Tetrahedron Letters 51 (2010) 2945–2947

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Retro-Claisen condensation versus pyrrole formation in reactions of amines and 1,3-diketones

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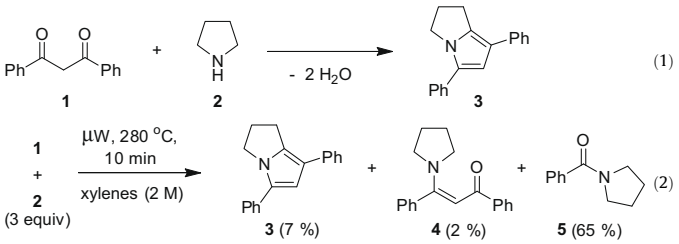
ARTICLE INFO

Article history:
Received 3 March 2010
Accepted 19 March 2010
Available online 25 March 2010

ABSTRACT

Cyclic amines and 1,3-diketones readily react under microwave irradiation to form ring-fused pyrroles in a single operation. A competing retro-Claisen pathway is efficiently suppressed by employing *p*-toluenesulfonic acid as an additive.

The ubiquity of pyrroles as substructures in natural products,[1] coupled with their usefulness as materials[2] and medicinal agents,[3] has stimulated the development of many methods for their synthesis.[4,5] Not surprisingly, there is a continued interest in the identification of methods that allow for the synthesis of pyrroles from simple and readily available starting materials, ideally in a single operation.[6] Here we report a one step synthesis of ring-fused pyrroles from 1,3-diketones and cyclic amines.



Given our interest in the redox neutral α-functionalization of amines,[7–9] we were intrigued by a publication of Soeder and Cartaya-Marin who reported the reaction of dibenzoylmethane (**1**) and pyrrolidine (**2**) to form ring-fused pyrrole **3** (Eq. 1).[10,11] Specifically, these researchers stated that heating of **1** with 1.7 equiv of **2** 'in a limited amount of benzene for one hour at

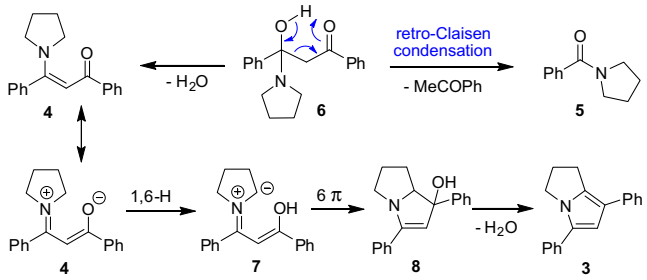
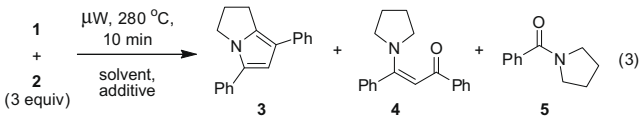


Figure 1. Proposed mechanisms for the formation of amide and pyrrole.

Table 1
Optimization of the pyrrole formation[a]



Entry	Additive (equiv)	Solvent (concentration)	**3** (%)	**4** (%)	**5** (%)
1	—	Xylenes (2 M)	7	2	65
2	*p*-TSA (0.2)	Xylenes (2 M)	50	10	5
3	*p*-TSA (0.2)	Toluene (2 M)	48	12	8
4	*p*-TSA (0.2)	THF (2 M)	30	10	10
5	*p*-TSA (0.2)	DMF (2 M)	10	20	20
6	*p*-TSA (0.2)	*n*-BuOH (2 M)	15	15	25
7	$PhCO_2H$ (0.2)	Xylenes (2 M)	11	40	10
8	*m*-Cl-$PhCO_2H$ (0.2)	Xylenes (2 M)	5	20	15
9	AcOH (0.2)	Xylenes (2 M)	10	—	20
10	TFA (0.2)	Xylenes (2 M)	13	2	18
11	$Zn(OTf)_2$ (0.2)	Xylenes (2 M)	—	5	—
12	$Mg(OTf)_2$ (0.2)	Xylenes (2 M)	2	—	10
13	$Sc(OTf)_3$ (0.2)	Xylenes (2 M)	—	—	50
14	Amberlyst 15	Xylenes (2 M)	2	40	5
15	Silica gel (excess)	Xylenes (2 M)	5	30	5
16	*p*-TSA (1)	Xylenes (2 M)	35	25	12
17	*p*-TSA (0.75)	Xylenes (2 M)	38	20	7
18	*p*-TSA (0.5)	Xylenes (2 M)	53	7	5
19	*p*-TSA (0.1)	Xylenes (2 M)	20	30	10
20	**p-TSA (0.5)**	**Xylenes (1 M)**	**53**	**8**	**5**
21	*p*-TSA (0.5)	Xylenes (0.5 M)	40	25	14
22	*p*-TSA (0.5)	Xylenes (0.25 M)	15	20	12
23	*p*-TSA (0.5)	Xylenes (0.1 M)	10	15	10
24	*p*-TSA (0.5)	Xylenes (5 M)	35	30	25

[a] All reactions were performed on a 1 mmol scale. All yields are isolated yields after column chromatography.

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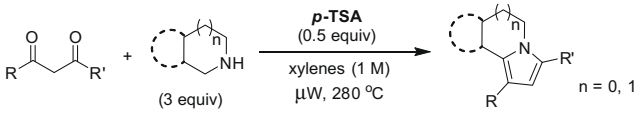
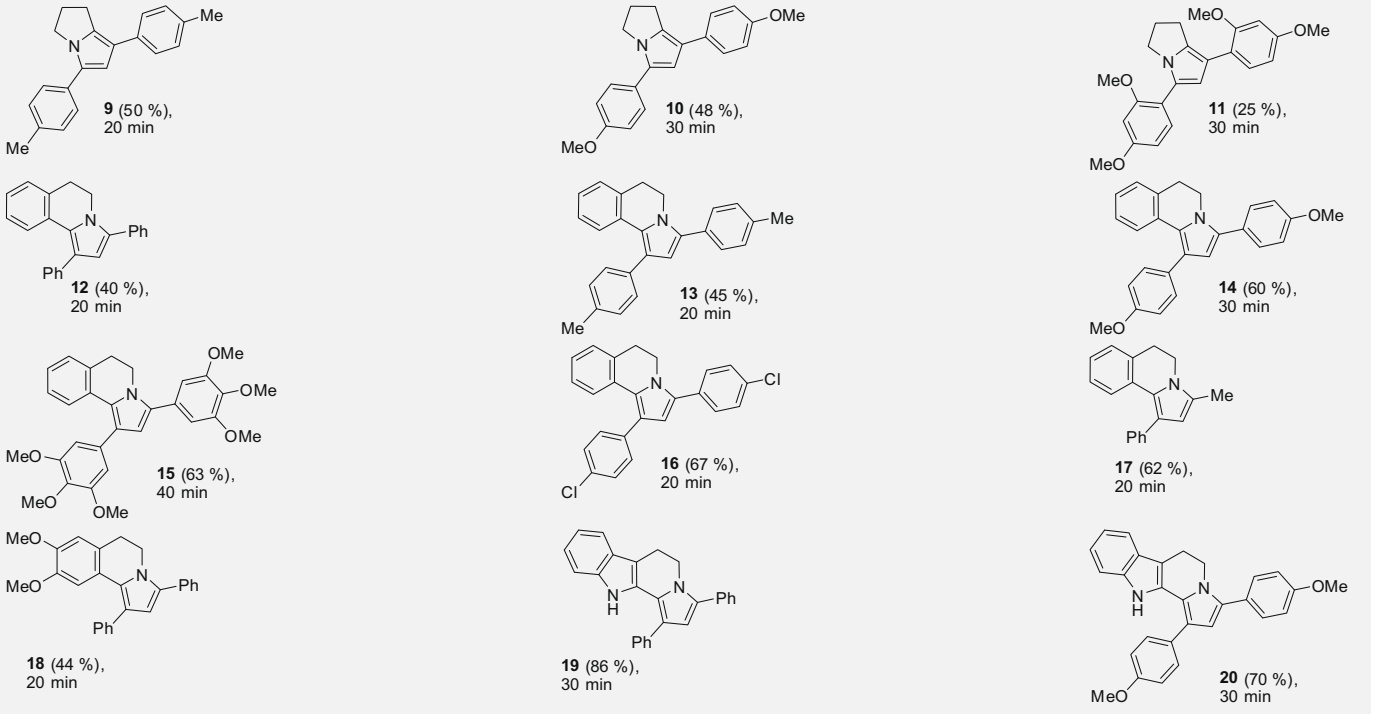
doi:10.1016/j.tetlet.2010.03.086

Table 2
Scope of the pyrrole formation[a]





[a] All reactions were performed on a 2 mmol scale and run for the indicated amount of time. All yields are isolated yields after column chromatography.

high temperature using a Dean–Stark trap for the removal of water produced compound **3** in 60% yield after recrystallization.' Unfortunately, no further details were provided and no substrate scope or proposed mechanism was presented. In our hands, reactions of varying ratios of **1** and **2** conducted in refluxing benzene, toluene or xylenes in the presence or absence of molecular sieves and with or without Dean–Stark trap, lead to only trace formation of **3**. Enaminone **4** was isolated as the main product in all cases. Interestingly, a reaction conducted under more forceful conditions (280 °C, microwave irradiation) led to the formation of *N*-benzoyl pyrrolidinone (**5**) as the major product (Eq. 2). In addition to amide **5**, small amounts of pyrrole **3** and enaminone **4** were isolated.

The formation of amide **5** can be rationalized by a retro-Claisen condensation of the initially formed *N,O*-acetal **6**, a process that simultaneously generates 1 equiv of acetophenone (Fig. 1).[12] Alternatively, dehydration of **6** leads to enaminone **4**, a likely intermediate in the formation of pyrrole **3**. The latter may be formed through a sequence involving a 1,6-H-shift to give **7**. Compound **7** is envisioned to undergo a 6π-electrocyclization to yield intermediate **8**. Subsequent loss of water gives rise to pyrrole **3**.

We rationalized that pyrrole formation may become the predominant reaction pathway if conditions could be indentified that favor formation of the enaminone **4** over the competing retro-Claisen process. Toward this end, we evaluated the reaction between **1** and **2** in different solvents and in the presence of selected Brønsted or Lewis acidic additives (Table 1). The best yield of pyrrole **3** (53%) was obtained in the presence of 0.5 equiv of *p*-toluenesulfonic acid (*p*-TSA), using xylenes as the solvent (1 M concentration). Prolonged reaction times, which were expected to lead to full conversion of the remaining enaminone **4** into pyrrole **3**, led to a lower overall yield. Attempts to perform the reaction at lower temperatures (250 °C and below) led to little pyrrole formation, even if run for extended periods of time. Perhaps not surprisingly,[12] the use of scandium triflate gave rise to the exclusive formation of the retro-Claisen product **5**.

The scope of this reaction was evaluated under the optimized conditions (Table 2). Reactions of 1,3-diketones with 3 equiv of pyrrolidine, tetrahydroisoquinolines or β-carboline gave rise to the formation of fused pyrroles in moderate to good yields.[13–16] A reaction between tetrahydroisoquinoline and 1-phenylbutane-1,3-dione gave rise to compound **17** as a single regioisomer (less than 2% of the other regioisomer was obtained). In all cases, pyrroles were isolated as the major product. Minor amounts of amides and/or enaminones were usually obtained as readily separable byproducts. Reactions between pyrrolidine and acetylacetone did not yield any appreciable amounts of pyrrole under identical reaction conditions.

In summary, we have reported one-step syntheses of ring-fused pyrroles from readily available 1,3-diketones and cyclic amines.

Acknowledgment

We thank the National Science Foundation for support of this research (Grant CHE-0911192).

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13. *Typical procedure for the synthesis of fused pyrroles*: The 1,3-diketone (2 mmol), amine (6 mmol), $TsOH{\cdot}H_2O$ (1 mmol) and xylenes (2 mL) were placed in a 10 ml microwave vessel which was subsequently sealed. The sealed vessel was irradiated in a CEM discovery microwave apparatus at 280 °C (power = 200 W, pressure = 250 psi) for the indicated reaction time. Following completion of the reaction, the solvent was removed and the crude product was purified by silica gel column chromatography. Yields refer to those of pure isolated products. All compounds were fully characterized by spectral (^{1}H and ^{13}C NMR) and analytical data.
14. *Characterization data for* **9**: pale yellow solid (R_f = 0.45 in 5% EtOAc/hex); mp: 35–36 °C; IR (KBr) 1610, 1569, 1500, 1444, 1144 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 7.42 (app d, *J* = 8.0 Hz, 4H), 7.18 (app dd, *J* = 13.0, 8.0 Hz, 4H), 6.57 (s, 1H), 4.15 (t, *J* = 7.1 Hz, 2H), 3.12 (t, *J* = 7.1 Hz, 2H), 2.5 (pentet, *J* = 7.1 Hz, 2H), 2.38 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 135.6, 135.1, 134.0, 133.53, 130.6 (×2), 129.3, 129.2, 125.7, 125.1, 115.9, 108.1, 46.5, 27.9, 25.2, 21.1, 21.0; *m*/*z* (ESIMS) 288.3 $[M+H]^+$.
15. *Characterization data for* **13**: pale yellow solid (R_f = 0.5 in 10% EtOAc/hex); mp: 37–38 °C; IR (KBr) 1606, 1567, 1498, 1380, 1330, 1290, 1243 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 7.53 (app d, *J* = 7.8 Hz, 2H), 7.51 (app, s, 1H), 7.43 (app d, *J* = 8.0 Hz, 2H), 7.33 (app d, *J* = 8.0 Hz, 2H), 7.20 (app d, *J* = 8.3 Hz, 3H), 7.10–7.16 (m, 2H), 6.43 (s, 1H), 4.17 (t, *J* = 6.1 Hz, 2H), 3.09 (t, *J* = 6.1 Hz, 2H), 2.49 (app s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) 136.7, 135.6, 134.4, 133.4, 132.3, 130.1, 129.6, 129.1, 129.1, 128.8, 128.6, 127.6, 126.5, 125.4, 125.3, 124.4, 122.7, 110.7, 42.3, 30.3, 21.2, 21.2; *m*/*z* (ESIMS) 350.4 $[M+H]^+$.
16. *Characterization data for* **19**: yellow solid (R_f = 0.30 in 20% EtOAc/hex); mp: 60 °C; IR (KBr) 1599, 1507, 1476, 1444, 1301, 1200 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 8.09 (s, 1H), 7.64 (app dd, *J* = 7.0, 1.1 Hz, 2H), 7.45–7.52 (m, 7H), 7.23 (app tdd, *J* = 14.6, 7.3, 1.2 Hz, 2H), 7.22–7.24 (m, 1H), 7.10–7.15 (m, 2H), 6.36 (s, 1H), 4.25 (t, *J* = 3.4 Hz, 2H), 3.16 (t, *J* = 3.4 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) 136.6, 135.9, 135.5, 132.7, 129.0, 128.6, 128.7, 128.5, 128.3, 127.2, 126.7, 126.4, 121.9, 121.6, 120.9, 119.8, 117.6, 110.9, 110.3, 106.6, 44.0, 21.3; *m*/*z* (ESIMS) 359.4 $[M-H]^+$.