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Annulation Reactions of Allene-Derived 1,3-Dipole with 3-Substituted-Chromones: Unusual Recognition of 4π-Component in 3-(*N*-Aryliminomethyl)chromones through [4 + 3] Annulation

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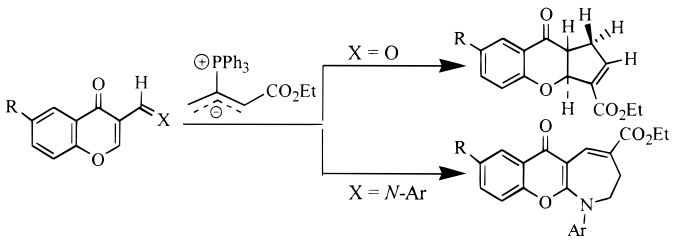
ABSTRACT



All-carbon dipole derived by the interaction of triphenylphosphine with allenic ester is able to locate the polarized 2π-component in 3-formylchromones through a regioselective [2 + 3] addition to the C2−C3 π-bond, which is followed by deformylation leading to novel 3a,9a-dihydro-1-ethoxycarbonyl-1-cyclopenteno[5,4-*b*]benzopyran-4-ones. On the contrary, the dipole recognizes azadiene in 3-(*N*-aryliminomethyl)-chromones through [4 + 3] annulation and initially formed adducts undergo tandem rearrangements to afford novel *N*-aryl-2,3-dihydro-4-ethoxycarbonylchromano[2,3-*b*]azepine-6-ones in good yield.

Allenes have proven to be valuable synthons, and cycloaddition to one of the π-bonds of allenic moiety has been the most common method of their involvement in organic synthesis.[1] However, recently Zhang and Lu[2] introduced a method for generating a 1,3-dipole (**A**) from alkyl 2,3-butadienoates by interaction with various phosphines. The dipole **A** has been shown to undergo (3 + 2) annulation with a variety of dipolarophiles including polarized double bonds and imines.[2] The reaction is reportedly initiated by attack of the anionic carbon of dipole at the electrophilic center in dipolarophile, and the addition, therefore, occurs only across the polarized 2π systems. However, quite often the addition is nonregioselective, leading to mixture of products.[2a−e] Recent isolation of some natural cyclopentanobenzopyran-

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(2) (a) Zhang, C.; Lu, X. *J. Org. Chem*. **1995**, *60*, 2906. (b) Xu, Z.; Lu, X. *Tetrahedron Lett*. **1997**, *38*, 3461. (c) Xu, Z.; Lu, X. *J. Org. Chem*. **1998**, *63*, 5031. (d) Shu, L. H.; Sun, W. Q.; Zhang, D. W.; Wu, S. H.; Xu, J. F.; Lao, X. F. *Chem. Commun*. **1997**, 79. (e) O'Donovan, B. F.; Hitchcock, P. B.; Meidine, M. F.; Kroto, H. W.; Taylor, R.; Walton,. D. R. M *Chem. Commun*. **1997**, 81. (f) Zhu, G.; Chen, Z.; Jiang, Q.; Xiao, D.; Cao, P.; Zhang, Z. *J. Am. Chem. Soc*. **1997**, *119*, 3836.

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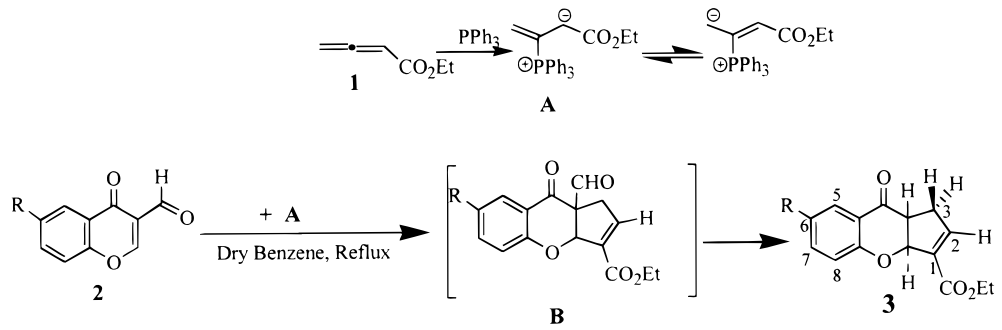
Scheme 1



4-ones which have been ascribed antifungal and other medicinal properties,[3] and whose synthesis involves multistep processes,[4] prompted us to investigate the reactions of dipole **A** with 3-formylchromones. The latter possess a highly polarized C2−C3 π-bond, and a successful annulation across this bond was anticipated to afford a simple route to the carbon framework of the above-mentioned cyclopentanochromones. We report herein that as envisaged dipole **A** adds regioselectively to the C2−C3 π-bond and the annulation is followed by concomitant deformylation leading to novel 3a,9a-dihydro-1-ethoxycarbonyl-1-cyclopenteno[5,4-*b*]benzopyran-4-one (**3**) in good yield (Scheme 1, Table 1).

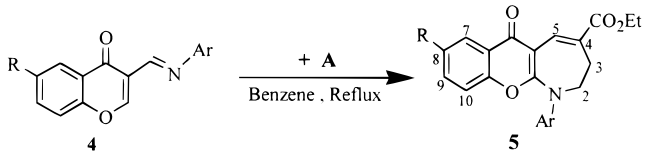
Table 1. Dipolar Addition of Allenic Ester (**1**) with 3-Formylchromones (**2**)

	R	reaction time (h)	yield (%) of **3**
a	H	80	74
b	Cl	80	72
c	Me	80	72

The assigned structures of adducts (**3a**−**c**) are based on spectroscopic (^{1}H and ^{13}C NMR, IR, and MS) and microanalysis. The assigned regiochemistry of addition is based on obtaining of C9a-H resonance in ^{1}H NMR as a doublet (at δ 5.64 in the case of **3c**) which is coupled only with C3a-H; the latter hydrogen appeared as multiplet (at δ 3.08−3.25 in the case of **3c**) and showed vicinal coupling with C3-Hs. The *trans*-arrangement along the C9a−C3a bond is based on the value of $^3J_{9a,3a}$ = 6.38 Hz and the structures are corroborated by ^{13}C NMR spectral assignments. Compounds **3a**−**c** are apparently derived from regioselective addition of dipole **A** to the highly polarized C2−C3 π-bond of 3-formylchromones which is followed by deformylation; such facile deformylation is precedented in 2,3-dihydrochromone derivatives.[5] Overall, the formyl group plays an important role in directing the regiochemistry of addition by enhancing the electrophilic character of C2 in **2a**−**c** and is knocked off after annulation. The work is also in progress for conversion of obtained cyclopentenochromones (**3**) to naturallly occurring, biologically active molecules or their analogues.

Subsequently, the additions of dipole **A** were extended to 3-(*N*-aryliminomethyl)chromones (**4**), which were of considerable interest both from the chemistry point of view as these molecules possess two highly electrophilic centers (C2 and the carbon of imine moiety) and synthetically as a route to potentially biologically active chromone moieties bearing heterocycles.[6] In light of the known behavior of azadienes (**4**) in reactions with 1,3-dipoles (nitrile imines)[7] and the reported reactions of dipole **A** with 1-aryl-4-phenyl-1-aza-1,3-butadiene,[2c] it was anticipated that addition would occur only accross C═N in **4**. However, in view of the known[5] high electrophilicity of C2 in **4** there was a distinct probability that the reaction may be initiated by attack of dipole at C2 leading to either (2 + 3) or (4 + 3) annulation. We report that the reaction of dipole **A** with azadiene (**4**) is indeed initiated by attack of the negative end of the dipole at C2 in **4**; however, contrary to the reaction of dipole **A** with 3-formylchromones, the 4π-azadiene component is involved in the reaction, leading to [4 + 3] annelation. The initially formed adduct undergoes, in situ, tandem rearrangements affording novel *N*-aryl-2,3-dihydro-4-ethoxycarbonylchromano[2,3-*b*]azepine-6-ones(**5**) in good yield (Scheme 2, Table 2).

Scheme 2



The assigned structures are based on rigorous spectroscopic analysis (UV, IR, ^{1}H and ^{13}C NMR, MS) and microanalytical data. Though the formation of a 1:1 addition product was clearly established by mass spectral and microanalytical data,

(3) (a) Gloer, J. B.; Wang, H.-J.; Scott, J. A.; Malloch, D. *Tetrahedron Lett.* **1995**, *36*, 5847. (b) Fujimoto, H.; Inagaki, M.; Satoh, Y.; Yoshida, E.; Yamazaki, M. *Chem. Pharm. Bull.* **1996**, *44*, 1090. (c) Lin, L.-J.; Topcu, G.; Lotter, H.; Ruangrungsi, N.; Wagner, H.; Pezzuto, J. M.; Cordell. G. A. *Phytochemistry* **1992**, *31*, 4333.

(4) Mori, K.; Audran, G.; Monti, H. *Synlett* **1998**, 259.

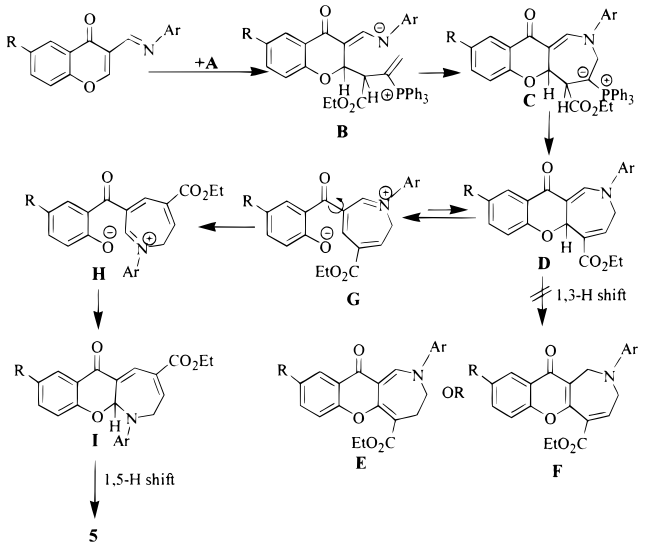
(5) Sabitha, G. *Aldrichimica Acta* **1996**, *29*, 15 and references therein.

Table 2. Dipolar Addition of Allenic Ester (**1**) with 3-(*N*-Aryliminomethyl)chromones (**4**)

	R	Ar	reaction time (h)	yield (%) of **5**
a	H	*p*-anisyl	80	55
b	H	*p*-chlorophenyl	90	57
c	Me	*p*-anisyl	85	64
d	Me	*p*-chlorophenyl	90	60
e	Cl	*p*-anisyl	80	59
f	Cl	*p*-chlorophenyl	80	64

the assigned structures are based mainly on NMR spectral evidences, which clearly indicated the preservation of the chromone moiety and involvement of the 4π system. The absence of a methine carbon (CH) in the downfield olefinic region (>135 ppm) of the ^{13}C NMR spectrum of **5** along with the absence of an oxygen-linked methine carbon resonance (in the anticipated region) indicated the involvement of the 4π system[8] of the diene as well as the rearrangement of the initially formed adducts as it ruled out structures **D** and **E** for the product. The assigned structure is supported by the presence of an upfield shifted (at δ 99−100 ppm) quaternary olefinic carbon resonance assigned to C5a and the corresponding downfield shifted (at δ 160−162 ppm) quaternary olefinic carbon resonance (C11a). The presence, inter alia, of two methylene (2 × CH_2) groups (^{1}H and ^{13}C NMR) further corroborated the assigned structures; the ^{13}C NMR chemical shifts of these methylene carbons (C2 and C3) were critical in ruling out structure **F** (Scheme 3). The assigned structures are also supported by proton connectivities of the ^{1}H NMR spectrum and UV and IR spectroscopic data.

Scheme 3



Mechanistically, the formation of **5** can be rationalized (Scheme-3) in terms of an initial regioselective (orientation of dipole **A** being controlled by interaction between the negative end of the dipole and most electrophilic center in **4**) annulation leading to intermediate **D** which is followed by thermal opening of the chromone ring yielding **G**; rotation around a C−C single bond in **G** followed by recyclization yields **I** and the latter after a 1,5-H shift leads to **5**. Such opening of the chromone ring and recyclization is precedented,[5] and recently we also reported a similar intramolecular reorganization in some chromone derivatives.[8b]

The obtianed (4 + 3) addition of dipole **A** in reactions with azadienes (**4**) is apparently a consequence of the high electrophilicity of C2 in **4** as well as preferred s-cis conformation of these dienes.[9] On the contrary acyclic azadienes such as 1-aryl-4-phenyl-1-aza-1,3-butadiene to which addition of dipole **A** has been reported,[2c] do not possess a comparable electron deficiency at C4; consequently the addition of dipole occurs only accross C=N.[2c] At present work is in progress to further delineate the factors controlling chemoselectivities in additions of dipole **A** to heterodienes with an aim of affecting easy (4 + 3) annulations, leading to azepines/diazepines; the targetted heterocyclic systems are known to possess valuable biological activities.[10]

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Supporting Information Available: Experimental procedures and complete characterization data for compounds **3a−c** and **5a−f**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(6) (a) Dewick, P. M. *The Flavonoids: Advances in Research since 1986*; Harborne, J. B., Ed.; Chapman & Hall: New York, 1994. (b) Turner, W. B.; Aldridge, D. C. In *Fungal Metabolites II*; Academic Press: New York, 1983; pp 3−43. (c) Yang, D. M.; Takeda, Y.; Sankawa, U.; Shibata, S. *Tetrahedron* **1973**, *29*, 519. (d) Nakatani, K.; Saito, I. *Angew. Chem., Int. Ed.* **1999**, *38*, 3378.

(7) Baruah, A. K.; Prajapati, D.; Sandhu, J. S. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1995.

(8) (a) In case in which only the imine moiety of **4** was involved in the reaction, the C2 of the chromone moiety is anticipated to appear as a methine carbon (CH) resonance at around ~δ 160,[8b] and in case in which only the C2−C3 π bond of **4** was involved in the reaction, the spectral parameters of the chromone moiety will have drastically altered. For instance, in the absence of of a π bond between C2 and C3, the carbonyl carbon of the chromone moiety is shifted downfield by ~14 to 17 ppm;[8b,c] C4 in chromone appears at δ 177.40.[8c] (b) Ishar, M. P. S.; Kumar, K.; Singh, R. *Tetrahedron Lett.* **1998**, *39*, 6547. (c) Breitmaier, E.; Voelter W. In *Carbon-13 NMR Spectroscopy;* VCH: New York, 1987; p 279.

(9) Molecular modeling and energy minimization (molecular mechanics) have suggested that s-cis is the low-energy conformation in the case of **4** (with *anti*-arrangement around C=N) and two avoid compression between the imine-H and *ortho* hydrogens of the *N*-aryl group there is a twist along −CH=N−Ar, i.e., the aryl group is out of plane by around 24°.

(10) (a) Smalley, R. K. In *Comprehensive Organic Chemistry*, Sammes, P. G., Ed.; Pergamon Press: Oxford, 1979; p 565 (b) Smalley, R. K. In *Comprehensive Heteocyclic Chemistry*; Lwowski, W., Ed.; Pergamon Press: Oxford, 1984; p 516.