ORGANIC LETTERS

2006
Vol. 8, No. 13
2675−2678

1,3-Diketones from Acid Chlorides and Ketones: A Rapid and General One-Pot Synthesis of Pyrazoles

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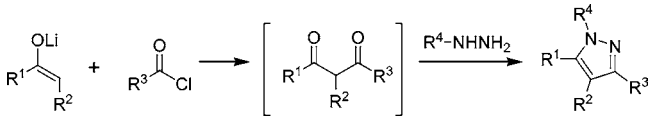
Received March 8, 2006 *(Revised Manuscript Received May 10, 2006)*

ABSTRACT



1,3-Diketones were synthesized directly from ketones and acid chlorides and were then converted in situ into pyrazoles by the addition of hydrazine. This method is extremely fast, general, and chemoselective, allowing for the synthesis of previously inaccessible pyrazoles and synthetically demanding pyrazole-containing fused rings.

Pyrazoles are an important class of heteroaromatic ring systems that find extensive use in the pharmaceutical industry.[1] To date, the synthesis of these compounds has been somewhat limited by the available chemistry. By far the most prevalent method of obtaining pyrazoles is by the reaction of 1,3-diketones with hydrazine and hydrazine derivatives.[2] However, if a diversity-oriented synthesis of pyrazoles[3] is desired, this method becomes cumbersome as each 1,3-diketone must be purified and is often obtained as a mixture of condensation products. Furthermore, most electrophilic functional groups such as aldehydes, nitriles, esters, and alkyl halides do not survive the transformation. Other methods for the synthesis of pyrazoles that do not require 1,3-diketones have been reported[4−7] but tend to have serious drawbacks such as being step-intensive. In light of this, it is clear that using 1,3-diketones as an intermediate is the broadest and most efficient route to pyrazoles.

Yet as shown earlier, an expedient, simple, and general method for the synthesis of pyrazoles — indeed, 1,3-diketones in general — is still needed. We hypothesized that an enolate might react smoothly with acid chlorides if the proper conditions were employed to slow side reactions. This method would alleviate the problem of using esters, and given the right conditions would be selective in the presence of other weaker electrophiles such as nitriles. Methods exist for the indirect coupling of acid chlorides and enolates[8,9] and also for substrate specific reactions[10−13] but are not broad in scope or accessibility.

There are two examples of direct coupling of enolates to acid chlorides, although one reports extremely low yields.[14] The other could not be reproduced by us, affording a complex mixture of products with only a trace amount of 1,3-

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10.1021/ol060570p CCC: $33.50
Published on Web 05/27/2006

diketone.[15] Nonetheless, this last source helped to inspire a starting point.

By employing a hydrocarbon solvent, we thought that side reactions might be slowed by disfavoring a charged intermediate, only allowing the enolate to react with the very electrophilic acid chloride. We tested our hypothesis by reacting 4-bromoacetophenone enolate with 4-methoxybenzoyl chloride.[16]

When toluene was used as a solvent and LDA or MHMDS was used as the base, no homocondensation was observed and the generated diketone did not react to form a vinylogous species. However, Table 1 shows a trend based on the ionic

Table 1. Effect of Base and Solvent on the Yield of **5**

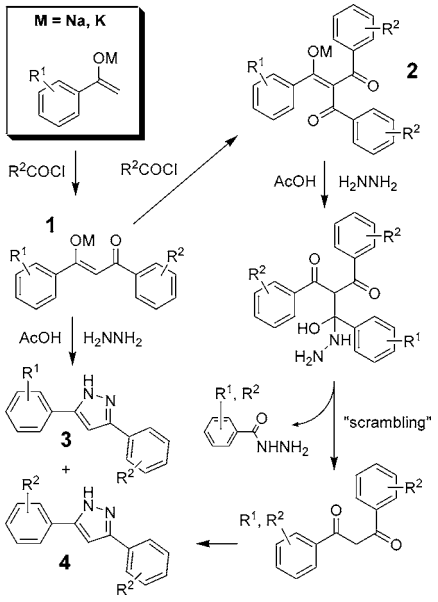
base	solvent	yield[a] (%)
LiHMDS (1.0 M THF)	toluene	89
LiHMDS (1.0 M THF)	toluene	47[b]
NaHMDS (0.6 M toluene)	toluene	77[c]
KHMDS (0.5 M toluene)	toluene	60[c]
LDA (2.0 M THF)	toluene	64
KO^{t}Bu	toluene	trace
LiHMDS (1.0 M THF)	THF	27

[a] Isolated yield of **5**. [b] 1 equiv of 4-bromoacetophenone. [c] Isolated by column chromatography (acetone/DCM, 1:1).

nature of the enolate. When NaHMDS or KHMDS were used, 15 and 20%[17] of the detected diketone intermediate **1** was actually a triketone **2** arising from the metal diketonate reacting with another equivalent of acid chloride. Lithium bases gave no detectable amount of **2** and so were employed for further experimentation.

When hydrazine was added to this mixture, the unsymmetrical 3,5-disubstituted pyrazole **3** was formed along with some symmetrical product **4** containing two anisyl groups. This implies that one of the benzoyl groups is actually a leaving group, an idea further backed by the isolation of a small amount of 4-methoxybenzoic hydrazide and 4-bromobenzoic hydrazide. A suggested mechanism for this elimation giving rise to the two products in a statistical distribution is displayed in Scheme 1. The difference in yield between bases shown in Table 1 is mostly attributable to this scrambling effect.

Scheme 1. Regiochemical Scrambling via Triketone Intermediates



We then attempted to synthesize a variety of pyrazoles derived from diketone intermediates to test the generality of the method. The results of our efforts are displayed in Table 2. Yields were generally good to excellent, though we made no attempt to optimize the conditions for each reaction. Electronic effects on the aromatic coupling partners did not affect reaction yields or purity systematically, although steric effects could be observed in the case of **10** and the sterically demanding **11**.

A wide range of functional groups were tolerated in both coupling partners. Of particular interest is the cyano functionality carried through in **9** and **13**. As expected, aldehydes did not survive the enolization step. Electrophiles containing enolizable α-protons were successfully coupled to the enolate to form 1,3-diketones. Finally, primary halides were tolerated without any observed elimination. Although esters were also tolerated in the enolate condensation step, the addition of hydrazine was problematic.

Substituted hydrazines typically gave a mixture of regioisomers that was dependent on the aryl substitution. Compound **21** is essentially symmetrical electronically; thus, a 1:1 mixture was formed. Compounds **6** (~3:1, **a**:**b**) and **17**, which gave only a single isomer, further elaborate this trend.

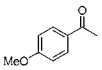
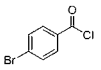
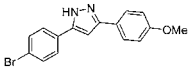
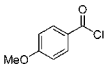
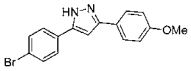
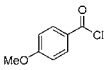
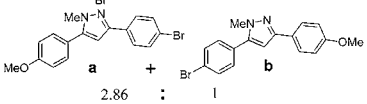
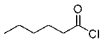
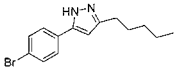
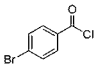
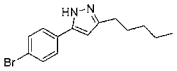
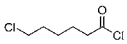
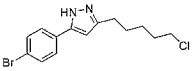
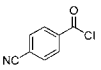
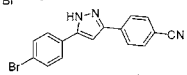
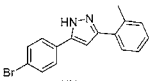
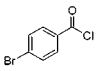
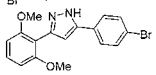
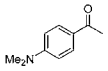
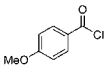
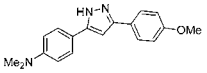
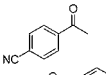
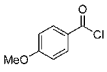
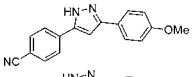
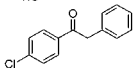
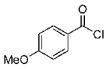
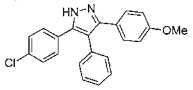
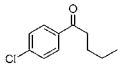
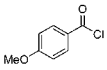
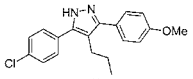
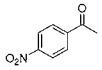
The conditions used gave rise to kinetic control of enolate formation as witnessed by **7**, which was isolated almost exclusively as the kinetic product. It is likely that the short time frame of the reaction combined with a high barrier of activation between enolates caused by the nonpolar solvent and lithium base add to the kinetic selectivity in the face of relatively high temperature.

(15) Vavon, G.; Conia, J. M. *C. R. Acad. Sci.* **1951**, *233*, 876.

(16) **Representative Proecedure. Preparation of 5.** 4′-Bromoacetophenone (0.3981 g, 2 mmol) was dissolved in 5 mL of dry toluene in a screw cap vial (with septum), and then the solution was cooled to 0 °C under nitrogen. LiHMDS (2.1 mL, 1.0 M in THF, 2.1 mmol) was added quickly via syringe with stirring, and the formed anion was allowed to sit for approximately 1 min before the addition of 4-methoxybenzoyl chloride (0.1706 g, 1.354 mL, 1 mmol) in one portion with stirring. The vial was then removed from the ice bath and allowed to stand for 1 min, and then 2 mL of AcOH was added with stirring. EtOH (10 mL) and THF (5 mL) were added to form a homogeneous mixture, then hydrazine hydrate (2 mL, 1.1 g, 34.3 mmol) was added. The mixture was allowed to auto-reflux and was held at that temperature for 5 min, when LCMS showed that all diketone had reacted. The resulting solution was added to 1.0 M NaOH solution and extracted with EtOAc. The organic fraction was then washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure. The resulting residue was recrystallized from 2-propanol/water to afford white crystalline product **5** (0.293 g, 89%): ^{1}H NMR (400 MHz, d_6-DMSO) δ 13.30 (s, 1H), 7.80 (d, J = 7.6 Hz, 2H), 7.75 (d, J = 8 Hz, 2H), 7.64 (d, J = 7.6 Hz, 2H), 7.11 (s, 1H), 7.03 (d, J = 8 Hz, 2H), 3.80 (s, 3H).

(17) Approximate values from LCMS characterization. NaHMDS yielded 4% and KHMDS yielded 7% 3,5-bis(4-methoxyphenyl)-1*H*-pyrazole after chromatography.

Table 2. Preparation of 3,5-, 1,3,5-, 3,4,5-, and Fused Ring-Substituted Pyrazoles

product	ketone	acid chloride	hydrazine	product structure	yield
5			NH_2NH_2		66
5			NH_2NH_2		89
6a,b			Me—$NHNH_2$	 2.86 : 1	83
7			NH_2NH_2		74
7			NH_2NH_2		62[a]
8			NH_2NH_2		49
9			NH_2NH_2		68
10			NH_2NH_2		50
11			NH_2NH_2		trace
12			NH_2NH_2		87
13			NH_2NH_2		74
14			NH_2NH_2		50
15			NH_2NH_2		83
16			NH_2NH_2		81
17					43[b]
18			NH_2NH_2		0[c]
19			NH_2NH_2		59
20			NH_2NH_2		72
21a,b			Me—$NHNH_2$	1 : 1	82
22			NH_2NH_2		71
23			NH_2NH_2		67
24			NH_2NH_2		65
25			NH_2NH_2		82

[a] Greater than 95% 3-(4-bromophenyl)-5-pentyl-1*H*-pyrazole by ^{1}H NMR. Remainder is 3-(4-bromophenyl)-5-butyl-4-methyl-1*H*-pyrazole. [b] mp = 176−178 °C and ^{1}H NMR agree with literature (lit.[6] mp = 178−179 °C). [c] Diketone observed in LCMS as sole intermediate but no pyrazole formed.

Since our method proved successful with a wide variety of ketones and acid chlorides, we envisaged that fused rings, an interesting class of molecules with pharmacological activity,[18,19] might also be accessible. Both saturated and aryl acid chlorides were used to synthesize **22**−**25**. Heteroatoms and, importantly, Boc-protected aliphatic amines could be used in the reaction, as could aliphatic ketones and acid chlorides.

In summary, we have developed an efficient and extremely rapid synthesis of 1,3-diketones from readily available ketones and acid chlorides. These diketones were treated in situ with hydrazines to form pyrazoles in good to excellent yields. Most functional groups were tolerated with little or no side product formation, including nitriles, esters, alkyl halides, and electrophiles with enolizable α-protons. Our method proved useful for the preparation of fused bicyclic pyrazole systems as well. We are currently applying this method to the synthesis of other heterocycles that originate from 1,3-diketones.

Acknowledgment. We thank Mark Holmes for NMR support and Bernard Choi for HRMS support.

Supporting Information Available: ^{1}H NMR data and purification procedures for all compounds and ^{1}H and ^{13}C data for all previously unreported compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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