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A facile entry into a novel class of dispiroheterocyclic framework through 1,3-dipolarcycloaddition of azomethine ylides with 3-arylidene-4-chromanones as dipolarophiles

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ABSTRACT

The cycloaddition reaction of azomethine ylides, generated through decarboxylation, with (*E*)-3-arylidene-4-chromanones as dipolarophiles has been investigated. A high degree of regioselectivity has been observed in the synthesis of a new class of functionalized dispiroheterocyclic compounds bearing chromanone and acenaphthenequinone framework. The structures were established by spectroscopic techniques as well as single crystal X-ray analysis.

Spiroheterocycles represent an important class of naturally occurring substances characterized by their highly pronounced biological activities.[1–3] Intermolecular 1,3-dipolar addition reactions are considered as one of the most useful processes for the construction of five-membered ring containing the pyrrolidine structural unit.[4,5] This method is widely used for the synthesis of natural products such as alkaloids and pharmacologically important compounds.[6] 1,3-Dipolar cycloaddition provides a way for the synthesis of many dispiroheterocyclic systems through the cycloaddition reaction of azomethine ylides with the definite dipolarophiles.

Pyrrolidine and oxindole alkaloids[7] constitute another class of compounds with significant biological activity which are normally found in rhyncotylline, corynoxeine, nitraphylline, vincatine, horsifiline, etc. Highly substituted pyrrolidines have attracted much interest as they contribute to the central structural element of many alkaloids and pharmacologically active compounds.[8,9] Although highly substituted spiropyrrolidines are known, there seems to be no report on the synthesis of dispiroheterocycles using acenaphthenequinone and chromanone moiety. In pursuit of our research on the synthesis of novel dispiropyrrolidinyl derivatives (**4a–g**), we herein report the 1,3-dipolar cycloaddition reactions of (*E*)-3-arylidene-4-chromanones (**3**) with the azomethine ylides generated from acenaphthenequinone (**1**) and sarcosine (**2**) through decarboxylation method.

Refluxing a solution of (*E*)-3-benzylidenechroman-4-one (**3**) in boiling aqueous methanol with acenaphthenequinone (**1**) and sarcosine (**2**) afforded 1-*N*-methyl-spiro[2.2′] acenaphthen-1′one-spiro[3.3″](chroman-4″-one)-4-aryl pyrrolidine (**4**) (Scheme 1, Table 1). The reaction gave a single product in all cases as evidenced by thin layer chromatography (TLC). The reaction afforded a series of novel spiro derivatives (**4a–g**)[15–21] through regioselective cycloaddition of azomethine ylides with the exocyclic double bond of 3-arylidene-chroman-4-ones (**3**) in all cases. No trace of the other regioisomer (**5a–g**) was detected. The cycloaddition proceeded smoothly to afford the *syn-endo* cycloadduct.[10] The regio and stereochemical outcome of the cycloaddition was determined by spectrochemical and single crystal X-ray analysis.[11]

The IR spectral analysis of 4 showed two carbonyl peaks at 1690 cm^{-1} and 1718 cm^{-1} which correspond to the chromanone and acenaphthenequinone ring carbonyls, respectively. The ^1H NMR spectrum of the cycloadduct **4**, exhibited a singlet at δ 2.09, which corresponds to $N–CH_3$ protons. A triplet at δ 4.98 corresponds to benzylic proton. The regiochemical outcome of the azomethine ylide cycloaddition with conformationally restricted *S-cis* enones, 3-arylidenechroman-4-ones (**3**) is probably attributed to the involvement of the antiylide[12] in the transition state, where the *exo* orientation of the dipolarophile to *W*-periphery of the ylide prevents the formation of the *syn* ylide which is not observed due

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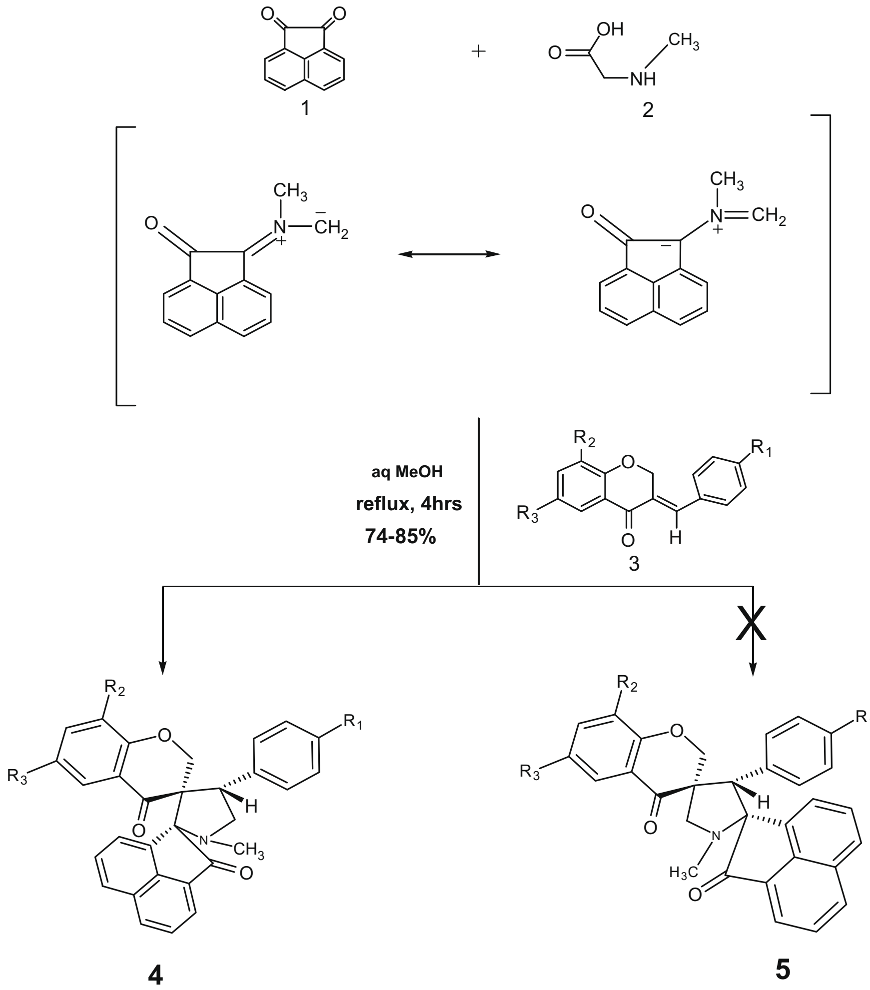

Scheme 1.

to the unfavorable steric repulsions between the carbonyl oxygen of acenaphthenequinone ring and chroman-4-one ring systems.[13] Further the NOE studies show the nonbonded interactions between the conformationally nearer protons in the molecules, which is further confirmed in the crystal structure of the compound.[14]

Further, the regiochemistry of the cycloadduct **4** was established by the ^{1}H NMR spectrum where a doublet at δ 4.56 corresponds to aryloxymethyl protons and a doublet at δ 3.28 corresponds to N–CH_2 proton. Also the ^{13}C NMR showed two signals at δ 62.00 and δ 71.47 due to the spiro carbon atoms and peaks at δ 192.02 and δ 206.31 due to the chromanone and acenaphthenequinone ring carbonyls, respectively. The mass spectrum of the compound showed a peak at *m/z* 474.02 (M^+), which corresponds to the molecular weight of the compound. Identical results were observed for the other derivatives irrespective of the nature of the substituent present in the arylidene moiety.

Table 1

Synthesis of 1-*N*-methyl-spiro[2.2′]acenaphthen-1′-one-spiro[3.3″](chroman-4″-one)-4-aryl pyrrolidines (**4a–g**)[15–21] via Scheme 1

Compound	R_1	R_2	R_3
4a	H	H	OCH_3
4b	CH_3	OCH_3	CH_3
4c	H	OCH_3	CH_3
4d	CH_3	OC_2H_5	CH_3
4e	OCH_3	OC_2H_5	CH_3
4f	OCH_3	OCH_3	$CH{=}CH\ (CH_3)$
4g	CH_3	H	OCH_3

As part of our ongoing research, another series of novel spiropyrrolizines (**7a–f**)[22–27] were synthesized (Scheme 2, Table 2), which are structurally similar to compounds **4a–g** but differ in the *N*-methyl group where a pyrrolizine moiety replaces the *N*-methyl group.