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Metal-free regioselective construction of diazabenzo[*e*] acephenanthrylene-1,2-dicarboxylates *via* a phosphine-mediated cycloadditon

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ABSTRACT

A number of new diazabenzo[*e*]acephenanthrylene-1,2-dicarboxylate derivatives have been prepared regiospecifically in moderate to good yields from the triphenylphosphine-mediated cyclocondensation reaction of dialkyl acetylenedicarboxylates with 1-(4-aryl)-2-(11*H*-indeno[1,2-*b*]quinoxalin-11-ylidene) ethanones, derived from reaction of ninhydrin, *o*-phenylenediamine, and 1-aryl-2-(triphenylphosphoranylidene)ethanones.

1. Introduction

The synthesis of polyheterocycles is important in the generation of complex natural compounds, medicinal and functional materials.[1] Among them, polycyclic nitrogen heterocycles are vital scaffolds due to their prevalence in pharmaceutical active natural compounds.[2] Isoindolo-quinoxalies **1**[3] and imidazo-quinoxaline represent interesting antineoplastic activity and potent inhibitor of IKK-2, respectively.[4] Pyrido[1,2-*a*]quinoxalines exhibit pH-dependent UV–visible absorption and fluorescence characteristics.[5] Another group of polycyclic quinoxalines namely, indenoquinoxalines, are widely utilized as building block for the construction of spiro compounds[6] and organic semiconductors.[7] They are also known as potent AChE inhibitor,[8] antimetabolic,[9] antibacterial,[10] and anticancer agents **2**.[11] 5-Thia-1,8b-diazaacenaphthylene derivatives were known to be effective in reducing plasma lipoprotein and specially *N*-[1-(3-phenylpropan-1-yl)piperidin-4-yl]-5-thia-1,8*b*-diazaacenaphthylen-4-carboxamide **3** decreases non-high density lipoprotein cholesterol and triglycerides in hamsters and has potential for preventing atherosclerosis (Fig. 1).[12] Therefore, the development of general protocols for the construction of polyheterocycles is of great interest.

Various synthetic methodologies have been developed to synthesis heterocycles. Among them zwitterion chemistry has been regarded as one of the most interesting strategies.[13] Nucleophilic addition of phosphorus at unsaturated carbon like dialkyl acetylenedicarboxylate yields zwitterion that in reaction with dipolarophile results phosphorus or non-phosphorus containing products. For example 2,5-dihydro-1,2-oxaphospholes were synthesized from the reaction of triphenylphosphine, acetylenic compounds and ethyl 3-bromopyruvate.[14] Also three-component reaction of amine, diketene and dibenzoylacetylene in the presence of triphenylphosphine yielded functionalized furamide derivatives as non-phosphorous products.[15]

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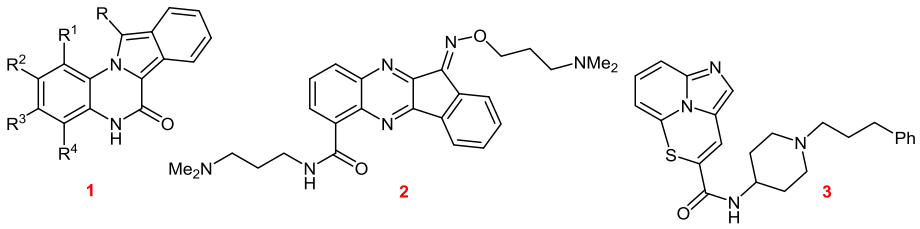


Fig. 1. Structure of some polycyclic nitrogen heterocycles with biological activities.

Since polycyclic nitrogen heterocycles have widely been applied in discovery of novel bioactive compounds,[16] it promoted us to choose zwitterion resulted from triphenylphosphine and dialkyl acetylenedicarboxylate as 1,3-dipole for reaction with 1-(4-aryl)-2-(11*H*-indeno[1,2-*b*]quinoxalin-11-ylidene)ethanone having the chalcone structure which has been applied for the production of spiro indenoquinoxalines by Shaabanzadeh et al.[17]

2. Results and discussion

Initially we explored the preparation of 1-(4-aryl)-2-(11*H*-indeno[1,2-*b*]quinoxalin-11-ylidene)ethanone **4** (Scheme 1) through 11*H*-indeno[1,2-*b*]quinoxalin-11-one described by Deady et al.[18] 11*H*-Indeno[1,2-*b*]quinoxalin-11-one previously was used as intermediate for construction of various compounds like spiropyrrozolidines,[19] and pyrroles.[20]

The reaction of *o*-phenylenediamine and ninhydrin in EtOH at room temperature in the presence of sodium acetate gives known 11*H*-indeno[1,2-*b*]quinoxalin-11-one.[16] Addition of acetophenone to the reaction mixture in the presence of different bases like Et_3N, piperidine, and KOH at ambient temperature or reflux conditions in different solvents did not yield the product. Next, we screened conditions for the Wittig olefination of 11*H*-indeno[1,2-*b*]quinoxalin-11-one. Surprisingly, in the presence of 1-aryl-2-(triphenylphosphoranylidene)ethanone, the reaction proceeded effectively and was completed to afford the desired 1-(4-aryl)-2-(11*H*-indeno[1,2-*b*]quinoxalin-11-ylidene)ethanone **4**.

In continuation of this research, we became interested in the application of **4** as dipolarophile in reaction with a 1,3-dipole generated from dialkyl acetylenedicarboxylate and triphenylphosphine for manufacture of polycyclic nitrogen heterocycles. Our strategy to reach this goal is outlined in Scheme 2. To a solution of **4a** and triphenylphosphine, in DCM was added dimethyl acetylenedicarboxylate **5a**. After the work-up and chromatographic purification, a dark green solid product was isolated in 88% yield. Compound **4a** have one enone and one enimine unit, so two products are possible. The ^1H and ^{13}C NMR spectra of the product clearly indicated the formation of **6a**.

We went on to consider similar reactions using **4** equiv. of reactants in different solvents. The highest yield was obtained in DCM. Finally, the reaction was also tested in the presence of catalytic amount of triphenylphosphine. Unfortunately, the yield of the product decreased significantly (see Table 1).

Having optimized the reaction conditions, we turned our attention to examine the scope of reactions. The results are summarized in Table 2. It was noticeable that diisopropyl acetylenedicarboxylate did not work in this reaction, probably due to the greater steric hindrance of the isopropyl group. Furthermore, the use of substituted *o*-phenylenediamines like 4-bromo or chloro-*o*-phenylenediamine did not give compound **4**.

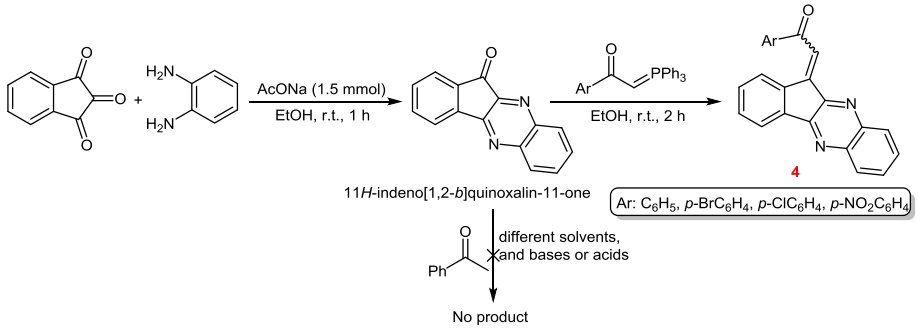
The structures of all the products **6a**–**g** were deduced from their IR, mass, ^1H NMR, and ^{13}C NMR spectra and unambiguously confirmed by X-ray crystal structure analysis of **6e** (Fig. 2).

Although the reaction yielded only the product **6**, presumably because of a [1,5]-H shift, two tautomers were recognized in NMR spectroscopies and two signals were observed for most of chemically different carbons and hydrogens (Scheme 3).

In its ^1H NMR spectrum of **6a** four singlet signals at 3.53, 3.64, 3.71, and 3.75 ppm are related to two methoxy groups of two isomers. The CH groups were appeared as two separate singlet signals at 7.03 and 7.11 ppm. The observation of four distinct signals in the ^1H-decoupled ^{13}C NMR spectrum of **6a** at 51.67, 51.8, 53.22, and 53.3 ppm related to methoxy groups is in agreement with the proposed two tautomers.

Based on these results, a plausible mechanism for the synthesis of polycyclic nitrogen heterocycle **6** has been proposed (Scheme 4).

Based on the well-recognized chemistry of trivalent phosphorus nucleophiles,[14,15] it is reasonable to assume that initial addition of triphenylphosphine to the dialkyl acetylenedicarboxylate and subsequent attack of the resulting zwitterion **7** to the double bond of **4** yields the intermediate **8**. Then **8** apparently cyclizes through the attack of nitrogen and removal of triphenylphosphine (**8** to **9**). Finally the product **6** is produced through a keto-enol tautomerization (**9** to **10**) and a [1,5]-H shift respectively.



Scheme 1. Synthesis of 1-(4-aryl)-2-(11*H*-indeno[1,2-*b*]quinoxalin-11-ylidene)ethanone **4.**