Tetrahedron 73 (2017) 3040–3047

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

$ZnBr_2$ catalyzed domino Knoevenagel-hetero-Diels–Alder reaction: An efficient route to polycyclic thiopyranoindol annulated [3,4-*c*] quinolone derivatives

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ARTICLE INFO

Article history:
Received 24 February 2017
Received in revised form
26 March 2017
Accepted 10 April 2017
Available online 12 April 2017

Keywords:
Domino reaction
Knoevenagel-hetero-Diels–Alder
Indole
Indolin-2-thione
3,4-Dihydroquinolone
$ZnBr_2$ catalyzed

ABSTRACT

Various novel polycyclic thiopyranoindol annulated [3,4-*c*]quinolone derivatives were synthesized via domino Knoevenagel-hetero-Diels–Alder reactions of indoline-2-thions and novel *N*-acrylated anthranilaldehydes in refluxing ethanol as a solvent in the presence of 20 mol% $ZnBr_2$ as a Lewis acid catalyst. All reactions proceed with high yields with excellent regio- and stereoselectivity.

1. Introduction

Indole derivatives are important heterocycles. They are widespread in nature and have various biological activities,[1] such as topical anti-inflammatory,[2] anti-HIV[3] and antitumor activities.[4] Also compounds possessing tetrahydrothiopyrano indole moieties are very important because of their different biological and medicinal activities.[5] On the other hand, the dihydroquinolone (3,4-dihydroquinolin-2-one) structure is found in many pharmacologically important natural products and synthetic compounds.[6] Simple alkoxydihydroquinolones form the core of the commercial drugs such as carteolol,[7] cilostazol[8] and aripiprazole.[9] Many 3,4-disubstituted dihydroquinolones have cardiovascular, anti-inflammatory and phosphodiesterase inhibitory activities.[10] The 3,4-dihydroquinolone structure is also embedded within pentacyclic alkaloids of the Melodinus scandens family, exemplified by scandine, meloscine and epimeloscine,[11] as well as the structurally unique alkaloids of the Trigolutesin A,[12] scandomelonine and episcandomelonine that have both indole and 3,4-dihydroquinolone moieties.[11b] Not surprisingly, methods for the synthesis of 3,4-disubstituted dihydroquinolones have attracted significant attention. Protocols, such as Friedlander/Friedel–Crafts cyclization,[13] Skraup–Doebner–Von Miller reaction,[14] oxidative cyclization,[15] radical reactions,[16] photocyclizations,[17] palladium-catalyzed cyclocarbonylation[18] and rhodium-catalyzed reaction[19] approaches have been reported. Despite their efficiencies, most of the reported reactions are either multi-step, or are not suited for the synthesis of 3,4-disubstituted dihydroquinolones containing other heterocyclic groups.

The domino Knoevenagel-hetero-Diels–Alder (DKHDA) reaction is a popular strategy for the synthesis of polycyclic heterocycles and natural products.[20] A wide range of heterocyclic compounds, especially polycycles with a pyran or chroman moiety have been synthesized by domino-Knoevenagel-hetero-Diels–Alder reaction.[21] In addition there are some reports of domino-Knoevenagel-hetero-Diels–Alder reactions for the synthesis of polycycles with a benzosultone or benzosultam moiety.[22] In this regard, previously we reported domino Knoevenagel-hetero-Diels–Alder reactions of

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http://dx.doi.org/10.1016/j.tet.2017.04.017
0040-4020/

O-acrylated salicylaldehyde derivatives for synthesis of pentacycles with a dihydrocoumarin ring.[23] The goal of the present study was to introduce a new methodology for synthesis of pentacyclic heterocycles with 3,4-disubstituted dihydroquinolones, in one step. To the best of our knowledge, this is the first example of using *N*-acrylated anthranilaldehydes in the domino Knoevenagel-hetero-Diels–Alder reaction with indolin-2-thiones. In the context of our general interest in the domino Knoevenagel-hetero-Diels–Alder reactions,[21a,22b,23] and synthesis of heterocyclic compounds using indolin-2-thiones,[24] we herein report a new and highly efficient reaction for the preparation of pentacyclic compounds **3a-k**, which consist of an indole ring (A), a tetrahydrothiopyran ring (B) annulated to a 3,4-dihydroquinolone ring (C) (Scheme 1).

2. Results and discussion

2.1. Preparation of N-acrylated anthranilaldehyde derivatives for domino Knoevenagel-hetero-Diels–Alder reaction

N-alkylanthranilaldehydes **4a-b** were prepared from the corresponding *N*-alkylquinoline salts on the basis of the previously reported method.[25] *N*-acrylated anthranilaldehyde derivatives **1a-f** were then prepared from condensation of *N*-alkylanthranilaldehydes **4a-b** and (*E*)-acryloyl chloride derivatives (acryloyl chloride, (*E*)-crotonoyl chloride and (*E*)-cinnamoyl chloride) **5a-c** in the presence of $NaHCO_3$ in CH_2Cl_2 within 2–5 h in good yields (Scheme 2). *N*-Acrylatedanthranilaldehyde derivatives **1a-f** were completely characterized using their analytical and spectral data. For example, the ^{1}H NMR spectrum of **1c** exhibited characteristic singlet at δ 3.37 ppm for NMe followed by two doublet at 6.05 and 7.64 for the = CH (J = 15.4 Hz) in *trans*-relation with each other, together with a singlet at 10.05 due to CHO.

2.2. Domino Knoevenagel-hetero-Diels–Alder reaction of N-acrylated anthranilaldehyde derivatives with indolin-2-thiones

To optimize the reaction conditions, we screened the domino Knoevenagel-hetero-Diels–Alder reaction of compound **1b** with 1-methylindoline-2-thione **2a** as a model. The effect of several solvents and catalysts were studied (Table 1). Using refluxing water or acetonitrile as a solvent under catalyst-free conditions for 24 h, the products were obtained in 10% and 12% yield respectively (Entries 1 and 2, Table 1). When the reaction was carried out in the presence of ZnO as a Lewis acid in acetonitrile for 24 h at refluxing temperature, the yield was increased to 35% (Entry 3). The effect of other solvents in the presence of ZnO was studied. Using MeOH and EtOH as solvents did not give the significant influence to the yield of product (Entries 4 and 5). Surprisingly the addition of $ZnBr_2$ as a catalyst and ethanol as solvent dramatically increased the yield of reaction to 88% and decreased the time of reaction to 3 h (Entry 6). Decreasing the ratio of $ZnBr_2$ to 50 mol% and 20 mol% afforded the same results, but with 10 mol% of $ZnBr_2$ in the same times, gave lower yield (Entries 7, 8 and 9). We also examined other conditions, for example Lewis base (Entry 10) or $ZnCl_2$ (Entry 11), also we checked $ZnBr_2$ in water (Entry 12), but the best conditions was entry 9. In all the cases the product was obtained as a *cis* isomer.

Under the optimized conditions, we next investigated the effect of substitutions on the yield as well as regio- and stereoselectivity of domino Knoevenagel-hetero-Diels–Alder reaction of *N*-acrylated anthranilaldehyde derivatives **1a-f** and indoline-2-thiones **2a–c** (Table 2).

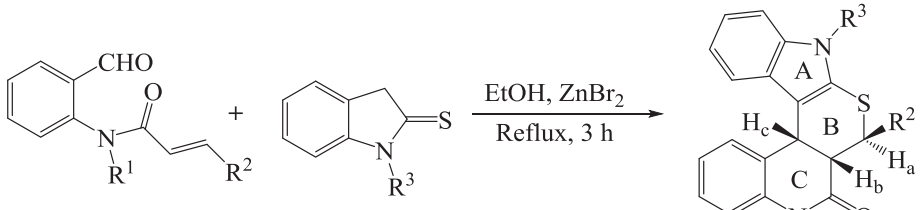
The structures of the products **3a-k** were established on the basis of their spectral data (^{1}H and ^{13}C NMR, DEPT and IR), as well as HRMS analysis. The relative configurations were determined from the coupling constants of the relevant H-atoms and also by direct comparison with the reported data in literature.[20–23] For instance, the characteristic peaks for **3b** in the ^{1}H NMR spectra are a doublet of doublet (J = 9.6, 4.6 Hz) at δ 2.99 ppm for the H_b followed by a multiplet for the H_a at δ 3.48–3.59 ppm and a doublet for the H_c with J = 4.5 Hz at δ 4.71 ppm that show *trans*-relation between H_a and H_b also *cis*-relation between H_a and H_c respectively. In all the synthesized products, the relative orientations of the H-atoms were found to be same.

A plausible mechanism for the domino Knoevenagel-hetero-Diels–Alder reaction is shown in Scheme 3. Initially aldehydes **1** undergo a Knoevenagel condensation with indolin-2-thiones **2** in the presence of $ZnBr_2$ ($ZnBr_2$ as a Lewis acid can facilitate the condensation) to afford an alkene intermediate, which has not been isolated. The stereochemistry of the final products depends on the *endo*- and *exo*-orientation of the dienophile in the transition state. We assume that the *trans*-cycloadducts **6** could form via an *exo*-transition state (intermediates **7**), whereas the *cis*-isomers **3a-k** resulted from an *endo*-transition state (intermediates **8**), as represented in Scheme 3. Here only the products **3a-k** were isolated which shows that the *endo*-transition states are more stable than *exo*-transition states, due to secondary orbital interaction, so reactions proceed via intermediates **8** to produce the *cis*-isomers **3a-k** with excellent regio- and stereoselectivity.

3. Conclusion

We have reported a $ZnBr_2$-catalyzed domino Knoevenagel-intramolecular-hetero-Diels–Alder reaction of novel *N*-acrylated anthranilaldehydes and indoline-2-thions with high efficiency and excellent regio- and stereoselectivity to provide various novel pentacyclic thiopyranoindol annulated [3,4-*c*]quinolone derivatives in a single step.

The major advantages of this reaction are the ease of the work-



1a-f **2a-c** **3a-k**

R^1= Me, Et

R^2= H, Me, Ph

R^3= Me, Et, Ph

Scheme 1. Domino Knoevenagel-hetero-Diels–Alder reaction of *N*-acrylated anthranilaldehydes with indolin-2-thiones.