Tetrahedron Letters 52 (2011) 6643–6645

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Multicomponent synthesis of 2,3-dihydrochromeno[4,3-*d*]pyrazolo[3,4-*b*]pyridine-1,6-diones: a novel heterocyclic scaffold with antibacterial activity

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ARTICLE INFO

Article history:
Received 6 September 2011
Revised 3 October 2011
Accepted 4 October 2011
Available online 12 October 2011

Keywords:
MCR
Aminopyrazole
Antibacterial activity
Benzopyranopyridines

ABSTRACT

A multicomponent reaction of 3-aminopyrazol-5-ones with substituted salicylic aldehydes and acetylacetic ester leading to the formation of novel 2,3-dihydrochromeno[4,3-*d*]pyrazolo[3,4-*b*]pyridine-1,6-diones was discovered. The elucidation of the reaction scope revealed that 5-aminopyrazoles, 3-amino-1,2,4-triazoles and 6-aminouracil could be used as the heterocyclic amine component. Selected heterocyclic products were found to possess notable antibacterial activities.

Multicomponent reactions (MCRs) are a powerful synthetic tool. In this approach, three or more reactants are combined together in a single reaction flask to generate a product incorporating most of the atoms contained in the starting materials. MCRs have been widely exploited in combinatorial and medicinal chemistry and they are particularly useful for the preparation of polycondensed heterocyclic systems.[1]

In this connection, hetero-fused benzopyranopyridines are a poorly studied class of polycondensed heterocycles (Fig. 1a). Only four types of scaffolds (**A** and **C**–**E**) have been reported in the literature out of the six possible molecular frameworks (**A**–**F**) and the synthetic approaches used by researchers to access these structures have invariably involved multistep sequences.[2–13] Importantly, compounds based on these heterocyclic systems have been reported to possess anti-inflammatory,[2] antibacterial[2,10], and antifungal[10] activities (Fig. 1b). As part of our efforts aimed at the discovery of MCRs to synthesize compounds with anti-cancer and -bacterial activities,[14–25] we discovered a new approach to access the type **C** molecular framework. Herein, we describe this synthetic finding as well as the preliminary biological evaluation of compounds synthesized using this new method.

Specifically, we found that combining 3-aminopyrazol-5-ones **1a–c** with substituted salicylic aldehydes **2a–h** and acetylacetic ester (**3**) leads to the formation of 2,3-dihydrochromeno[4,3-*d*]pyrazolo[3,4-*b*]pyridin-1,6-diones **4a–o** (Scheme 1). Generally good yields of these polyheterocyclic compounds are obtained when mixtures of the three starting components and one drop of piperidine are refluxed in acetic acid for 3 h. This three-component process works well in any tested combination of substituted salicylic aldehydes **2** and 3-aminopyrazol-5-ones **1**. The desired products precipitate upon cooling of the reaction mixtures and a simple filtration provides analytically pure material (>95%).[26]

We propose that the mechanistic route for this transformation involves an in situ formation of 3-acetylcoumarins **5** and their subsequent condensation with aminopyrazolones **1** (Scheme 2). Indeed, we demonstrated that this process can be conducted stepwise by condensing salicylic aldehyde (**2a**) with acetylacetic ester (**3**) and isolating 3-acetylcoumarin (**5a**) in a quantitative yield (Scheme 2a). Compound **5a** was further reacted with 3-amino-1*H*-pyrazol-5(4*H*)-one (**1a**) under the same reaction conditions and gave a comparable yield of polyheterocycle **4a** (Scheme 2b).

To investigate the scope of this process with respect to the acetylacetic ester component, we attempted to replace it with ethyl benzoylacetate. However, the reaction was unsuccessful in this case, possibly due to the change in electronic and steric environment of the ketone carbonyl. On the other hand, the replacement

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doi:10.1016/j.tetlet.2011.10.012

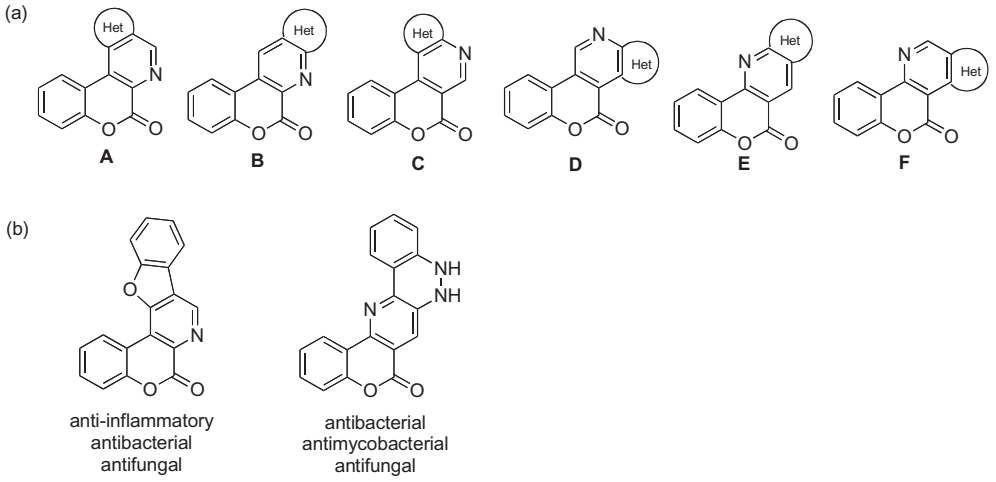
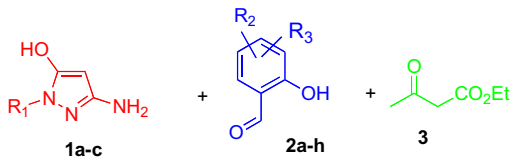


Figure 1. (a) Six possible types of hetero-fused benzopyranopyridines (b) and representative compounds with biological activities.

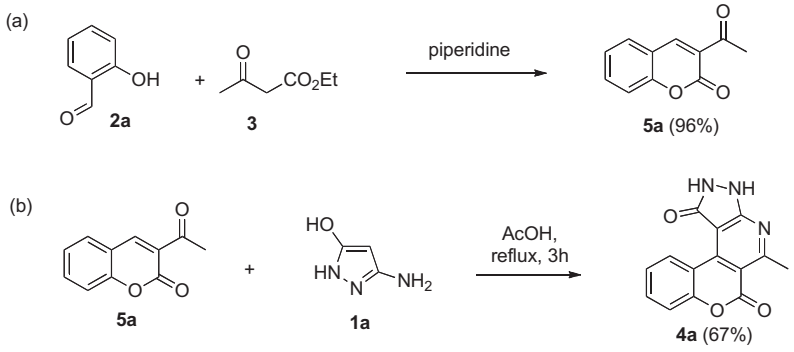


1a R_1 = H
1b R_1 = Ph
1c R_1 = 2,5-di-Cl-Ph

2a R_2 = R_3 = H
2b R_2 = 5-Br, R_3 = H
2c R_2 = 3-Cl, R_3 = 5-Cl
2d R_2 = 5-NO_2, R_3 = H
2e R_2 = 5-Cl, R_3 = H
2f R_2 = 5-Me, R_3 = H
2g R_2 = 3-OMe, R_3 = H
2h R_2 = 4-OH, R_3 = H

4a R_1 = R_2 = R_3 = H	60%
4b R_1 = R_3 = H, R_2 = 10-Br	67%
4c R_1 = R_3 = H, R_2 = 10-NO_2	77%
4d R_1 = R_3 = H, R_2 = 10-Cl	73%
4e R_1 = R_3 = H, R_2 = 8-MeO	63%
4f R_1 = R_3 = H, R_2 = 9-OH	53%
4g R_1 = Ph, R_2 = R_3 = H	70%
4h R_1 = Ph, R_2 = 10-Br, R_3 = H	74%
4i R_1 = Ph, R_2 = 8-Cl, R_3 = 10-Cl	82%
4j R_1 = Ph, R_2 = 10-NO_2, R_3 = H	79%
4k R_1 = Ph, R_2 = 10-Cl, R_3 = H	76%
4l R_1 = Ph, R_2 = 10-Me, R_3 = H	71%
4m R_1 = Ph, R_2 = 8-MeO, R_3 = H	64%
4n R_1 = 2,5-di-Cl-Ph, R_2 = 10-Me, R_3 = H	74%
4o R_1 = 2,5-di-Cl-Ph, R_2 = 8-MeO, R_3 = H	66%

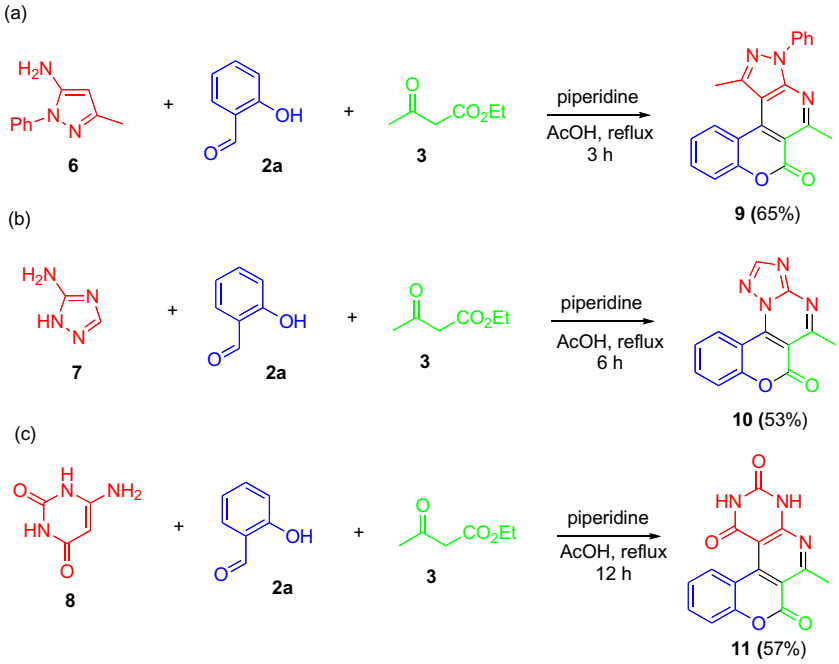
Scheme 1. MCR synthesis of 2,3-dihydrochromeno[4,3-*d*]pyrazolo[3,4-*b*]pyridin-1,6-diones **4a**–**o**.



Scheme 2. 3-Acetylcoumarins as intermediates in the discovered MCR.

of the aminoheterocyclic component was much more forgiving. Thus, we explored the corresponding reactions of 5-amino-1-phenyl-3-methylpyrazole (**6**), 3-amino-1,2,4-triazole (**7**), and 6-aminouracil (**8**, Scheme 3). The desired polyheterocycles **9**–**11** were obtained in acceptable yields, indicating the potential of this MCR to be used as a general method to access polyheterocyclic scaffolds **C** (see Fig. 1).[27]

The initial evaluation of the synthesized polyheterocycles for antimicrobial activities revealed significant antibacterial properties associated with several analogs specifically against Gram-(+)



Scheme 3. MCR synthesis of polyheterocycles **9**–**11**.

strains. Thus, compounds **4i** and **4o** inhibited the growth of *Staphylococcus epidermidis* with the MIC values of 6.3 and 25 μM, respectively. Furthermore, heterocycle **4i** was also effective against methicillin-resistant *Staphylococcus aureus* (MRSA), inhibiting the growth of this clinically important nosocomial pathogen with an MIC value of 25 μM. Further exploration of the MCR scope and antimicrobial activities associated with these novel heterocyclic structures are underway and will be reported in due course.

Acknowledgment

US National Institutes of Health (Grants RR-16480 and CA-99957) are gratefully acknowledged for financial support of this work.

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26. *Synthetic procedure* (**4a**–**o**, **9**–**11**): To a mixture of acetylacetic ester, substituted salicylic aldehyde (**2a**–**h**) and aminoheterocycle (**1a**–**c**, **6**–**8**) was added 1 drop of piperidine. The mixture was stirred for 15 min after which time acetic acid (5 mL) was added and the reaction mixture was refluxed for 3–12 h. The desired products precipitate upon cooling of the reaction mixtures, and a simple filtration and washing with ethanol provides analytically pure material (>95%). *Selected characterization data*: **4a**: 60%; ^{1}H NMR (DMSO-d_6, 373 K) δ 9.95 (d, J = 7.98 Hz, 1H), 7.67 (t, J = 7.14 Hz, 1H), 7.42–7.36 (m, 2H), 2.96 (s, 3H); ^{13}C NMR (DMSO-d_6, 373 K) δ 164.9, 157.3, 152.9, 133.9, 131.9, 124.6, 117.6, 117.1, 113.7, 28.1; HRMS m/z (ESI) calcd for $C_{14}H_9N_3O_3-$ H$^-$ 266.0566, found 266.0562. **9**: 65%; ^{1}H NMR (DMSO-d_6, 373 K) δ 8.33 (d, J = 7.68 Hz, 1H), 8.19 (d, J = 7.17 Hz, 2H), 7.73 (t, J = 7.24 Hz, 1H), 7.59–7.30 (m, 6H), 3.36 (s, 3H), 3.02 (s, 3H); ^{13}C NMR (DMSO-d_6, 373 K) δ 162.9, 159.8, 152.9, 143.8, 139.2, 133.9, 130.4, 129.8, 129.6, 127.3, 124.8, 122.5, 122.2 117.6, 117.6, 111.2, 28.0, 19.3; HRMS m/z (ESI) calcd for $C_{21}H_{15}N_3O_2$+ Na$^+$ 364.1062, found 364.1067. **10**: 53%; ^{1}H NMR (DMSO-d_6, 373 K) δ 9.79 (d, J = 8.25 Hz, 1H), 8.94 (s, 1H), 7.93 (t, J = 7.68 Hz, 1H), δ 7.65 (d, J = 8.25 Hz, 1H), 7.59 (d, J = 7.98 Hz, 1H), 3.11 (s, 3H); ^{13}C NMR (DMSO-d_6, 373 K) δ 167.6, 158.3, 156.2, 154.7, 136.5, 130.6, 126.0, 118.0, 117.6, 112.3, 106.0, 27.9; HRMS m/z (ESI) calcd for $C_{13}H_8N_4O_2$+Na$^+$ 275.0545, found 275.0537. **11**: 57%; ^{1}H NMR (DMSO-d_6, 323 K) δ 10.27 (bs, 1H), 9.87 (bs, 1H) 8.17 (d, J = 8.22 Hz, 1H), 7.65 (t, J = 8.22 Hz, 1H), 7.37 (d, J = 8.22 Hz, 1H), 7.27 (t, J = 8.25 Hz, 1H), 3.05 (s, 3H); ^{13}C NMR (DMSO-d_6, 323 K) δ 169.1, 166.3, 162.4, 159.1, 156.2, 152.9, 150.7, 134.4, 132.8, 123.6, 117.0, 116.1, 113.1, 103.2, 27.7; HRMS m/z (ESI) calcd for $C_{15}H_{10}N_3O_4$ + H$^+$ 296.0671, found 296.0670.
27. As our work was in progress, a similar reaction between salicylic aldehyde, acetylacetic ester, and 3-methyl-5-aminopyrazole leading to the formation 1,4-dihydropyridine analogs of **9**, appeared in the literature: Svetlik, J.; Veizerova, L.; Mayer, T. U.; Catarinella, M. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 4073.