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# Michael addition of α-azido ketones on iminocoumarin derivatives: an efficient access to new functionalized azido chromenes

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ABSTRACT

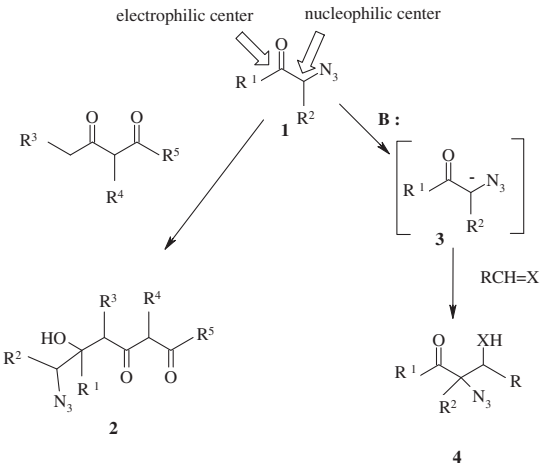
A facile one-pot synthesis of functionalized azido chromenes was achieved by Michael addition of α-azido ketones on iminocoumarin derivatives obtained from salicylaldehydes and malononitrile. Synthesized azido chromenes were successfully transformed into triazolyl chromenes by the [3+2] cycloaddition reaction.



α-Azido ketones **1** are a synthetically valuable group of azides that exhibit double reactivity in C–C bond formation. The electrophilic carbonyl function provides a target for the attack of carbanions leading to adducts such as compounds **2** and the chemistry has been utilized by Langer et al.[1] (Scheme 1). On the other hand, α-azido ketones possessing an α-hydrogen show enhanced C–H acidity due to the anion stabilizing effect of the azido group. The controlled generation of carbanions **3** followed by trapping with various carbon electrophiles results in the formation of aldol-type products **4** (Scheme 1).

α-Azido ketones represent useful precursors of the synthetically important 1,2-amino alcohols,[2] 2-azido alcohols,[3] α-amino ketones[4] by the reduction process. The reaction of phenacyl azides with trivalent phosphorous compounds (phosphines, phosphites, etc.) leads to iminophosphoranes which upon hydrolysis provides amines.[5] Addition of carbanion of α-azidoacetophenone to highly stabilized Michael acceptors, such as methyl 2-arylidenecyanoacetate, 2-arylidene-2-cyanoacetophenone, or 2-arylidenemalononitrile was reported to give polysubstituted pyrroles via the attack of the carbanion to electron-deficient C-β carbon of the Michael acceptor followed by deprotonation-induced formation of an imino anion by loss of nitrogen. Finally, an intramolecular nucleophilic addition to the ester, ketone, or cyano function leads to pyrroles.[6] Although α-azidoketones are widely employed in reduction, oxidation reactions, but their applicability as nucleophilic species in multicomponent reactions to synthesize heterocycles has not been explored to any great extent. As part of our program aimed at developing new methods for the preparation of heterocyclic compounds in one-pot, multicomponent reactions,[7] we report an efficient and simple synthesis of highly functionalized azido chromene derivatives.

2-Aminochromenes are employed as pigments,[8] cosmetics, agrochemicals,[9] and are major constituents of many natural products. In continuation of our work involving three component reaction of salicylaldehydes, malononitrile and various other nucleophiles,[10] we herein introduce phenacyl azides as new nucleophiles in these three-component reactions.




**Scheme 1.** Reactivity of α-azido ketones in C–C bond formation reactions.

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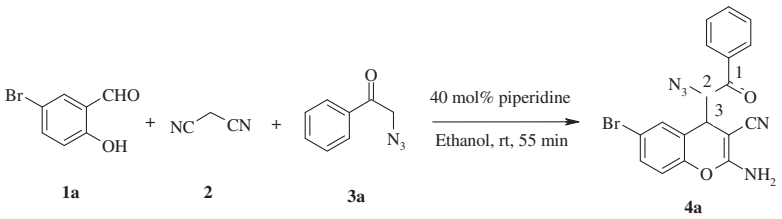


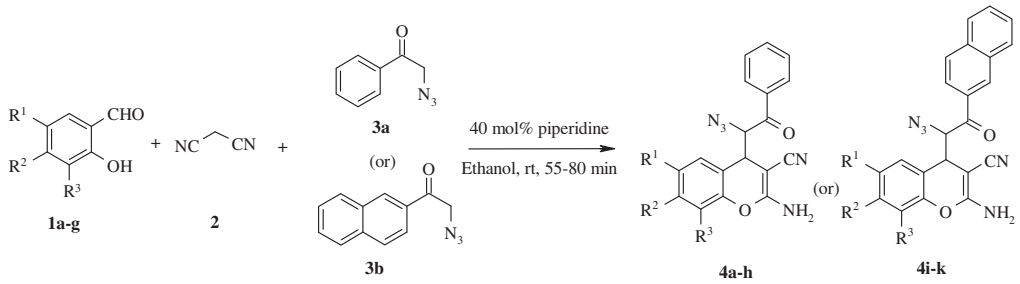

**Scheme 2.**

We commenced our study by the addition of phenacyl azide **3a** to iminocoumarin derivative obtained from the reaction of salicylaldehyde **1a** and malononitrile **2**, in ethanol in the presence of an equivalent amount of piperidine at room temperature. The reaction went to completion within 30 min and resulted in the formation of azido chromene **4a** in 67% yield as a mixture of *syn* and *anti* isomers in the ratio of 77:23, as determined by crude $^1$H NMR analysis. When we carried out the reaction by employing a catalytic amount of piperidine, the reaction was clean affording product **4a** in 85% yield as a mixture of *syn* and *anti* isomers in the ratio of 88:12 with the preference of *syn* diastereoselectivity and took 55 min for the completion of the reaction. Column chromatography afforded a diastereomerically pure *syn*-**4a** isomer (Scheme 2). Assignment of *syn* and *anti* isomers was done by comparison with the previous literature data.[11] In $^1$H NMR, the *syn* isomer showed signal for H-2 hydrogen at higher field $\delta = 5.07$ ppm with $J = 3.8$ Hz, whereas for the *anti* isomer H-2 resonated at lower field $\delta = 4.87$ ppm with $J = 5.35$ Hz. Further the *syn* stereochemistry of the compound **4c** has been confirmed using 1-D NOE experiment (see the Supplementary data). Selective irradiation of the $C_3$–H hydrogen effected the enhancement of the signals of $C_2$–H. Based on these diagnostic tools, we assigned the stereochemistry in the entire series of the compounds. The compound **4k** (Table 1, entry 11) was isolated as its diastereopure *syn* form. This may be attributed to the steric factors. Table 1 summarizes our results on the one-pot reaction of various salicylaldehydes and malononitrile with α-azido ketones.

Different salicylaldehydes either bearing electron-withdrawing groups (such as halide) or electron-donating groups (such as alkoxy group) gave expected products in good to high yields under the same reaction conditions.[18] As indicated in Table 1, 6-substituted azido chromenes exhibit *syn* selectivity as a preference, whereas in the case of 8-substituted azido chromenes, the *anti* diastereoselectivity was observed.

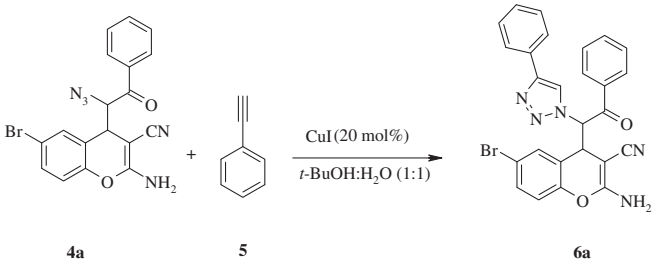
Nitrogen-containing heterocycles (azaheterocycles) occur in a wide variety of natural and biologically active compounds.[12] Although efficient methods for the synthesis of nitrogen-containing molecules merit further investigations, very little attention has been focused on the copper promoted C–N bond formation-based protocols.[13] Among them, undoubtedly, 'click reaction'[14] and in particular Huisgen [3+2] cycloaddition[15] has emerged as a 'near perfect' (very fast, selective, high-yield, and wide scope) carbon–nitrogen bond forming reaction toward the synthesis of N-substituted 1,2,3-triazoles. This process that occurs between organic azides and alkynes is significantly accelerated by Cu(I) catalysis,[16] and it offers easy access to the 1,4-disubstituted

**Table 1**
Three component synthesis of azido chromenes




| Entry | $R^1$ | $R^2$ | $R^3$ | Azido ketone | Product | Time (m) | Yield[a,b] (%) | *syn*/*anti*[c] |
|---|---|---|---|---|---|---|---|---|
| 1 | Br | H | H | **3a** | **4a** | 55 | 85 | 88:12 |
| 2 | Cl | H | H | **3a** | **4b** | 60 | 81 | 68:32 |
| 3 | H | H | OCH3 | **3a** | **4c** | 75 | 79 | 40:60 |
| 4 | H | H | $OCH_2CH_3$ | **3a** | **4d** | 70 | 75 | 41:59 |
| 3 | H | H | H | **3a** | **4e** | 63 | 83 | 48:52 |
| 6 | Br | H | Br | **3a** | **4f** | 80 | 73 | 47:53 |
| 7 | I | H | I | **3a** | **4g** | 85 | 69 | 49:51 |
| 8 | H | $OCH_3$ | H | **3a** | **4h** | 80 | 80 | 26:74 |
| 9 | H | H | H | **3b** | **4i** | 75 | 84 | 50:50 |
| 10 | H | H | $OCH_3$ | **3b** | **4j** | 72 | 77 | 48:52 |
| 11 | Br | H | H | **3b** | **4k** | 63 | 82 | 100:0 |

[a] Yield of the isolated purified compounds **4a**–**k**.
[b] Conditions: salicylaldehyde (1 mmol), malononitrile (1 mmol), azido ketone (1.5 mmol), piperidine (40 mol %).
[c] Determined by $^1$H NMR analysis.




4a 5 6a

**Scheme 3.**

isomer. To contribute in this area of research, here we report an interesting application of the 'click reaction' to α-azido chromenes with the aim to obtain new heterocyclic scaffolds. In this regard we attempted the [3+2] cycloaddition reaction between phenyl acetylene and the synthesized azido chromenes. As we are able to separate only *syn* isomers of the azido chromenes in diastereomerically pure form by repeated column chromatography, we employed only the *syn* isomers for the [3+2] cyclo addition reactions. In a typical experiment the *syn*-**4a** diastereomer is treated with phenyl acetylene in 1:1 mixture of *t*-BuOH and water with CuI as catalyst to afford expected 1,4-disubstituted 1,2,3-triazole derivative **6a** in 71% yield (Scheme 3) (Table 2, entry 1).[19] In an attempt to optimize the efficiency of this reaction, we have changed the ratio of the alkyne employed. It was observed that upon increasing the amount of phenyl acetylene no significant improvement of the yield was observed.

The product was confirmed by IR, $^1$H NMR and $^{13}$C NMR spectroscopy. In $^1$H NMR, triazolyl proton was resonated at $\delta$ 8.45 ppm and the peaks at $\delta$ 146.9 and 130.5 ppm correspond to the triazolic carbon atoms. The *syn* stereochemistry of compound **6c** has been assigned using 1-D NOE experiment. Further the regiochemistry and the absolute configuration of the triazolyl chromene **6c** are additionally confirmed by the impure (iminocoumarin part can be seen in the structure) single crystal X-ray structure as depicted in the ORTEP diagram (Fig. 1).[17]

To explore the generality of the reaction, we have also tried the reaction with aliphatic alkyne such as propargyl alcohol, but the product was not able to be isolated due to decomposition during column chromatography. Moreover, as expected, disubstituted acetylene, such as diphenylacetylene and dimethyl acetylene dicarboxylate, did not react under these conditions.

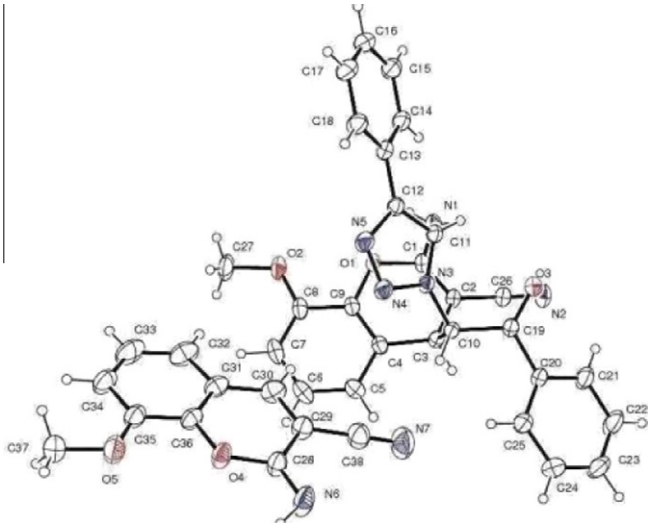
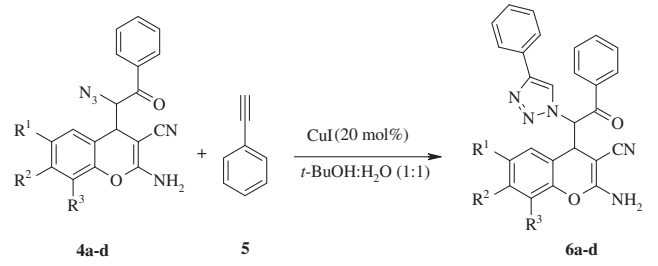


**Figure 1.** ORTEP diagram of compound **6c**.

In summary, to the best of our knowledge, this Letter represents the first report on the three component synthesis of azido chromenes by employing α-azido ketones as nucleophiles on iminocoumarin derivatives. The synthesized azido chromenes were successfully transformed into N-substituted 1,2,3-triazole derivatives by [3+2] cycloaddition with phenyl acetylene.

**Table 2**
Synthesis of triazolyl chromenes




4a-d 5 6a-d

| Entry | $R^1$ | $R^2$ | $R^3$ | Product[a] | Time (h) | Yield[a,b] (%) |
|---|---|---|---|---|---|---|
| 1 | Br | H | H | **6a** | 1.5 | 71 |
| 2 | Cl | H | H | **6b** | 1.7 | 68 |
| 3 | H | H | $OCH_3$ | **6c** | 2.0 | 61 |
| 4 | H | H | $OCH_2CH_3$ | **6d** | 2.1 | 63 |

[a] Yield of the isolated purified compounds **6a–d**.
[b] Conditions: *syn* azido chromene (1 mmol), phenyl acetylene (1 mmol), CuI (20 mol %), *t*-BuOH/$H_2O$ (1:1).


## Acknowledgment

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.05.101.

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17. Crystallographic data for compound **6c** in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplemental publication No. 821386 Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, deposit@ccdc.cam.ac.uk).
18. *General procedure for synthesis of azido chromenes* (**4a**–**k**): To a stirred solution of salicylaldehyde (1 mmol) and malononitrile (1 mmol) in ethanol (5 ml), was added piperidine (40 mol %) and allowed stirring until the formation of precipitate. To this formed precipitate, was added azido ketone (1.5 mmol) and stirring was continued for the specified time. The progress of the reaction was monitored by thin layer chromatography using ethyl acetate: pet ether (3: 7) as an eluent. After the specified reaction time the ethanol was removed under vacuo and the crude product was purified by flash chromatography on silica gel (neutralized with five drops triethyl amine) (petroleum ether–ethyl acetate, 90/10–75/25).

*Spectral data of compound syn-***4b:** 2-amino-4-(1-azido-2-oxo-2-phenylethyl)-6-chloro-4*H*-chromene-3-carbonitrile; white puffy solid, mp 128–130 °C; (30% AcOEt/petroleum ether); IR (KBr): 3431, 3315, 3192, 2185, 2105, 1650, 1417, 1228, 691 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 4.19 (d, $J$ = 3.8 Hz, 1H), 4.92 (s, 2H, $D_2O$ exchangeable), 5.01 (d, $J$ = 3.8 Hz, 1H), 6.80 (s, 1H), 6.95 (d, $J$ = 8.4 Hz, 1H), 7.22 (dd, $J$ = 2.3, 6.1 Hz, 1H), 7.57 (t, $J$ = 7.65 Hz, 2H), 7.67 (t, $J$ = 6.85 Hz, 1H), 7.98 (d, $J$ = 7.6 Hz, 2H).; $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ 38.9, 55.0, 69.2, 117.8, 119.0, 119.5, 128.3, 128.6 (2), 129.3 (2), 129.4, 129.9, 134.3, 134.6, 148.9, 162.1, 194.2.

19. *General procedure for the synthesis of triazolyl chromenes* (**6a**–**d**): To a to stirred suspension of phenyl acetylene (1 mmol) and CuI (20 mol %) in *t*-BuOH/$H_2O$ (1:1) (10 ml), was added, azido chromene and continued stirring until the specified time. After the reaction was complete as indicated by thin layer chromatography the reaction content was filtered through the bed of Celite to remove the CuI and the filtrate was diluted with water (30 ml) and extracted with ethyl acetate (3 × 15 mL). The organic layers were then combined, dried ($Na_2SO_4$), filtered and concentrated under vacuum to provide crude product which was purified by column chromatography on silica gel (neutralized with five drops of $NEt_3$) (petroleum ether–ethyl acetate, 85/15–50/50).

*Spectral data of compound* **6b:** 2-amino-6-chloro-4-(2-oxo-2-phenyl-1-(4-phenyl-1*H*-1,2,3-triazol-1-yl)ethyl)-4*H*-chromene-3-carbonitrile; off white solid, mp 162–164 °C (35%) AcOEt/petroleum ether); IR (KBr): 3475, 3352, 3138, 2195, 1645, 1414, 1244, 691 $cm^{-1}$; $^1H$ NMR (500 MHz, DMSO-$d_6$): $\delta$ 4.55 (d, $J$ = 5.35 Hz, 1H), 6.04 (s, 2H, $D_2O$ exchangeable), 6.53 (d, $J$ = 5.35 Hz, 1H), 6.83 (d, $J$ = 9.2 Hz, 1H), 7.16 (d, $J$ = 9.15 Hz, 1H), 7.22 (s, 1H), 7.32 (t, $J$ = 7.6 Hz, 1H), 7.41 (t, $J$ = 7.65 Hz, 2H), 7.51 (t, $J$ = 7.65 Hz, 2H), 7.63 (t, $J$ = 6.9 Hz, 1H), 7.85 (d, $J$ = 7.65 Hz, 2H), 8.00 (d, $J$ = 7.65 Hz, 2H), 8.33 (s, 1H); $^{13}C$ NMR (125 MHz, DMSO-$d_6$): $\delta$ 50.8, 68.5, 117.9, 119.1, 120.6, 121.0, 125.7 (2), 128.1, 128.3, 128.7 (2), 128.8 (2), 129.1 (2), 129.2 (2), 130.0, 130.5, 134.5, 134.7, 147.7, 148.8, 163.1, 192.9.