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An unusual and facile N-hetero cyclisation of 2-amino-4-(2-oxo-2-arylethyl)-4H-chromene-3-carbonitrile derivatives using hypervalent iodine in alcohol under ambient condition

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ABSTRACT

A very important functionalized benzopyran moiety has been further functionalized along with an unusual N-heterocyclic ring formation in a single step under ambient condition in room temperature under the influence of hypervalent iodine to produce a structurally interesting motif which can have some interesting biological properties having a similar but modified structure as that of bio-active chromene moieties.

The attention of synthetic chemists towards *N*-heterocyles has increased over the years. Thus, being a skeleton for a number of biologically active compounds, the benzo-fused heterocycles have drawn the attention of synthetic chemists and the medicinal chemists alike [1,2]. An important member of such heterocycles is benzopyran or chromene moiety which is a bi-cyclic organic compound which originates from the fusion between a benzene ring and a pyran ring [3–5]. This valuable heterocycle is available in various levels of saturation and oxidation synthetically as well as naturally and a huge variety of work is reported in the literature on the said moiety [6–10]. The activities of chromenes also include anti-cancer [11a-c], anti-HIV [12] apart from anti-microbial [13] and anti-fungal [14] activities. Various approaches have been made so far to prepare suitably functionalized derivatives of −2H and −4H and −6H chromenes following metal catalyzed as well as metal-free protocols [15a-e]. In recent times, it is common practice among the synthetic chemists to develop conditions that eliminates the use of metals to avoid its toxicity. Hypervalent iodine reagents, therefore, are quite favorable in the context of metal-free approach by virtue of its eco-friendly nature and unique reactivity. For example, a very interesting methodology has been developed by *Ahmad et al.*, [16] where by the use of Koser's reagent; a suitable functionalization on certain chosen benzopyran moieties has been made possible along with directed ring contraction in some cases. Another report by Liu [17] and his group showcases the versatility of the hypervalent reagent in the formation of 3-arylquinolin-2-ones. There are many other roles the hypervalent iodine plays like oxidation of alcohols in water and transformation of a huge range of interesting organic molecules by c-c bond formation. However, in our report we have investigated further the role the hypervalent reagent can play on benzopyran moiety so as to transform it into some novel organic molecule that might further broaden the scope of its application in medicinal field. Our work here is inspired from an earlier work reported by *Mandha et al.* [18] who had reported of an unusual and quite an interesting migration of an amine, which we have noticed, can be utilized in formation of a very stable cyclic imine in one-pot to give rise to a hexahydropyrano[3,4–b]pyrrole system (Fig. 1) which is quite hard-accessible part of any compound.

In our study, we were initially curious to know if the migration depicted by *Mandha et al.* [18] is possible in our type of chromenes which was a little different from their moiety structurally. So, we followed the exact protocol given by them. In ethanol medium, equivalent amount of iodobenzene di-acetate and our chromene derivatives were dissolved together and left to stir at room temperature for 20 min. A new spot generated in TLC and then it was isolated and characterized by NMR. In the ^{1}H NMR spectra, we found that the protons corresponding to the amine which was subjected to migration were missing. Further, upon performing ^{13}C NMR, it

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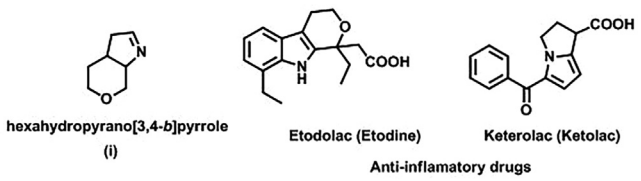
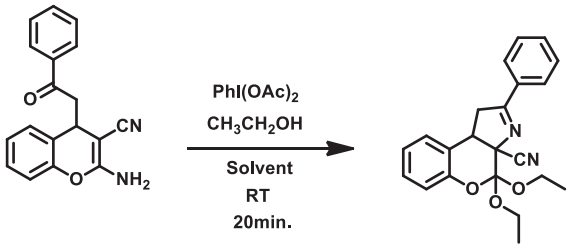


Fig. 1. Some marketed *N*-heterocycle containing anti-inflammatory drugs analogous with our synthesized motif (i).

was found that the peak corresponding to the carbonyl carbon initially present in our chromenes shifted from 190 to 170, clearly suggesting that the carbonyl carbon has transformed itself into an imine carbon by virtue of being in close proximity with the migrated amine. As a result, a new 5-membered ring must have formed as per the most probable mechanism. Our assumption was corroborated by ^{13}C-DEPT (135) NMR, for example, in case of compound (1), at δ (ppm) 45.29, the –'C—H' and at δ (ppm) 44.18 the –'CH_2' carbon of the newly formed five member ring went 'Up' and 'Down' respectively. And, obviously the Carbon at around δ (ppm) 170 went missing. The proton NMR and the mass value obtained are also in accordance with our proposed structure. In the proton NMR of compound (1) shows 9 protons in the aromatic zone from δ 7.88 ppm to δ 6.95 ppm at 400 MHz. The proton at the ring junction adjacent to cyanide (–CN) and protons adjacent to the newly formed imine bond appears at δ 4.25–4.19, δ 4.12 and δ 3.19 as three 1H areas respectively. We get another two set (one pair) of −2H and 3H areas at the aliphatic region for two ethyl groups from alcohol as expected from our proposed structure.

Our observation was in accordance with the mass value obtained. Therefore, we went on to optimize the reaction condition (Table 1). The reaction can be actually performed in different solvents apart from ethanol provided there is sufficient amount of ethanol present to maintain the stoichiometry. We found that a 4:1 ratio i.e. 20% ethanol must be present to convert 0.5 mmol of chromenes into the cyclized product. However, in DCM, the yield was 70% and in THF it reduced to 54% and in DCE it was around 60% while in acetonitrile it again reduced to 50%. In water, the reaction doesn't yield any product at all. The best result was obtained in only ethanol medium with the yield going up to 100% if the ethanol was super dried over magnesium under reflux for several hours after keeping over lime (CaO) overnight. Even in moderately dry ethanol, that is, only dried over CaO (lime) overnight, the yield is not below a quite satisfactory value of 90%. Therefore we carried out our reactions in moderately dry ethanol and other alcohols wherever used to avoid the cumbersome process of drying the alcohols and avoiding wastage of time. The other solvents used for optimization are of technical grade. We prepared the chromene derivatives from chalcones using Malonitrile (1 equiv.) and $NaHCO_3$ as base at RT [1]. Completion of the reaction was checked by TLC. We have synthesized 20 examples to study the substrate scope for the reaction. Apart from ethanol, the reaction was carried out in methanol and butanol as well. However, we have noticed that in butanol the yield decreases compared to ethanol (Fig. 2).

Table 1
Optimization of the reaction condition.



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Entry	Solvent	Vol. of Solvent (ml)	Vol. of R-OH (ml)	Yield[a] %
1	DCM	4	1	70
2	DCM	4	0.5	52
3	DCM	4	1.5	70
4	DCM	4	0	0
5	DCE	5	1	62
6	CH_3CN	4	1	50
7	H_2O	5	2	0
8.	H_2O	5	0	0
9.	THF	4	1	54
10	EtOH	5	0	90

[a] isolated yield after column chromatography.

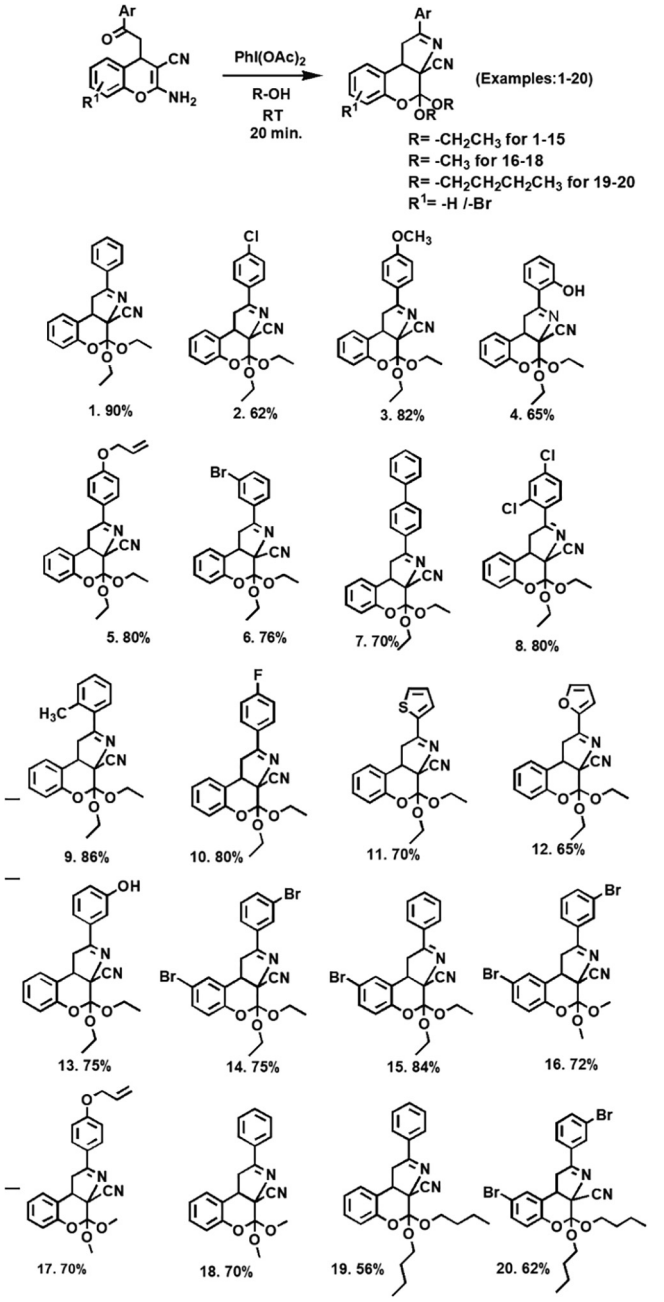

Fig. 2. Substrate scope study for the synthesis of the chromeno-pyrrole derivatives.

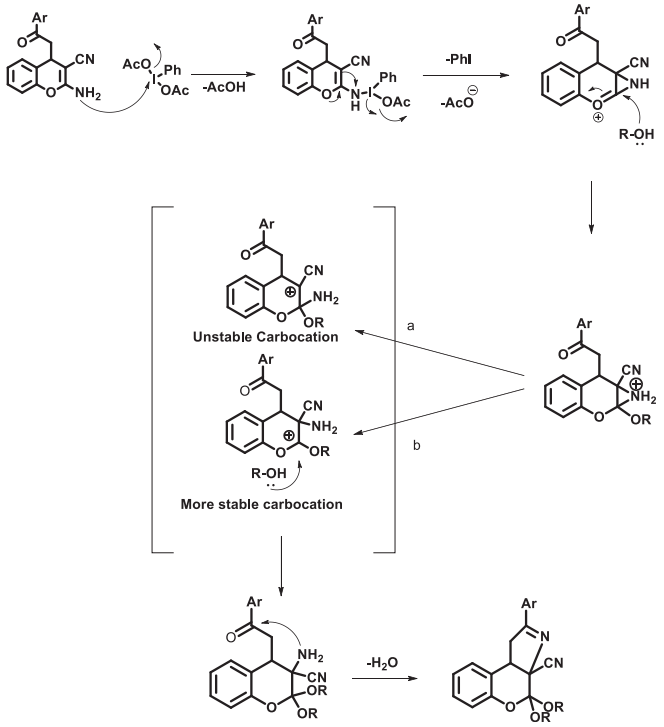

Fig. 3. Plausible mechanism for the cyclic product formation.

The product isolated is very stable and doesn't decompose easily and can stand heat also. We checked the substrate scope by varying the substituent on the aromatic rings present in the initial chromenes and by changing the aromatic system adjacent to the carbonyl group. Apart from non hetero aromatic system some hetero cyclic systems like thiophene or furan rings have been incorporated. In all the cases, we obtained good to satisfactorily reasonable yield. The insertion of a thiophene ring or a furan ring didn't cause any remarkable variation in the percentage of yield. However, as for the alcohol part, ethanol and methanol medium based reactions gave the best yields while in case of butanol, the yield dropped a little, the reason for it might be the difficulty of drying the solvent due to its high boiling point. Some steric factors may also be involved due to its higher chain length. The use of alcohol as reaction medium is also preferred over other solvents because it is convenient to deal with a uniform solution rather than a mixture of two. Solvents with higher water content results in generation of a side impurity which reduces the yield as water gives competition to alcohol as a nucleophile to attack at the intermediate stages. The plausible mechanism is predicted to go through the product of the previous work by *Mandha et al.* [18] *Mukherjee et al.* also supports the formation of aziridium intermediate [19]. Further formation of imine bond is the next obvious step to follow. The route 'a' produces the unstable intermediate and route 'b' produces the more stable intermediate which ultimately leads to product. The mechanism is described in Fig. 3.

Therefore, a new type of heterocycle has been developed by smartly utilizing the nucleophilicity of an amine towards a strategically placed electrophilic carbonyl carbon centre. This new motif can have some useful biological activity. The synthesis of target heterocycles by our method [20] doesn't involve any drastic conditions, besides having a reasonably wide substrate scope. The reaction requires very short time at room temperature and it doesn't even require a high-level purification of the alcohols.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2020.152355.

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[20] (a) General procedure for the synthesis of tetrahydrochromeno [3,4-b] pyrroles (for details see figure 2): chromenes (1mmol) were dissolved in desired alcohol and stirred at room temperature for 20 min. in presence of iodobenzene di-acetate (1mmol). The completion of the reaction was checked by TLC followed by removal of the alcohol under vacuum. The crude mixture thus obtained was subjected to column chromatography with a mixture of pet-ether and ethyl acetate as eluent.(b) Analytical and spectroscopic data of a representative compound 4,4-diethoxy-2-phenyl-1,3a,4,9b-tetrahydrochromeno [3,4-b] pyrrole-3a-carbonitrile (1) :Rf = 0.6 in (9:1) pet-ether-Ethyl acetate. Mp 86°C-90°C.IR (KBr): vmax (cm-1) 3423, 3060, 2977, 2931, 2904, 2242, 1920, 1824, 1605 1H- NMR (400 MHz, CDCl3) δ 7.88-7.86 (m, 2H, ArH),7.52-7.48 (m, 1H, ArH), 7.45-7.41 (m, 2H, ArH), 7.20-7.17(m, 2H, ArH), 7.06-7.03 (m, 1H, ArH), 6.98-6.95 (m, 1H, ArH), 4.25-4.19 (m, 1H), 4.12 (dd, 1H, J=8.8 Hz, 6.4Hz), 3.91-3.84 (m, 2H), 3.74-3.65 (m, 2H), 3.19 (dd, 1H, J=16.4Hz, 6.4Hz), 1.26 (t, 3H, J=7.2Hz), 1.04 (t, 3H, J=7.2Hz) 13C-NMR (100 MHz, CDCl3) δ 178.7(C), 150.1(C), 132.9(C), 131.9(CH), 128.62(CH), 128.3(CH), 123.7(C), 123.1(CH), 118.9(C), 117.9(CH), 110.7(C), 76.7(C), 60.0(CH2), 59.4 (CH2), 45.3(CH), 44.2(CH2), 15.2(CH3), 15.0(CH3) HRMS: m/z [M+Na]+ calcd. for C22H22N2O3: 385.1523.Found: 385.1520.