International Journal of Modern Agriculture, Volume 9, No. 4, 2020
ISSN: 2305-7246

A ONE-POT DOMINO PROTOCOL FOR THE SYNTHESIS OF PYRAZINE AMINE

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Abstract

A green and efficient synthetic protocol has been developed for the synthesis of pyrazolo[3,4-b]quinolin-5-ones A and B starting from 1,3-cyclohexanedione, DMF–DMA, 3-aminocrotononitrile and the appropriate arylhydrazines. Subsequently an exocyclic double bond has been introduced at C-6 position of A to obtain C, which can serve as a key intermediate for the construction of several heterocyclic hybrids. Further these pyrazolo[3,4-b]quinolin-5-ones C were investigated for their sensitivity against picric acid.

Pyrazoles are five member ring heterocyclic compounds, consisting of a doubly unsaturated five membered ring with two adjacent nitrogen atoms and are also called as azoles. These are aromatic molecules due to their planar conjugated ring structures with six delocalized π-electrons.1 The term pyrazole was given by Ludwig Knorr in 1883. Being so composed and having pharmacological effects on humans, they are classified as alkaloids, although they are rare in nature. In 1959, the first natural pyrazole, β-[1-pyrazolyl]alanine was isolated from the seeds of water melons [Citurllus lanatus].2 Literature survey has revealed that till 1930s very little had been done for the synthesis of steroidal pyrazole derivatives. Several pyrazole derivatives have been found to possess significant activities such as 5-α-reductase inhibitor,3 antiproliferative,4 antiparasitic5 and herbicides.6

Introduction

Pyrazolo[3,4-*b*]quinoline ring systems are privileged class of nitrogen containing heterocycles endowed with profound biological activities such as antiasthmatic,[7] antitumor[8] and anti-inflammatory agents.[9] Pyrazolo[3,4-*c*]isoquinolines (**Figure 1)** are benzannelated analogues of pyrazolo[3,4-*b*]pyridines, the chemical properties and biological activity of which have been extensively studied.[10] Further, 3-substituted pyrazolo[1,5-*a*]quinoline derivatives have been developed for dopamine D4 antagonist agents,[11] GPR109a agonist agents[12] and organic light-emitting devices.[13] However, besides these examples, the pyrazolo[1,5-*a*]quinoline subunit has not been applied to seek further biologically and materially active compounds, which might be due to the lack of general methods for the synthesis of pyrazolo[1,5-*a*]quinoline derivatives.

Subsequently, the pyrazolo[3,4-*b*]quinolin-5-ones **9**, **10** were synthesized *via* a one-pot three-component sequential procedure in water (**Scheme 2**). Firstly, 3-aminocrotononitrile **6** and the appropriate arylhydrazines **7** were refluxed in water for 1 hour in the presence of L-proline (40 mol%) to obtain 3-methyl-1-aryl-1*H*-5-pyrazolamines **8**. Then without isolating **8**, the previously synthesized **4** or **5** was added and the reflux continued for another 1 h, which resulted in quantitative yields of **9**. The formation of **9** presumably occurs *via* a similar pathway as depicted by Perumal and co-workers. Incidentally, carrying out organic transformations in environmentally benign solvents such as water has gained considerable impetus. Water is a green solvent and has several advantages such as non-hazardous, non-toxic, non-exhaustible and inexpensive. Furthermore, L-proline has emerged as one of the efficient and most utilized organocatalyst in synthetic organic chemistry.

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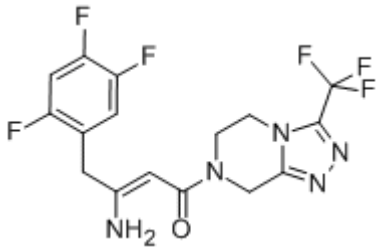

Entry	Comp	R^2	Yield (%)	m.p. (^oC)
1	**9a**	H	98 (87)[19]	123–124
2	**9b**	Cl	97	149–150
3	**9c**	Br	98	153–154
4	**9d**	F	96	165–166

Conclusions

A green and efficient synthetic protocol has been developed for the synthesis of pyrazolo[3,4-*b*]quinolin-5-ones. Subsequently novel 6-arylidene-pyrazolo[3,4-*b*]quinolin-5-ones have been synthesized using the above pyrazolo[3,4-*b*]quinolin-5-ones in quantitative yields.The structure of 6-arylidene-pyrazolo[3,4-*b*]quinolin-5-ones was elucidated using NMR techniques.

General procedure for the synthesis of 9

A mixture of 3-aminocrotononitrile **6** (1 mmol), arylhydrazine **7** (1 mmol) and L-proline (0.4 mmol) was taken in water (10 mL) and heated to reflux. After 1 hour of continuous reflux, 2-((dimethylamino)methylene)cyclohexane-1,3-dione **4** (1 mmol) was added and the reflux continued for another 1 hour. Upon addition of **4** the mixture turns homogeneous. The completion of the reaction was evident from the formation of precipitate, which was filtered, washed with water and dried under vacuum to afford pure **9**.

3-Methyl-1-phenyl-1,6,7,8-tetrahydro-5*H*-pyrazolo[3,4-*b*]quinolin-5-one (9a)

Pale yellow solid; Yield 98%; m.p. 100–101°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 2.24 (qui, *J* = 6.4 Hz, 2H), 2.66 (s, 3H), 2.77 (t, *J* = 6.5 Hz, 2H), 3.28 (t, *J* = 6.1 Hz, 2H), 7.31 (tt, *J* = 7.3, 1.2 Hz, 1H), 7.52 (t, *J* = 7.9 Hz, 2H), 8.28 (dd, *J* = 8.7, 1.2 Hz, 2H), 8.76 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 12.5, 22.0, 33.7, 38.8, 116.7, 120.9, 123.0, 125.9, 129.0, 130.4, 139.1, 145.1, 163.8, 197.5 ppm.

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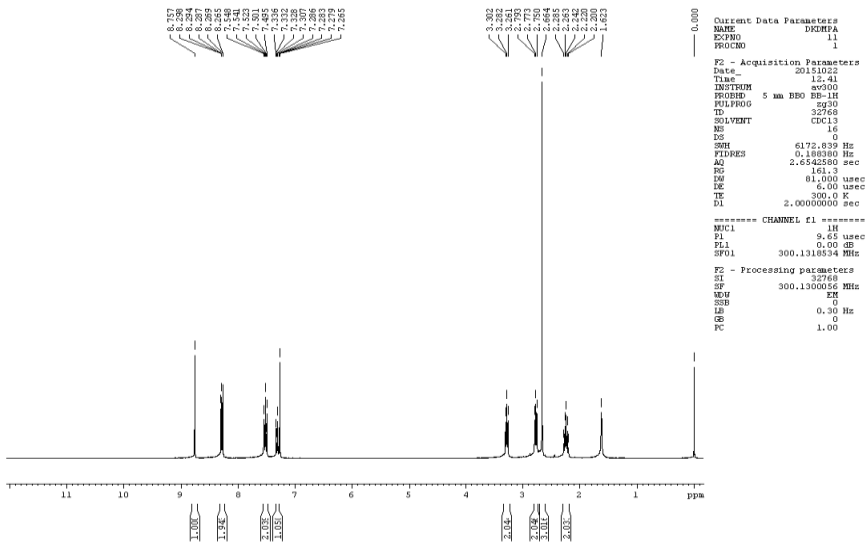

Figure 25. ^{1}H NMR spectrum of **9a**

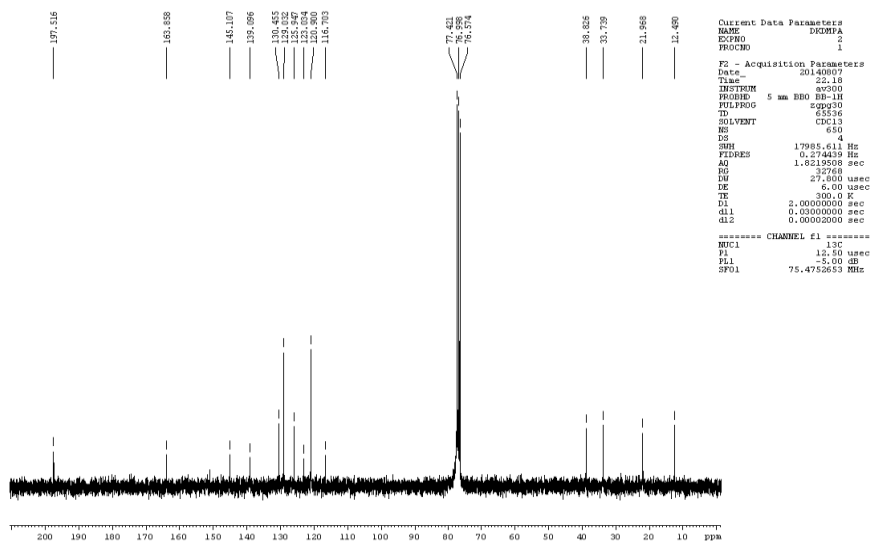

Figure 26. ^{13}C NMR spectrum of **9a**

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