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Synthesis of 4-aryl-3-methyl-6-oxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*b*]-pyridine-5-carbonitrile via a one-pot, three-component reaction

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ABSTRACT

A one-pot, three-component condensation reaction of an aldehyde, 3-amino-5-methylpyrazole and ethyl cyanoacetate in ethanol to give 4-aryl-3-methyl-6-oxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitriles, in high yields, at reflux, using a catalytic amount of *p*-toluenesulfonic acid, is described.

Multi-component condensation reactions (MCRs) occupy an advantageous position because of high atom economy, their convergent character and simple procedures. Therefore, the development of novel MCRs are of interest for chemists.[1]

Pyrazolo[3,4-*b*]pyridines and pyrazolo[1,5-*a*]pyrimidine are examples of condensed heterocycles, and are attractive compounds for drug discovery since many of such scaffolds exhibit a wide range of biological and pharmaceutical activities. These include hypotensives, vasodilators, anti-inflammatories, analgesics and antipyretics,[2] inhibitors of xanthine oxidases,[3] B-Raf kinase,[4] cSRC kinase,[5] cyclin dependent kinase[6] and HIV reverse transcriptase,[7] anti-tumor and anti-proliferative agents,[8] anxiolytics,[9] as well as compounds for the treatment of Alzheimer's disease, gastrointestinal diseases, anorexia nervosa, drug and alcohol withdrawal symptoms, drug addiction and infertility.[10] The development of simple synthetic methods for these derivatives is therefore important in organic synthesis.

A literature survey revealed that although a number of methods have been reported for the synthesis of pyrazolo[3,4-*b*]pyridines,[11] so far, none have dealt with the synthesis of 6-oxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*b*]pyridines. In this Letter, a multi-component procedure for the synthesis of these compounds is described.

Arising from our studies of syntheses based on aminoazole MCRs,[12] herein we report the synthesis of 4-aryl-6-oxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitriles[13] **4** via a one-pot, three-component condensation reaction of an aldehyde **1** and 3-amino-5-methylpyrazole (**2**) in the presence of ethyl cyanoacetate (**3**) under reflux conditions in ethanol using *p*-toluenesulfonic acid (*p*-TsOH) as the catalyst (Scheme 1).

Initial studies to optimize the reaction conditions indicated that the best solvent for this reaction was ethanol with heating at reflux temperature.

To explore the scope and limitations of this reaction, we extended it to various substituted benzaldehydes. As shown in Table 1, the reaction proceeds efficiently with electron-withdrawing and electron-releasing substituted benzaldehydes.

The structures of products **4a–h** were deduced from their IR, ^{1}H NMR, ^{13}C NMR and mass spectra and by elemental analysis.

The ^{1}H NMR spectra of the products indicated the formation of two diastereoisomers (*cis* and *trans*) (Scheme 2). The ^{1}H NMR spectrum of a mixture of *cis*- and *trans*-**4b** is presented in Figure 1. Benzaldehydes with electron-releasing substituents tended to give slightly better yields and to produce a slightly higher ratio of *cis* to *trans* products (Table 1, entries 1–7). The *trans* isomer of **4h** predominated probably due to increased steric hindrance (Table 1, entry 8).

Another interesting feature of this reaction was revealed when ethyl acetoacetate and ethyl cyanoacetate were simultaneously added to a reaction mixture of *p*-methylbenzaldehyde and aminopyrazole. It was found that only ethyl cyanoacetate participated in the condensation reaction (Scheme 3). Using ethyl acetoacetate instead of ethyl cyanoacetate resulted in the formation of three products as presented in Scheme 4.

There are no established mechanisms for the formation of 6-oxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*b*]pyridines; a reasonable possibility is shown in Scheme 5. The reaction presumably proceeds via initial reaction between *p*-TsOH and the 3-aminopyrazole (**2**) to give the 3-aminopyrazolium salt **8**. Next, Michael addition of this compound to benzylidene compound **9**, itself produced by Knoevenagel condensation of aldehyde **1** and ethyl cyanoacetate (**3**) gives intermediate **10**. Elimination of one proton from the iminum group results in compound **11**. Subsequent cyclization of **11** results in condensed ring system **12**. Finally, compound **12** undergoes tautomerism to produce the 6-oxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*b*]pyridines **4** (Scheme 5).

To sum up, a novel and efficient three-component condensation reaction of an aldehyde, 3-amino-5-methylpyrazole and ethyl cyanoacetate has been developed for the synthesis of

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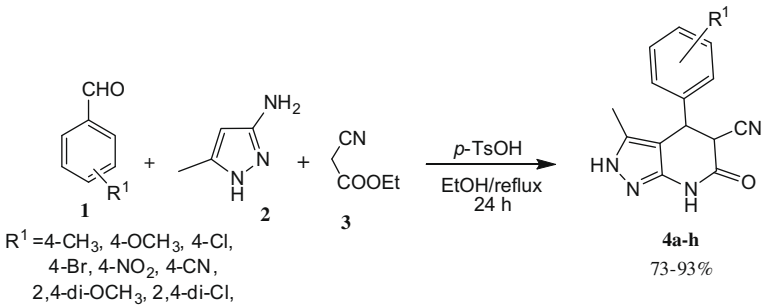
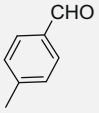
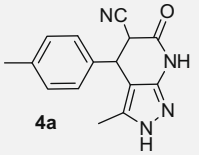
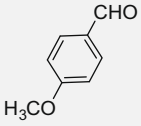
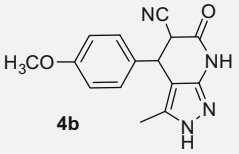
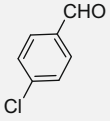
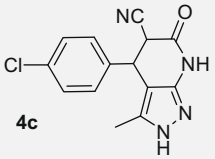
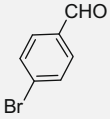
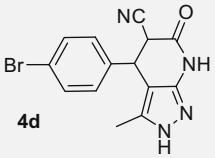
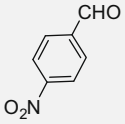
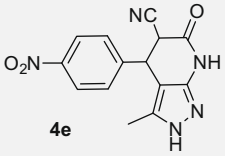
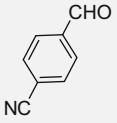
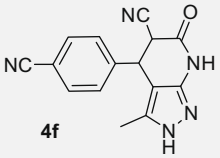
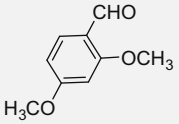
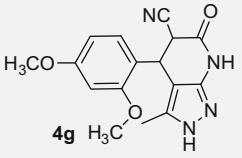
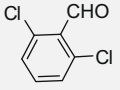
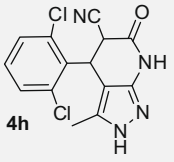
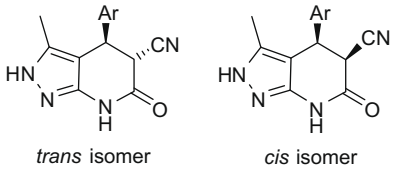


Scheme 1. Synthesis of 4-aryl-3-methyl-6-oxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitriles **4**.

Table 1
Synthesis of 4-aryl-3-methyl-6-oxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitriles **4**

Entry	Aldehyde	Product	Yield	*trans*:*cis* ratio	Mp (°C)
1		 **4a**	84	60/40	315–318
2		 **4b**	92	60/40	323–325
3		 **4c**	84	57/43	342–343
4		 **4d**	82	58/42	336–339
5		 **4e**	75	55/45	327–328
6		 **4f**	78	57/43	344–345
7		 **4g**	93	49/51	335–336
8		 **4h**	73	68/32	339–342



Scheme 2. The *cis* and *trans* isomers of 4-aryl-3-methyl-6-oxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitriles **4**.

4-aryl-3-methyl-6-oxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*b*]pyridines. The simple one-pot nature of the reaction makes it an interesting alternative to other multi-step approaches.

Representative data: 3-Methyl-6-oxo-4-p-tolyl-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-b]pyridine-5-carbonitrile (**4a**): White powder (84%); IR (KBr) cm^{-1}: 3579, 3395, 2780, 2244, 1703, 1539; MS (EI, 70 eV): *m/z* (%): 266 (M^+, 100), 251 (90), 239 (45), 224 (60), 198 (90). Anal. Calcd for $C_{15}H_{14}N_4O$: C, 67.65; H, 5.30; N, 21.04. Found: C, 68.01; H, 5.19; N, 21.53. (*trans* isomer) ^1H NMR (300 MHz, DMSO-d_6) δ: 1.45 (s, 3H, CH_3), 2.31 (s, 3H, CH_3), 4.39 (d, ^3J = 11.6 Hz, 1H, CH), 4.64 (d, ^3J = 11.7 Hz, 1H, CH), 7.21 (br s, 2H, $2CH_{arom}$), 7.25 (br s, 2H, $2CH_{arom}$), 10.95 (s, 1H, NH_{amide}), 11.97 (br s, 1H, $NH_{pyrazole}$) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ: 9.92, 21.18, 37.08, 44.00, 100.99, 117.69, 124.64, 129.78, 135.75, 136.41, 137.43, 147.62, 163.57 ppm. (*cis* isomer) ^1H NMR (300 MHz, DMSO-d_6) δ: 2.00 (s, 3H, CH_3), 2.25 (s, 3H, CH_3), 4.44 (d, ^3J = 5.5 Hz, 1H, CH), 4.85 (d, ^3J = 5.5 Hz, 1H, CH), 7.02 (d, ^3J = 6.5 Hz, 2H, $2CH_{arom}$), 7.12 (d, ^3J = 6.5 Hz, 2H, $2CH_{arom}$), 10.97 (s, 1H, NH_{amide}), 12.06 (br s, 1H, $NH_{pyrazole}$) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ: 9.53, 21.05, 37.08, 42.85, 101.92, 117.23, 127.54, 129.78, 135.36, 137.18, 137.52, 147.60, 163.35 ppm.

4-(4-Methoxyphenyl)-3-methyl-6-oxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-b]pyridine-5-carbonitrile (**4b**): White powder (92%); IR (KBr) cm^{-1}: 3563, 3043, 2244, 1694, 1640, 1535; MS (EI,

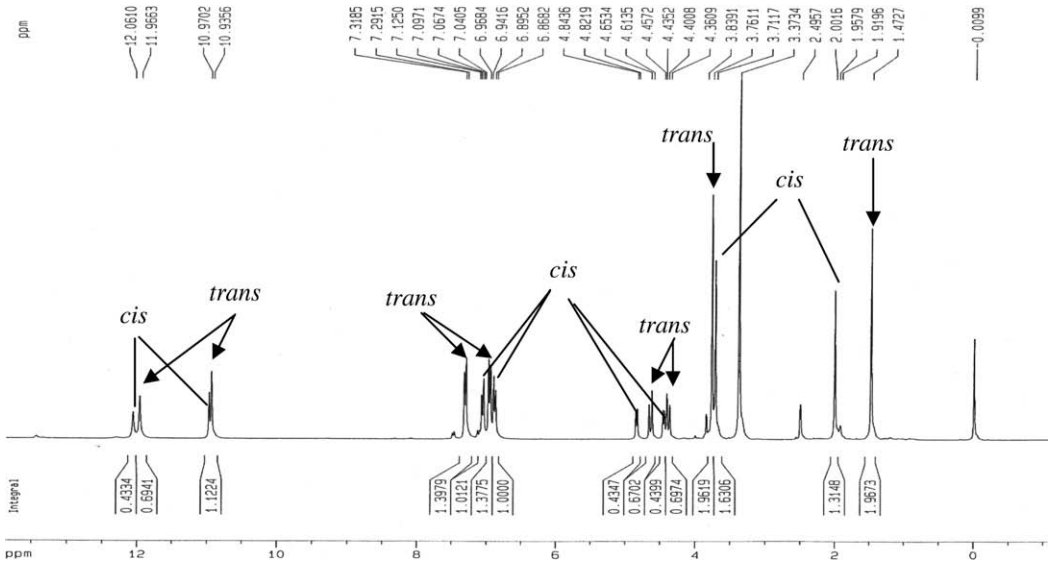
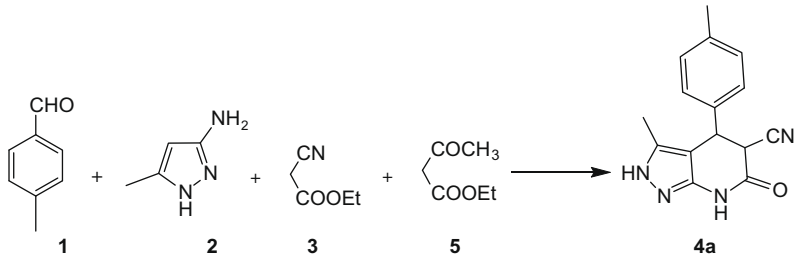
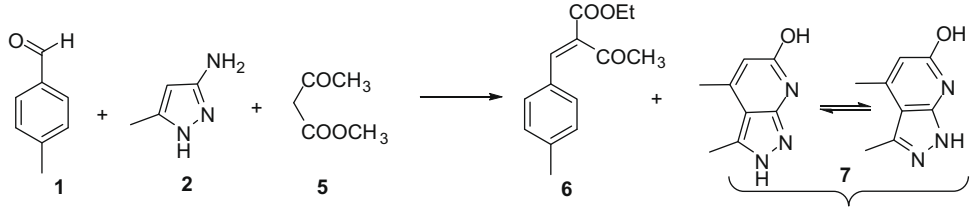


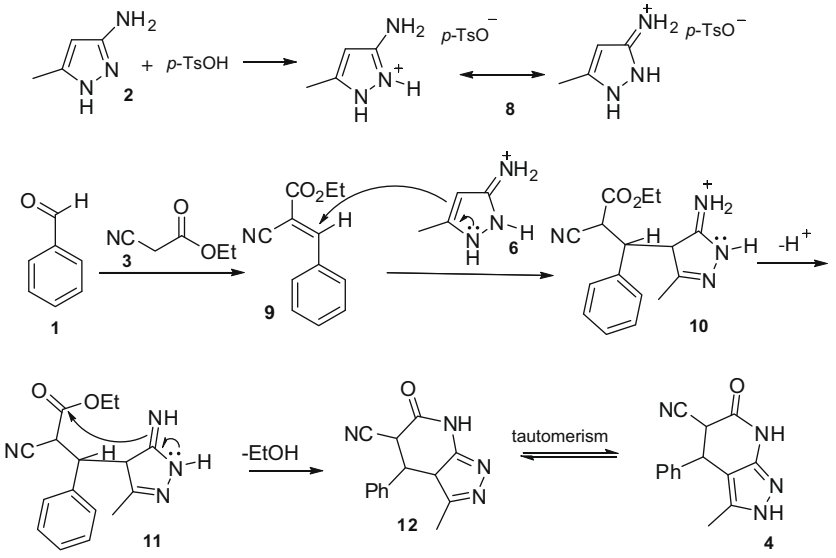
Figure 1. The ^1H NMR signals of the *cis* and *trans* isomers of 4-(4-methoxyphenyl)-3-methyl-6-oxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (**4b**).



Scheme 3.



Scheme 4.



Scheme 5.

70 eV): *m/z* (%): 282 (M^+, 100), 267 (15), 265 (17), 214 (20), 171 (15), 115 (25). Anal. Calcd for $C_{15}H_{14}N_4O_2$: C, 63.83; H, 5.00; N, 19.85. Found: C, 63.21; H, 4.73; N, 20.06. (*trans* isomer) ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.47 (s, 3H, CH_3), 3.83 (s, 3H, OCH_3), 4.38 (d, ^3J = 12.0 Hz, 1H, CH), 4.63 (d, ^3J = 12.0 Hz, 1H, CH), 6.95 (d, ^3J = 8.1 Hz, 2H, $2CH_{arom}$), 7.30 (d, ^3J = 8.1 Hz, 2H, $2CH_{arom}$), 10.93 (s, 1H, NH_{amide}), 11.97 (br s, 1H, $NH_{pyrazole}$) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ: 9.92, 36.68, 44.16, 55.52, 101.22, 114.51, 117.72, 129.86, 131.24, 135.75, 147.61, 159.18, 163.62 ppm. (*cis* isomer) ^{1}H NMR (300 MHz, DMSO-d_6) δ: 2.00 (s, 3H, CH_3), 3.71 (s, 3H, CH_3), 4.45 (d, ^3J = 6.6 Hz, 1H, CH), 4.83 (d, ^3J = 6.5 Hz, 1H, CH), 6.88 (d, ^3J = 8.1 Hz, 2H, $2CH_{arom}$), 7.05 (d, ^3J = 8.1 Hz, 2H, $2CH_{arom}$), 10.97 (s, 1H, NH_{amide}), 12.06 (br s, 1H, $NH_{pyrazole}$) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ: 9.53, 36.68, 43.01, 55.47, 102.07, 114.51, 117.27, 128.82, 132.38, 135.27, 147.61, 159.00, 163.34 ppm.

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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.2010.03.109.

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13. *General procedure for the synthesis of 4-aryl-3-methyl-6-oxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-b]pyridine-5-carbonitriles* **4a–h**: A solution of ethyl cyanoacetate (1 mmol), aldehyde (1 mmol), 3-amino-5-methylpyrazole (1 mmol) and *p*-TsOH (0.1 mmol) was heated at reflux in EtOH (10 ml) for 24 h. After completion of the reaction as indicated by TLC (EtOAc/*n*-hexene, 1:2), the reaction mixture was allowed to cool. The solvent was removed by evaporation and the residue was washed with H_2O (2×20 ml). The solid product recrystallized slowly from EtOH after 1–2 d.