



Dimerization of isoquinolinium ylide and 1,3-dipolar cycloaddition with isoquinoline: Synthesis of nitrogen-containing heterocyclic compounds

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KEYWORDS

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Abstract. Dimerization and 1,3-dipolar cycloaddition reactions of isoquinolinium ylide with isoquinoline have been investigated to prepare diaza-dibenzo compounds in good to excellent yields and in a short reaction time. These reactions occur in the presence of a base catalyst such as triethylamine, at room temperature.

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1. Introduction

Research in heterocyclic chemistry has gained momentum in recent times, because a high percentage of the active pharmaceutical compounds are heterocyclic, with a majority of being nitrogen heterocycles [1]. Nitrogen-containing heterocyclic compounds, are of high industrial interest for applications as intermediates to produce pharmaceuticals, herbicides, fungicides, dyes, etc. [2]. The conjugated heterocyclic *N*-ylides have been known as a subgroup of mesomeric betaines [3], widely used as building blocks for the synthesis of fused heterocyclic systems and natural products, due to its 1,3-dipolar character [4] that allows cycloaddition processes to take place efficiently. Today, cycloimmonium ylides are involved in a wide range of synthetically useful reactions, mainly in the field of heterocyclic chemistry [5].

Heteroaromatic *N*-ylides, such as pyridinium, thiazolium, quinolinium, and isoquinolinium methylides

are readily available from the alkylation of azaaromatic heterocycles and sequential deprotonation reaction [6,7]. The 1,3-dipolar cycloaddition of heteroaromatic *N*-methylides with electron-deficient compounds provided a convenient route to construct five-membered heterocycles [8,9]. A number of papers are available on inter- or intra-molecular cycloadditions involving 1,3-dipoles such as nitriloxides, nitrilimines, azides, nitrones, and azomethine ylides with various dipolarophiles [4,10]. The isoquinolinium *N*-ylides are of the most important dipoles in the construction of *N*-heterocycles. One of the most versatile synthetic strategies which starts from isoquinoline is the 1,3-dipolar cycloaddition of isoquinolinium *N*-ylides [11] with dipolarophiles such as acetylenic and olefinic compounds. Usually, these reactions released to pyrrolo(2,1-*a*)isoquinolines, which involve two distinct steps: In the first step, the isoquinolinium salts are prepared, and in the second step these react with acetylenic or olefinic dipolarophiles in the presence of a base whose role is to generate the *N*-ylide in situ [12]. In continuing our interest in the synthesis of heterocyclic compounds [13-15], now we wish to report a one-pot synthesis of a nitrogen-containing heterocyclic compounds by the use of dimerization of isoquinolinium ylide. So we describe an investigation

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of the 1,3-dipolar cycloaddition of isoquinolinium ylide with isoquinoline in a one step procedure.

2. Experimental

2.1. Materials and methods

Chemicals were either prepared in our laboratories or purchased from Merck or Fluka chemical companies, and were used without any further purification. Melting points were measured with an Electrothermal Engineering LTD apparatus and are uncorrected. IR spectra were measured with a Mattson 1000 FT-IR spectrometer. The proton and carbon NMR spectra were recorded with a BRUKER DRX-400 AVANCE spectrometer at 400 and 100 MHz, respectively. Mass spectra were recorded on a MS-QP2000A Shimadzu mass spectrometer operating at an ionization potential of 70 eV.

2.1.1. General procedure for the preparation of *N*-phenacyl isoquinolinium bromide (1):

A mixture of the α -bromophenylethanone (2.2 mmol) and isoquinoline (2.2 mmol) was stirred in CH_3CN (15 mL) at room temperature for 4 h. The resulting precipitate was collected with filtration. The crude product was laundered with CH_3CN (15 mL) to give the pure solid sample for analysis.

The spectral data of some selected compounds.

2.1.2. Spectra Data of *N*-phenacyl isoquinolinium bromide (1).

A 0.32 g white crystals; yield: 98%. M.p. 210-212°C. IR (KBr, $\nu_{\text{max}}/\text{cm}^{-1}$): 1695 (C=O), 1632 (C=N), 1593 (C=C). ^1H NMR (400 MHz, CDCl_3 -d): 10.12-7.33 (m, 12H, Ar), 7.14 (s, 2H, CH_2).

2.1.3. General procedure for the preparation of (14-Benzoyl-7,7a,14a-tetrahydro-6a,13a-diaza-dibenzo(a,h)anthracen-7-yl)-phenyl-methanone (2):

A mixture of the *N*-phenacyl isoquinolinium bromide **1** (2 mmol) and triethylamine (0.2 mL) in CH_2Cl_2 (20 mL) was stirred at room temperature for about 10 minute. The reaction was completed as indicated by TLC. The solvent was diluted with 50 mL of water, and the resulting precipitate was collected with filtration. The crude product was recrystallized with ethanol (30 mL) to give the pure solid sample for analysis.

2.1.4. Spectra Data of (14-Benzoyl-7,7a,14a-tetrahydro-6a,13a-diaza-dibenzo(a,h)anthracen-7-yl)-phenyl-methanone (2):

A 0.464 g. orange crystals; yield: 94%. M.p. 170°C (dec). IR (KBr, $\nu_{\text{max}}/\text{cm}^{-1}$): 1639 (C=O), 1596, 1587 (C=C). ^1H NMR (400 MHz, CDCl_3 -d): 7.80-6.85 (m, 16H, Ar), 6.42 (d, 2H, $N\text{-CH=CH}$, $^3J_{\text{H-H}}=8$ Hz), 5.63 (d, 2H, $N\text{-CH-C=O}$, $^3J_{\text{H-H}}=8$ Hz), 5.46 (d, 2H,

CH=CH , $^3J_{\text{H-H}}=8$ Hz), 5.03 (d, 2H, $N\text{-CH}$, $^3J_{\text{H-H}}=8$ Hz). ^{13}C NMR (100MHz, CDCl_3 -d): 194.55 (C=O), 138.11, 136.14, 133.23, 131.91, 128.72, 128.53, 128.03, 127.78, 126.84, 125.70, 123.53, 101.19, 65.06 (C14, C14-a), 50.06 (C7, C7-a). MS (m/z): 494 (M^+) (2), 479 (7), 402 (5), 375 (5), 260 (12), 247 (25), 170 (8), 129 (20), 105 (90), 89 (15), 77 (100), 63 (15), 51 (20).

2.1.5. General procedure for the preparation of (13,13a-Dihydro-6bH-6a,12a-diaza-dibenzo(a,g)fluoren-13-yl)-phenyl-methanone (4):

To a mixture of the *N*-phenacyl isoquinolinium bromide **1** (2 mmol) and isoquinoline **3** (2 mmol) in CH_2Cl_2 (20 mL) triethylamine (0.2 mL) was added. The reaction mixture was stirred at room temperature for about 15 minute. After the completed reaction which is indicated by TLC, the solvent was diluted with 50 mL of water and the resulting precipitate was collected with filtration. The crude product was recrystallized with EtOH.

2.1.6. Spectra Data of (13,13a-Dihydro-6bH-6a,12a-diaza-dibenzo(a,g)fluoren-13-yl)-phenyl-methanone (4):

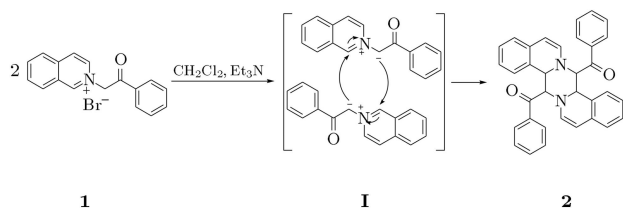
A 0.729 g. orange crystals; yield: 97%. M.p. 190°C (dec). IR (KBr, $\nu_{\text{max}}/\text{cm}^{-1}$): 1664 (C=O), 1618, 1596 (C=C). ^1H NMR (400 MHz, DMSO-d_6): 8.03-6.81 (m, 13H, Ar), 6.70 (d, 2H, $N\text{-CH=CH}$, $^3J_{\text{H-H}}=8$ Hz), 5.77 (s, ^1H , CH), 5.57 (d, 2H, CH=CH , $^3J_{\text{H-H}}=8$ Hz), 5.27 (d, 2H, $N\text{-CH-C=O}$, $^3J_{\text{H-H}}=8$ Hz), 5.21 (d, 2H, $N\text{-CH}$, $^3J_{\text{H-H}}=8$ Hz). ^{13}C NMR (100MHz, DMSO-d_6): 195.02 (C=O), 138.38, 135.40 (2 C), 133.72, 132.11, 129.22, 128.83 (2 C), 128.74, 128.52 (2 C), 127.94 (2 C), 127.18 (2 C), 125.79, 125.10, 123.31, 100.43 (2 C), 92.80, 63.70 (C13-a), 49.47 (C13). MS (m/z): 376 (M^+) (2), 375 (5), 298 (7), 246 (55), 218 (10), 129 (20), 115 (35), 105 (95), 89 (15), 77 (100), 63 (15), 51 (30).

3. Results and discussion

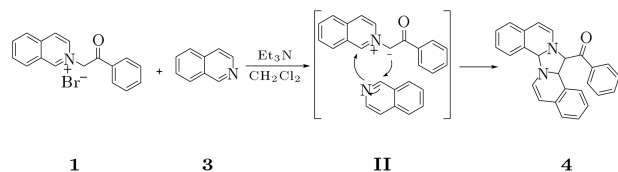
We began our study by examining the reactivity of isoquinolinium ylide **I** in the dimerization reaction. The *N*-phenacyl isoquinolinium bromide **1** is easily obtained by the reaction of isoquinoline with α -phenacyl bromide in acetonitrile, at room temperature, in 4 hours [16].

The isoquinolinium ylide **I** has been prepared in situ from *N*-phenacyl isoquinolinium bromide **1** in the presence of triethylamine as base catalyst, at room temperature, and then the dimerization occurred by 1,3-dipolar cycloaddition. This dimerization led to the synthesis of (14-benzoyl-7,7a,14a-tetrahydro-6a,13a-diaza-dibenzo(a,h)anthracen-7-yl)-phenyl-methanone **2** in excellent yield (Scheme 1).

The use of heteroaromatic *N*-ylides as 1,3-dipoles has received increasing interest in the syn-



Scheme 1. Dimerization isoquinolinium ylide **I** for synthesis of (14-benzoyl-7,7a,14a-tetrahydro-6a,13a-diaza-dibenzo(a,h)anthracen-7-yl)-phenyl-methanone **2**.



Scheme 2. Reaction of isoquinolinium ylide with isoquinoline **3** (13,13 *a*-dihydro-6*bH*-6*a*,12*a*-diaza-dibenzo (*a,g*)fluoren-13-yl)-phenyl-methanone **4**.

thesis of new condensed heterocyclic structures via [3+2] cycloaddition [4,17,18]. As part of our research interest towards the synthesis of new isoquinoline heterocycles, we report here a novel route to synthesis of (13,13*a*-dihydro-6*bH*-6*a*,12*a*-diaza-dibenzo(*a,g*)fluoren-13-yl)-phenyl-methanone **4** in good yield, via 1,3-dipolar cycloaddition of isoquinolinium ylide **I** with isoquinoline **3**. The isoquinolinium ylide **I** was prepared in situ by reaction of *N*-phenacyl isoquinolinium bromide **1** with triethylamine, as base catalyst (Scheme 2).

The structures of compounds **2** and **4** were elucidated and assigned from their IR, ¹H NMR, ¹³C NMR and mass spectra. The ¹H NMR spectra of compounds **2** and **4** showed five and six different kinds of proton signals respectively. The olefinic protons of 1,2-dihydroisoquinoline ring of compounds **2** and **4** appear as doublet signals with coupling constants ³J_{H-H}=8 Hz.

4. Conclusion

We have developed a procedure for simple synthesis of compounds such as (14-benzoyl-7,7a,14a-tetrahydro-6a,13a-diaza-dibenzo (*a,h*)anthracen-7-yl)-phenyl-methanone and (13,13*a*-dihydro-6*bH*-6*a*,12*a*-diaza-dibenzo(*a,g*)fluoren-13-yl)-phenyl-methanone as active pharmaceutical heterocyclic compounds. By this method, these compounds were rapidly constructed with good-to-excellent yields by simply stirring a reaction mixture of isoquinolinium ylide with isoquinoline or dimerization of isoquinolinium ylide, which catalyzed by triethylamine. The mild reaction conditions and short reaction times render these reactions as an attractive alternative for the synthesis of this type of *N*-containing heterocycles.

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