Reaction of dialkyl acetylenedicarboxylates with ninhydrin in the presence of secondary amines: synthesis of alkyl 4-(benzyl(alkyl)amino)-1',3',5-trioxo-1',3'-dihydro-5H-spiro[furan-2,2'-indene]-3-carboxylate derivatives

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INTRODUCTION

Multicomponent reactions allow more than two simple and flexible building blocks to be combined in practical, timesaving one-pot operations. Due to their valued features such as atom economy, inherent simple experimental procedures and one-pot character, they are perfectly suited for automated synthesis [1]. Therefore, MCRs have attracted much attention because of their exceptional synthetic efficiency [2–5]. Since all the organic reagents employed are used and moved toward the target compound, purification of products resulting from MCRs is simple [6], [7]. Isocyanide based multicomponent reactions (abbreviated to IMCRs by Ugi and Dömling) have an advantageous position. The special features of IMCRs including unique synthetic potential, high atom economy, convergent nature, ease of implementation, and the generation of molecular diversity are considered as acceptable factors in the relative advantage of the reactions [6–14].

For years, acetylenic esters have attracted the attention of organic chemists, mostly as Michael acceptors [7, 15, 16]. In recent years, there has been an increasing interest in the
applications of acetylenic esters in multicomponent syntheses [1, 7–9], specially for preparing stabilized phosphonium ylides [17–22]. Due to atom economy, convergent character and simplicity of one-pot procedures, multicomponent condensation reactions have great potentials in synthesis. The development of novel multicomponent condensation reactions is also receiving growing interest from industrial-chemistry research groups, and represents a challenge for organic chemists [1, 7].

Furans, benzofurans, and their reduced forms are important core structures in many biologically active natural products. Moreover, they are useful building blocks in the total synthesis of natural products and pharmaceuticals [23–26]. Many naturally occurring furans have exhibited considerable biological activities, such as antitumor and cytotoxic properties [27, 28], as well as antimicrobial [29, 30], antispasmodic [31], and several other potentially useful activities [32]. In addition, furans are also present in commercially important products, such as agrochemical bioregulators, essential oils, cosmetics, dyes, photosensitizers, flavoring and fragrance products, such as agrochemical bioregulators, essential oils, cosmetics, dyes, photosensitizers, flavoring and fragrance products, butyl) amine and N,N-dibenzylamine in this reaction, but they have not participated in the reaction. The presence of fairly high steric intractions in the amines may be plausible factors in the reduction of their reactivity.

The structures of the products were deduced from their 1H NMR, 13C NMR, Mass and IR spectra. For example, the 1H NMR spectrum of 4a consisted of a doublet for 2 CH₂ (δ₁ = 1.39 ppm), a singlet for OCH₃ (δ = 3.22 ppm), a singlet for CH₂ of the benzyl group at δ = 4.84 ppm, a multiplet for CH⁺ (δ = 4.89–4.97 ppm) and a multiplet at δ = 7.12–7.97 ppm for H-aromatic. The aryl groups exhibited characteristic signals in the aromatic region of the spectrum. The 1H decoupled 13C NMR spectrum of 4a showed 17 distinct resonances, partial assignment of these resonances is given in the experimental section. The 1H and 13C NMR spectra of compounds 4b–e were similar to those of 4a, except for the aromatic and aliphatic moieties, which exhibited characteristic signals with appropriate chemical shifts. For the compounds 4b–c, in the 1H NMR spectra the signals corresponding to the methyl group of the CO₂Et moiety are unusually shifted upfield (δ: 0.46 (t, 3H, J = 7.0 Hz, CH₃ of OEt) and δ: 0.57 (t, 3H, J = 7.3 Hz, CH₃ of OEt) for 4b and 4c, respectively). It may be resulted from a strong shielding (probably due to spatial arrangement of CO₂Et moiety) as one of the benzene rings.

A possible mechanism for the present reaction is shown in Scheme 2, which envisages a tandem sequence. On the basis of the well established chemistry of trivalent nitrogen nucleophiles, the successful nucleophilic attack by amines on a carbon atom is facilitated when the latter is conjugated with a carbonyl group, or when it is a part of an unsaturated

RESULTS AND DISCUSSION

We examined the reaction of the secondary amines with dialkyl acetylenedicarboxylate in the presence of ninhydrin in dry CH₂Cl₂, at room temperature (25 °C) and obtained the corresponding alkyl 4-(benzyl(alkyl)amino)-1',3',5-trioxo-1',3'-dihydro-5H-spiro[furan-2,2'-indene]-3-carboxylate derivatives 4a–e. Herein we report a hitherto unknown, one-pot three-component reaction, which, starting from readily available ninhydrin 3, affords 4a–e (Scheme 1).

![Scheme 1. Three-component synthesis of alkyl 4-(benzyl(alkyl)amino)-1',3',5-trioxo-1',3'-dihydro-5H-spiro[furan-2,2'-indene]-3-carboxylate derivatives 4a–e (See Table 1 and Experimental)](image-url)
Reaction of dialkyl acetylenedicarboxylates with ninhydrin in the presence of secondary amines

Scheme 2. Proposed mechanism for the formation of alkyl 4-(benzyl(alkyl)amino)-1',3',5'-trioxo-1',3'-dihydro-5'H-spiro[furan-2,2'-indene]-3-carboxylate derivatives 4a–e

EXPERIMENTAL

Starting materials and solvents were obtained from Merck (Germany) and Fluka (Switzerland) and were used without further purification. The methods used to follow the reactions are TLC and NMR, which indicated that there is no side product. IR spectra were measured on a Jasco 6300 FTIR spectrometer. 1H and 13C NMR spectra were measured (CDCl3) with a BRUKER DRX-250 AVANCE spectrometer at 250.0 and 62.5 MHz, respectively. Elemental analyses were performed using a Heraeus CHN-O-Rapid analyzer. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. Flash chromatography columns were prepared with Merck silica gel powder.

General procedure for the preparation of 4a–e

The solution of secondary amines 1 (1.0 mmol) and dialkyl acetylenedicarboxylate 2 (1.0 mmol) in CH2Cl2 (7 ml) was stirred for 1 h. Then ninhydrin 3 (1.0 mmol) was added, and the mixture was stirred for 15 h. The solvent was removed under reduced pressure and the viscous residue was purified by flash column chromatography (silica gel; petroleum ether–AcOEt (10 : 2)). The solvent was removed under reduced pressure and the products (4a–e) were obtained. The characterization data of the compounds are given below:

Methyl 4-(benzyl(isopropyl)amino)-1',3',5-trioxo-1',3'-dihydro-5H-spiro[furan-2,2'-indene]-3-carboxylate 4a

Yellow oil, yield 360 mg (86%); Rf = 0.40 (petroleum ether – AcOEt (10 : 2)); IR: 2953, 1781, 1723, 1615, 1454, 1080, 736 cm⁻¹; 1H NMR (CDCl3) δ: 1.39 (d, 6H, 2CH3, amine), 3.22 (s, 3H, OCH3), 4.84 (s, 2H, CH2 of benzyl group), 4.89–4.97 (m,
Ethyl 4-(benzyl(isopropyl)amino)-1’,3’,5-trioxo-1’,3’-dihydro-5H-spiro[furan-2,2’-indene]-3-carboxylate 4c

Yellow oil, yield 324 mg (83%); \( R_f = 0.45 \) (petroleum ether – AcOEt (10:2)); IR: 2982, 1781, 1725, 1623, 1454, 1088, 1774 cm\(^{-1}\); \( ^1H \) NMR (CDCl\(_3\)) \( \delta \): 21.20, 47.58, 51.32, 52.95, 109.85, 124.09, 127.17, 127.26, 128.41, 128.64, 136.03, 136.50, 140.93, 141.11(CH and C), 159.83, 167.65, 193.25. MS: m/e (%) 419 (M\(^+\), 14), 376 (19), 316 (14), 248 (17), 198 (34), 163 (33), 149 (46), 134 (98), 121 (32), 104 (82), 91 (100), 76 (60), 65 (96), 43 (63). Anal. calcd. for C\(_{24}\)H\(_{21}\)NO\(_6\) (405.40): C, 68.11; H, 4.68; N, 3.51.

Methyl 4-(benzyl(methyl)amino)-1,3,5-trioxo-1,3-dihydro-5H-spiro[furan-2,2’-indene]-3-carboxylate 4d

Yellow oil, yield 344 mg (85%); \( R_f = 0.47 \) (petroleum ether – AcOEt (10:2)); IR: 2989, 1781, 1725, 1623, 1454, 1088, 1774 cm\(^{-1}\); \( ^1H \) NMR (CDCl\(_3\)) \( \delta \): 21.19, 46.37, 51.40, 54.70, 106.81, 124.19, 127.60 (CH and C), 128.64 (CH and C), 136.49, 136.63, 140.98, 141.54, 161.04, 167.04, 193.87. Anal. calcd. for C\(_{24}\)H\(_{21}\)NO\(_6\) (405.40): C, 68.11; H, 4.68; N, 3.51.

Methyl 4-(benzyl(methyl)amino)-1,3,5-trioxo-1,3-dihydro-5H-spiro[furan-2,2’-indene]-3-carboxylate 4e

Yellow oil, yield 364 mg (84%); \( R_f = 0.43 \) (petroleum ether – AcOEt (10:2)); IR: 2989, 1781, 1725, 1623, 1454, 1088, 1774 cm\(^{-1}\); \( ^1H \) NMR (CDCl\(_3\)) \( \delta \): 21.20, 47.58, 51.32, 52.95, 109.85, 124.09, 127.17, 127.26, 128.41, 128.64, 136.03, 136.50, 140.93, 141.11(CH and C), 159.83, 167.65, 193.34. Anal. calcd. for C\(_{24}\)H\(_{21}\)NO\(_6\) (405.40): C, 68.14; H, 4.72; N, 3.46. Found: C, 68.19; H, 4.75; N, 3.44.

References

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DIALKILACETILENDIKARBOKSILATO REAKCIJA SU NINHIDRINU ESANT ANTRINIŲ AMINIŲ: ALKIL-4-(BENZIL(ALKIL)AMINO)-1',3',5-TRIOKSO-1',3'-DIHI- DRO-5H-SPIRO[FURAN-2,2'-INDEN]-3-KARBOKSILATO DARINIŲ SINTEZEI

Sa n t r a u k a

Del reakcijos tarp antrinio amino, dialkiletendikarboksilato ir ninhidrino, gauti nauji alkil-4-(benzil(alkil)amino)-1',3',5-trioksa-1',3'-dihidro-5H-spiro[furan-2,2'-inden]-3-karboksilato dariniai.