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Convergent synthesis of 2,3-bisarylpyrazolones through cyclization of bisacylated pyrazolidines and hydrazines

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Abstract—Cyclization of various bisacylated hydrazines and pyrazolidines using DBU or sodium hydride leads to the formation of various mono-, bi- and tricyclic pyrazolone scaffolds in 41–98% yield. The convergent nature by which the precyclization intermediates are constructed allows for rapid derivatization about the pyrazolone core.
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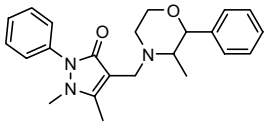
1. Introduction

Medicinal chemists have used pyrazolones extensively as scaffolds from which to design novel therapeutic agents. This heterocyclic ring system is found in a number of compounds showing analgesic (morazone **1** (Fig. 1)),[1] immunosuppressant (BTS-71412)[2] and anti-inflammatory (asprin–propyphenazone)[3] activity. Numerous methods for general pyrazolone synthesis have been reported. These methods include cyclocondensation reactions,[4] diphenylcyclopropenone reactions with hydrazines,[5] Mannich reactions of acylhydrazones with ketene silyl acetals,[6] and cyclization of diacyldimethylhydrazines.[7] These procedures have been limited primarily to the formation of simple di-, tri- and tetrasubstituted pyrazolones. During our efforts to develop novel anti-inflammatory agents, we became interested in the synthesis of fully substituted-2,3-bisarylpyrazolones for potential treatment of arthritis. This report describes a new procedure applicable to the rapid construction of these systems.



1

Figure 1. Anti-inflammatory agent morazone **1**.

The role of pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β) in the pathogenesis of numerous inflammatory disorders such as rheumatoid arthritis (RA), osteoarthritis (OA) and Crohn's disease has been well documented.[8] Cytokines are synthesized via a signal transduction cascade involving several members of the mitogen-activated protein (MAP) kinase family such as p38 and c-Jun N-terminal kinase (JNK). Regulating cytokine overexpression with small molecule kinase inhibitors is a major focus of many pharmaceutical companies.[9]

Our efforts in this area have resulted in the synthesis of a novel class of bicyclic pyrazolone inhibitors.[10] The synthesis of these heterocycles was originally accomplished via the route shown in Scheme 1. Aldol reaction between 4-fluorophenyl acetate **2** and 2-methylsulfanyl pyrimidine-4-carbaldehyde **3** provided β-hydroxyester **4**. This was followed by oxidation with chromium trioxide to afford β-ketoester **5**. Cyclization of **5** with pyrazolidine dihydrogen chloride produced the desired 2,3-bisarylpyrazolone **6**. Oxidation (Oxone®, THF/MeOH/H_2O)

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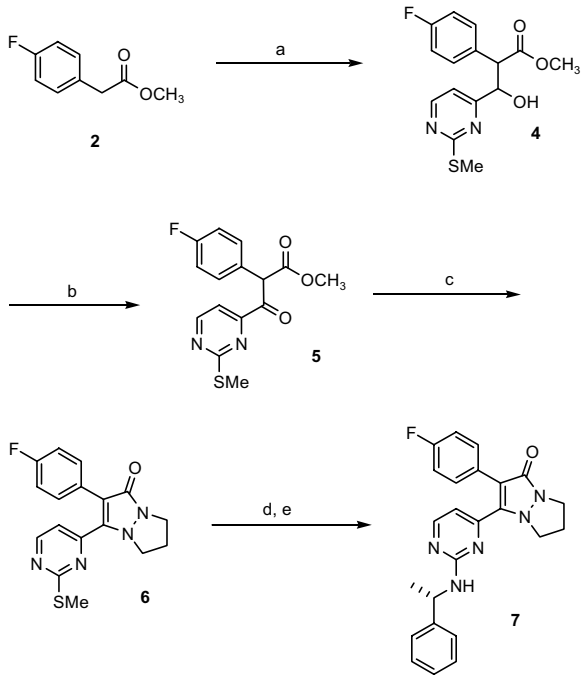
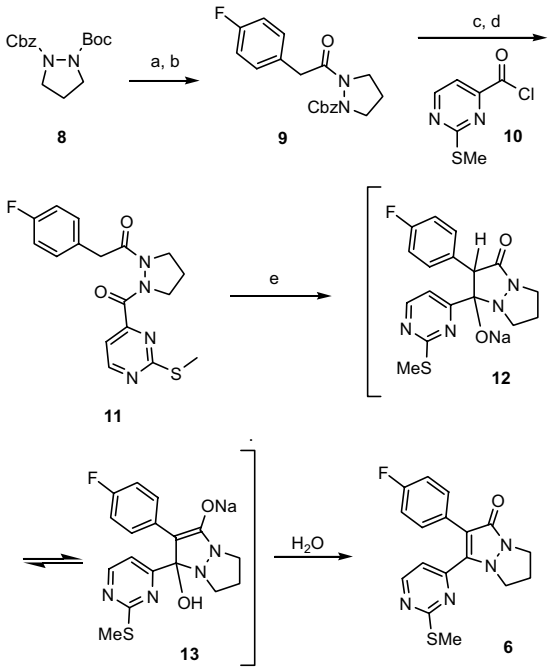


Scheme 1. Linear synthesis of bicyclic pyrazolones. Reagents and conditions: (a) LDA, 2-methylsulfanyl-pyrimidine-4-carbaldehyde **3**, THF, −78 °C, 76%; (b) CrO_3, CH_2Cl_2, pyridine, 43%; (c) Pyridine, pyrazolidine dihydrogen chloride, 90 °C, 28%; (d) Oxone, THF/MeOH/H_2O; (e) (*S*)-Methylbenzylamine, toluene, 120 °C, 50%.



Scheme 2. Synthesis of **6** via cyclization of a bis-acylated pyrazolidine. Reagents and conditions: (a) $SOCl_2$, MeOH, 90%; (b) 4-fluorophenylacetyl chloride, NaOH, H_2O/CH_2Cl_2, 96%; (c) H_2, Pd/C, methanol, 83%; (d) acid chloride **10**, NaOH, H_2O, CH_2Cl_2, 52%; (e) NaH, DMF, 0 °C, 49%.

and amine displacement (*S*-methylbenzylamine, toluene, 120 °C) of the thiomethyl group furnished bicyclic pyrazolone analog **7**. This linear sequence suffered from low yielding oxidation (**4**→**5**) and cyclization (**5**→**7**) steps as well as an inability to rapidly develop SAR about the two aryl substituents and the pyrazolidine ring. We now report the development of a new route to the 2,3-bisarylpyrazolone scaffold that addresses all of the above issues.

2. Results and discussion

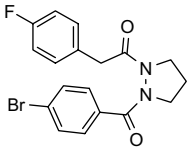
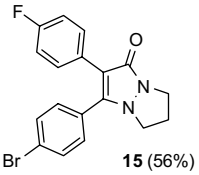
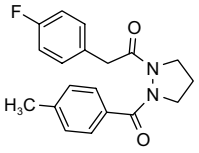
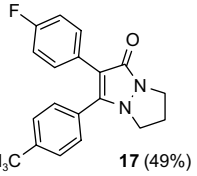
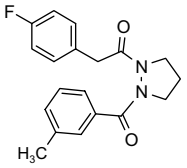
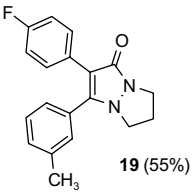
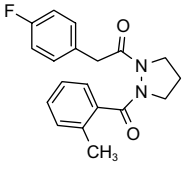
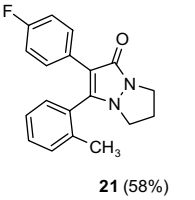
The modified synthesis of bicyclic pyrazolone **7** is described in Scheme 2. Beginning with the differentially protected pyrazolidine **8**,[11] removal of the Boc protecting group was accomplished with $SOCl_2$/MeOH. This was followed by acylation with 4-fluorophenylacetyl chloride to give monoacylated pyrazolidine **9**. Deprotection of the Cbz group under hydrogenation conditions followed by a subsequent second acylation with pyrimidine carbonyl chloride **10** gave the desired bis-acylated pyrazolidine **11** in excellent yield. When **11** was subjected to the cyclization conditions (2.5 equiv NaH, DMF, 0 °C), the desired bicyclic pyrazolone **6** was isolated in 49% yield.[12] A possible mechanism for this condensation/cyclization involves a stepwise process in which deprotonation of an acidic methylene proton on **11** would lead to intramolecular addition of the subsequent sodium enolate to the benzoyl carbonyl to give alkoxide **12**. Intermediate **12** would undergo a proton exchange to afford hydroxy enolate **13** which would eliminate NaOH, or water upon quenching, to produce pyrazolone **6**.

The modest yield for this reaction can in part be explained by the fact that significant amounts of deacylated material (30–40%) were often isolated from the reaction mixture presumably due to an in situ amide hydrolysis. Various combinations of bases (LiHMDS,[7] Et_3N, tetramethylguanadine (TMG), *t*-BuOK, DBU, pyridine, LDA, NaOEt) and solvents (DMF, THF, CH_2Cl_2, ethanol, toluene) were investigated in order to improve the yield of this reaction. Only the combination of DBU/DMF at 80 °C produced comparable results (53% yield) to the NaH/DMF/0 °C conditions.

The modest yield for this reaction is in line with previous reports in this area in which it is described that the steric bulk about the two acyl groups hinders both initial enolate addition to give intermediate **12** as well as the dehydration step (**13**→**6**).[13] An attempt at promoting the cyclization under acidic conditions (*p*TsOH, toluene, 80 °C) led to only recovered starting material and deacylated products.

Table 1 lists a series of variably substituted 2,3-bisaryl pyrazolones synthesized using this methodology. In these cases, the cyclization reaction was performed at 80 °C in DMF using excess DBU in the place of NaH. As discussed previously, the yields for these reactions under the alternative conditions are comparable. These examples highlight the utility of the methodology to rapidly investigate SAR about the pyrazolone core.

Table 1. Synthesis of 2,3-bisaryl bicyclic pyrazolones

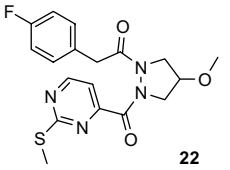
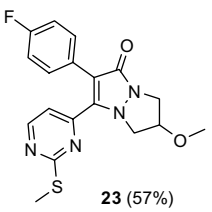
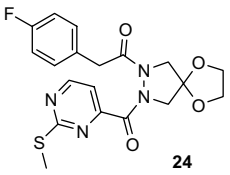
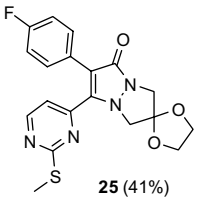
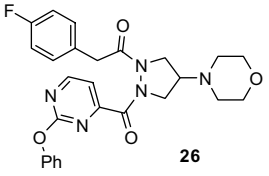
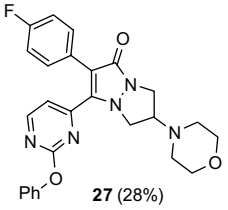
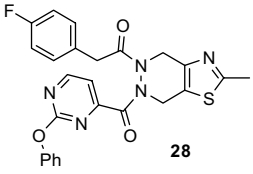
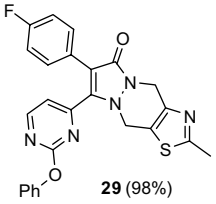
Entry	Bis-acylated hydrazine	Product (yield)[a]
1	 **14**	 **15** (56%)
2	 **16**	 **17** (49%)
3	 **18**	 **19** (55%)
4	 **20**	 **21** (58%)

[a] Conditions: DBU, DMF, 80 °C, 12 h.

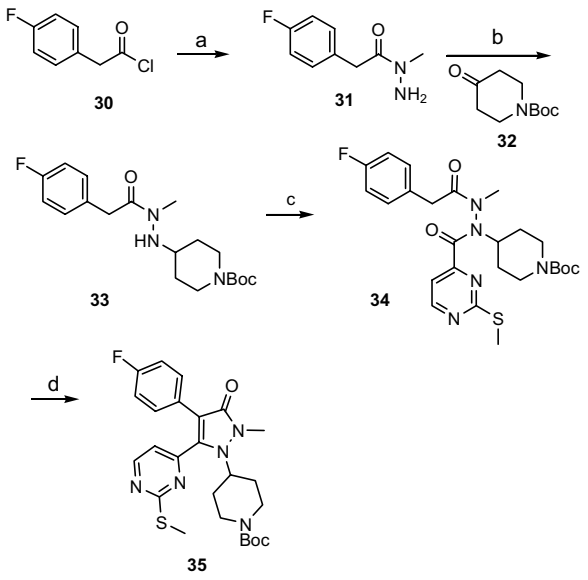
Cyclizations were also attempted with substrates where the simple pyrazolidine ring was replaced by variably substituted pyrazolidine and pyridazine ring systems. Table 2 describes results of these studies. Bisacylated intermediates **22**, **24**, **26** and **28** were synthesized using the route described within Scheme 2 in which the appropriately substituted analog of pyrazolidine **8** was used.[14] The yields for cyclization of substrates containing oxygen substituents including alkoxy (entry 1) and ketal (entry 2) were comparable to the simple unsubstituted case. Conversely, in the case of a pyrazolidine containing a nitrogen substituent (entry 3), a lower yield of the pyrazolone product was obtained. Finally, the cyclization of a fused heterocyclic pyridazine system (entry 4) resulted in a near quantitative yield of the desired tricyclic pyrazolone analog **29**.

This methodology has also been applied to the synthesis of differentially substituted monocyclic pyrazolones (Scheme 3).[15] Beginning with phenylacetyl chloride **30**, reaction with methylhydrazine at −78 °C led to selective formation of the 1,1-disubstituted hydrazide **31** in 61% yield. Reductive amination with piperidone **32** resulted in isolation of **33** in excellent yield. A second acylation with pyrimidine carbonyl chloride **10** gave the bisacylated precyclization intermediate **34**. This material was cyclized to the asymmetrically substituted monocyclic pyrazolone **35** in 73% yield. This represents a synthesis of a class of asymmetrically substituted pyrazolones that could not be previously obtained using the route outlined in Scheme 1.

Table 2. Synthesis of substituted 2,3-bisaryl bi- and tricyclic pyrazolones

Entry	Bis-acylated hydrazine	Product (yield)[a]
1	 **22**	 **23** (57%)
2	 **24**	 **25** (41%)
3	 **26**	 **27** (28%)
4	 **28**	 **29** (98%)

[a] Conditions: NaH, DMF, 0 °C.



Scheme 3. Synthesis of monocyclic pyrazolone **35**. Reagents and conditions: (a) methylhydrazine, CH_2Cl_2, −78 °C to rt, 61%; (b) piperidone **32**, EtOH, reflux, 15 min; then $NaBH_3CN$, MeOH, pH 4, 93%; (c) acid chloride **10**, pyridine, 20%; (d) NaH, DMF, 0 °C, 73%.

Conclusions

A methodology for the convergent synthesis of 2,3-bis-aryl pyrazolones has been developed highlighted by the cyclization of a bisacylated hydrazine intermediate using either NaH or DBU as base. The route allows for the synthesis of both simple and substituted bicyclic and tricyclic pyrazolone scaffolds as well as differentially substituted monocyclic pyrazolones in moderate to excellent yield. This new route allows for more rapid development of SAR about the pyrazolone ring, as well as entry into more complex and differentially substituted systems not available by this previous method. Further development of this methodology towards the synthesis of other heterocycles is being investigated.

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12. Representative procedure for the synthesis of pyrazolone **6** from pyrazolidine **11**: A solution of 2-(4-fluoro-phenyl)-1-[2-(2-methylsulfanyl-pyrimidine-4-carbonyl)-pyrazolidin-1-yl]-ethanone **11** (78.0 g, 0.217 mol) in DMF (400 mL) was added over 30 min to a 0 °C slurry of NaH (21.6 g of 60% dispersion in mineral oil, 0.540 mol) in DMF (150 mL). The mixture was stirred at 0 °C for 30 min, then quenched slowly with saturated aqueous ammonium chloride solution (6 L). The mixture was extracted with EtOAc (2×2L) and the combined organic layers dried over Na_2SO_4, filtered and concentrated in vacuo to give a viscous oil. The crude product was purified by flash chromatography on silica gel (600 g SiO_2, EtOAc to 10% MeOH/EtOAc to 20% MeOH/EtOAc) to give product **6** (36.0 g, 49%) as a yellow foam: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.42 (dd, $J = 5.4$, 1.5 Hz, 1H), 7.41 (dd, $J = 8.4$, 5.4 Hz, 2H), 7.07 (dd, $J = 8.4$, 8.4 Hz, 2H), 6.83 (dd, $J = 5.4$, 1.5 Hz, 1H), 4.17 (t, $J = 6.9$ Hz, 2H), 4.09 (t, $J = 6.9$ Hz, 2H), 2.76 (dddd, $J = 6.9$, 6.9, 6.9, 6.9 Hz, 2H), 2.60 (s, 3H); ESI/MS: 343 (M+H).
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