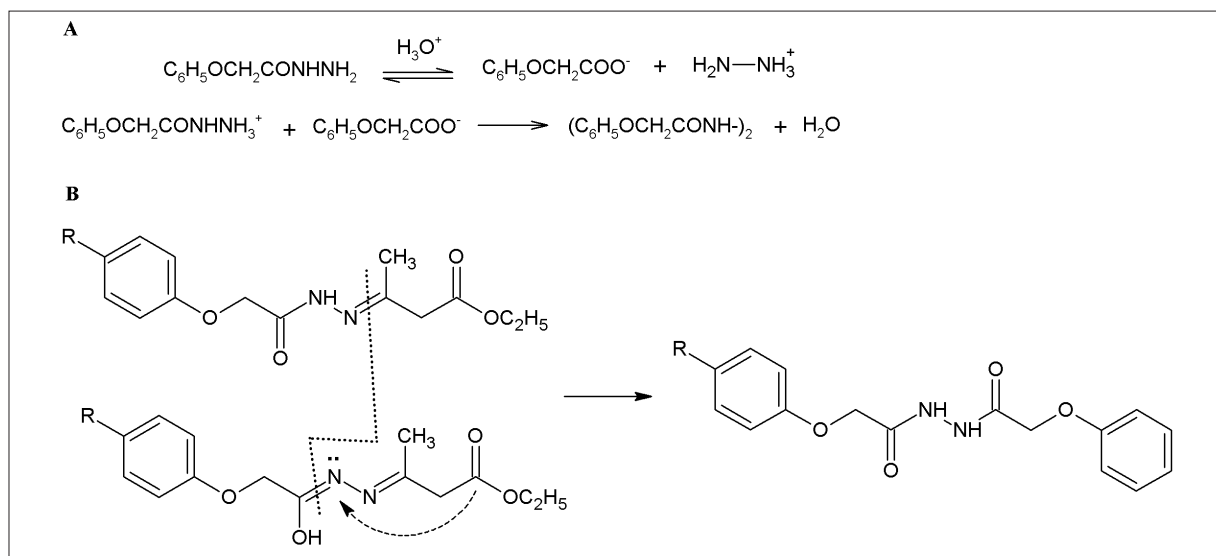
There are several methods for the synthesis of 4-thiazolidinone derivatives and their mechanism of cyclization have been re-

ported previously (Singh et al. 1981, Hamama et al. 2008; Tripathi et al. 2014, Kocabalkanlı et al. 2017). One of the most common methods for obtaining 4-thiazolidinone ring is refluxing equimolecular amounts of aldimines or ketimines with alkanic acids in dried aprotic solvents. In the course of our studies in the synthesis of spiro derivatives of 4-thiazolidinone, the reaction of *N'*-(4-ethylcyclohexylidene)phenoxyacetohydrazide with sulfanylacetic acid or 2-sulfanylpropanoic acid did not give the desired spirothiazolidinones, *N*-(8-ethyl-3-oxo-1-thia-4-azaspiro[4.5]dec-4-yl) or *N*-(8-ethyl-2-methyl-3-oxo-1-thia-4-azaspiro[4.5]dec-4-yl)-2-phenoxyacetamides. Surprisingly, an unexpected product was formed instead. The product was confirmed as *N,N*-bis(phenoxyacetyl)hydrazine by IR, <sup>1</sup>H-NMR, mass spectrum and microanalysis. When the same study was repeated with *N'*-(4-propylcyclohexylidene)phenoxyacetohydrazide the main product was again *N,N*-bis(phenoxyacetyl)hydrazine. In the cases of 4-methylcyclohexylidene, 4-phenylcyclohexylidene or 4-*tert*-butylcyclohexylidene derivatives of phenoxyacetohydrazide, *N,N*-bis(phenoxyacetyl)hydrazine was isolated as by-products with different yields together with the targeted products, spirothiazolidinones.

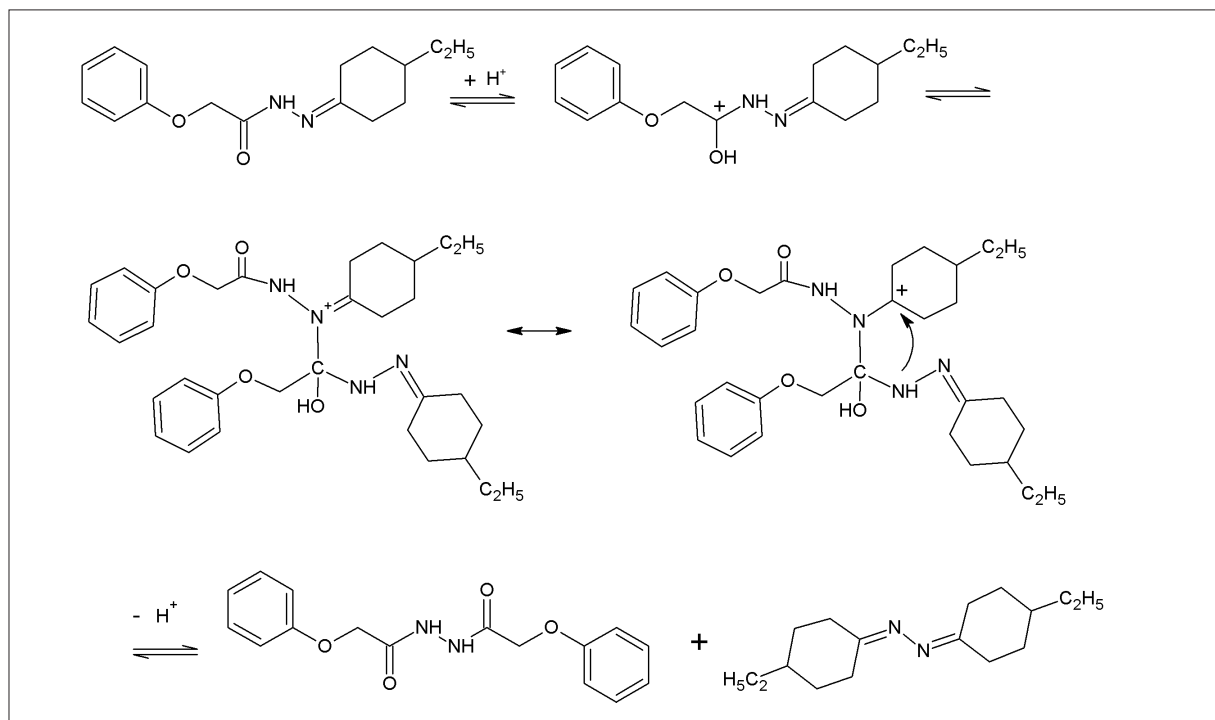
*N,N*-bis(phenoxyacetyl)hydrazine was firstly reported in 1955 (Baltazzi and Delavigne 1955). According to this study, the condensation of phenoxyacetohydrazide with some aldehydes or cyclic ketones such as cyclohexanone, cyclopentanone in aqueous acetic acid, the corresponding hydrazone derivatives were formed. However, when acetone or methyl propyl ketone was used, *N,N*-bis(phenoxyacetyl)hydrazine was isolated. The proposed mechanism (A) is shown in Figure 1.

In a study performed with a series of aryloxyacetic acids, it was reported that monocyclic hydrazides were obtained by heating methyl or ethyl esters of the acids with hydrazine in ethanol, whereas conducting the reaction without ethanol resulted in a mixture of monocyclic and *N,N*-bis(phenoxyacetyl)hydrazines (Mirek 1958).

It was also reported that the reaction of ethyl acetoacetate with hydrazides of phenoxyacetic or 4-nitrophenoxyacetic acids did



**Figure 1.** Suggested mechanisms for the unexpected synthesis of *N,N'*-bis(diacyl)hydrazines.



**Figure 2.** Proposed mechanism for the reaction of *N,N'*-bis(diacyl)hydrazine.

not result in the targeted *N'*-acylpyrazolones. Other products, mainly *N,N*-bis(diacyl)hydrazines were formed (Zawadowska 1961). The suggested mechanism for the unexpected synthesis of *N,N'*-bis(diacyl)hydrazines (B) is presented in Figure 1.

In general reaction conditions the acidic properties of the aliphatic acids we used did not promote the cycloaddition reaction in anhydrous toluene. *N,N*-bis(phenoxycetyl)hydrazine occurred directly from hydrazide-hydrazone derivatives. Repeating the reaction with *p*-toluenesulfonic acid again yielded the same derivative, which indicates that two molecules of phenoxycetylhydrazide-hydrazone were involved in the reaction. The possible mechanism of the reaction can be explained by the action of the oxygen atom of the phenoxy group. The electrophilic nature of the carbonyl carbon atom of hydrazide-hydrazone is being increased by the oxygen atom in the phenoxy residue inductively. Then the hydrazone group of the second molecule attacks the imine nitrogen. This directly results in a balance towards *N,N'*-bis(diacyl)hydrazine direction. And finally, *N,N'*-bis(phenoxycetyl)hydrazine occurs through a transition intermediate and electron shifts. Because the reaction proceeds under anhydrous conditions, an acid catalyzed hydrolysis possibility is excluded. Secondary product, probably azine, was not isolated. The proposed mechanism for the reaction is illustrated in Figure 2.

The reaction can be applied as a different and new procedure for the synthesis of several *N,N'*-bis(substituted phenoxyacetyl)hydrazine derivatives.

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pretation – Ç.B.A., Z.C.; Literature Search Ç.B.A., Z.C.; Writing Ç.B.A., Z.C.; Critical Reviews – Ç.B.A., Z.C.

**Conflict of Interest:** The authors have no conflict of interest to declare.

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