# A Simple Regioselective Synthesis of Ethyl 1,5-Diarylpyrazole-3-carboxylates



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Improved procedures for the regioselective preparation of ethyl 1,5-diarylpyrazole-3-carboxylates are described. The new procedures utilize readily prepared lithium aroylpyruvate intermediates which, when combined with arylphenylhydrazine hydrochlorides form 1,5-diarylpyrazole-3-carboxylates regioselectively in good to excellent yield.

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In connection with our synthetic efforts toward tepoxalin [1a-d] and related 1,5-diarylpyrazole antiinflammatory agents, we required a regioselective synthesis of ethyl 1,5-diarylpyrazole-3-carboxylates. The most convenient method for synthesizing compounds of this type involves the condensation of an aroylpyruvate with an arylhydrazine [2a-c]. This reaction generally affords mixtures of the 1,3- and 1,5-diarylpyrazole-3-carboxylates [3].

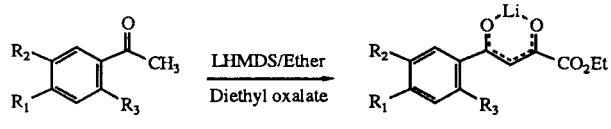
Initially, we viewed ethyl benzoylpyruvate as the key intermediate for construction of the 1,5-diphenylpyrazoles. Acylation of a substituted acetophenone with diethyl oxalate in sodium methoxide/methanol and subsequent acidification generated the free ethyl benzoylpyruvate [4]. The ethyl benzoylpyruvate is then condensed with an appropriately substituted phenylhydrazine hydrochloride in alcohol/triethylamine or alcohol/pyridine to afford a modestly regioselective (~3:1) mixture of ethyl 1,5-diarylpyrazole-3-carboxylates to ethyl 1,3-diarylpyrazole-5-carboxylates. This reaction generally proceeds in 60-75% yields. We attempted the same condensations using the intermediate sodium benzoylpyruvates and the requisite phenylhydrazine hydrochloride. This procedure gave similar ratios to those described above with somewhat lower (55-70%) yields. The intermediate sodium benzoylpyruvates are difficult to work with due to their slow filtering properties and insolubility once they have been dried. During the isolation of the sodium ethyl pyruvates, varying amounts (2-13%) of benzoylpyruvic acids are produced. These reactions also show reduced yields on scale up.

We investigated alternative salts and solvent systems for these reactions. We found that stable lithio ethyl benzoylpyruvate salts could be synthesized by preforming the requisite acetophenone anion in ether at −78° with lithium hexamethyldisilazide. The addition of one equivalent of diethyl oxalate in ether, followed by warming to room temperature, deposits the lithium ethyl benzoylpyruvate as a solid. The salt is then filtered, washed with ether, dried and stored [5]. These lithium salts appear to be stable indefinitely. Reactions utilizing these intermediates are summarized in Table I.

The lithium ethyl benzoylpyruvates described above could be used without further purification in the preparation of ethyl 1,5-diarylpyrazole-3-carboxylates. When the lithium salts are stirred with one equivalent of the substituted phenylhydrazine hydrochloride, at room temperature in ethanol, they afford an excellent ratio (10:1 or greater) of the desired ethyl 1,5-diarylpyrazole-3-carboxylates in 70 to 91% yield [Table II]. The pyrazole isomers can readily be distinguished by their nmr spectra. The pyrazole C-4 proton in the 1,5-isomer always resonates between δ 6.95 and 7.05, while the 1,3-isomer C-4 proton resonates between δ 7.24 and 7.28. Other differences are described in Table III. The synthesis of compound **19** was investigated more extensively and we are able to isolate and characterize the intermediate hydrazone, ethyl 3-(4-methoxybenzoyl)-2-oxopropanoate-2-(4-chlorophenyl)hydrazoe **21**. This hydrazone is readily converted to pyrazole **19** in quantitative yield by heating it to reflux in ethanol. We did not observe intermediate hydrazone formation in any of our other pyrazole syntheses. There are,

Table I

Litium Ethyl Benzoylpyruvate Forming Reaction

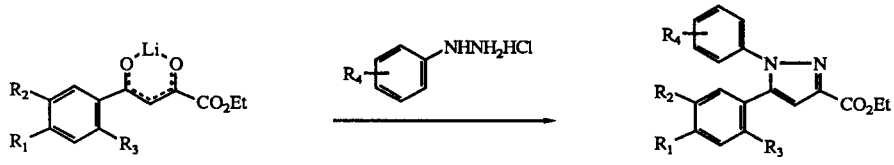



| # | $R_1$ | $R_2$ | $R_3$ | Yield (%) |
|---|---|---|---|---|
| 1 | Cl | H | H | 96 |
| 2 | $CH_3$ | H | H | 88 |
| 3 | $OCH_3$ | H | H | 95 |
| 4 [a] | H | H | $CH_3$ | 100 |
| 5 | $OCH_3$ | $OCH_3$ | H | 84 |
| 6 | F | H | H | 86 |
| 7 | $CH_3$ | $CH_3$ | H | 88 |
| 8 | Cl | Cl | H | 85 |

[a] Not crystalline, isolated as the crude residue.

Table II

Regioselective Formation of 1,5-diarylpyrazole-3-carboxlates




| [b] # | $R_1$ | $R_2$ | $R_3$ | $R_4$ [a] | Ratio 1,5:1,3 | Yield of 1,5 |
|---|---|---|---|---|---|---|
| 9 | $CH_3$ | H | H | $OCH_3$ | 12:1 | 77 |
| 10 | Cl | H | H | $OCH_3$ | 10:1 | 76 |
| 11 | $OCH_3$ | H | H | $OCH_3$ | 19:1 | 91 |
| 12 | F | H | H | $OCH_3$ | 13:1 | 79 |
| 13 | $CH_3$ | $CH_3$ | H | $OCH_3$ | 12:1 | 81 |
| 14 | $OCH_3$ | $OCH_3$ | H | $OCH_3$ | 11:1 | 83 |
| 15 | Cl | Cl | H | $OCH_3$ | 10:1 | 79 |
| 16 | $OCH_3$ | H | H | H | >20:1 | 72 |
| 17 [b] | H | H | $CH_3$ | $OCH_3$ | 12:1 | 70 |
| 18 | $OCH_3$ | H | H | Cl | 20:1 | 82 |
| 19 | $OCH_3$ | H | H | Cl [c] | >20:1 | 86 |
| 20 | $OCH_3$ | H | H | F | >20:1 | 83 |

[a] Unless otherwise noted. $R_4$ is at the 4-position. [b] The crude isolate of the lithium acylpyruvate was used due to the lack of crystallinity of the intermiate. [c] The $R_4$ chloro is at the 2-position. The hydrazone intermediate of this compound has been isolated. [d] The isomer ratios were calculated by $^1H$ nmr intergration. The ratios were verified in the case of compounds **9**, **10**, and **18** by weighing the dried chromatographed residues of the 1,3 and 1,5 isomer.

however, literature examples of intermediate hydrazones [6].

The preparations of the lithium aroylpyruvates and the 1,5-diaroylpyrazole-3-carboxylates are amenable to scale up without loss of yield, *e.g.*, the synthesis of compound **10** has been carried out on kilo scale.

## EXPERIMENTAL

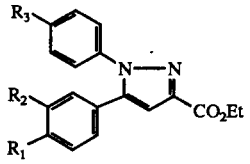
Melting points (mp) were determined on a Thomas-Hoover apparatus and are uncorrected. The infrared spectra (ir) were recorded on a Beckman Instruments IR-B spectrophotometer and are expressd in reciprocal centimeters. Nuclear magnetic resonance (nmr) spectra for hydrogen atoms were measured in the indicated solvent with tetramethylsilane (TMS) as the internal standard on a GE QE 300 or an IBM WP-100 spectrometer. The values are expressed in parts per million downfield from TMS. Parenthesized, underlined hydrogens were assigned to the resonance positions immediately before the parentheses. EI and CI mass spectra were obtained on a Finnigan 1015D quadrupole mass spectrometer coupled to a Finnigan 9500 gas chromatograph or a Finnigan MAT 8230 Double Focusing high resolution mass spectrometer.

General Procedure for the Synthesis of Lithium Ethyl Benzoylpyruvates.

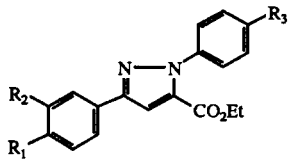
Lithium hexamethyldisilazide (1.2 molar, 208 mℓ, 0.25 mole) was added to anhydrous ether (1 liter). The solution was then cooled to −78° under a nitrogen atmosphere. After 15 minutes, the acetophenone (0.25 mole) in anhydrous ether (200 mℓ) was added and stirred for 30 minutes at −78°. Diethyl oxalate (36.5 g, 0.25 mole) in anhydrous ether (200 mℓ) was added at once. The solution was then allowed to warm to room temperature. After stirring for 2 hours at room temperature, stirring was discontinued and the solid was allowed to settle. After 2 hours, the solid was filtered and washed twice with anhydrous ether (100 mℓ). The solid was then dried *in vacuo* overnight. Recrystallization from acetone afforded an analytically pure sample.

Table III

NMR Data of Representative Isomer Pairs [a]




A




B

| # | $R_1$ | $R_2$ | $R_3$ | Data (δ) |
|---|---|---|---|---|
| 12A | F | H | $OCH_3$ | 1.42 (3H, t, J = 7 Hz) -$CH_2CH_3$, 3.82 (3H, s) -$OCH_3$, 4.45 (2H, t, q, J = 7 Hz) -$CH_2CH_3$, 6.86 (2H, d, J = 9 Hz), 7.00 (1H d) pyrazole-*H*, 7.01 (2H, J = 8 Hz), 7.23 (2H, d, J = 9 Hz), 7.17-7.27 (2H, m) |
| 12B | F | H | $OCH_3$ | 1.28 (3H, t, J = 7 Hz) -$CH_2CH_3$, 3.86 (3H, s) -$OCH_3$, 4.26 (2H, q, J = 7 Hz) -$CH_2CH_3$, 6.98 (2H, d, J = 9 Hz), 7.10 (2H, t, J = 8 Hz), 7.24 (1H, s) pyrazole-*H*, 7.39 (2H, d, J = 9 Hz), 7.8-7.86 (2H, m) |
| 15A | Cl | Cl | $OCH_3$ | 1.42 (3H, t, J = 7 Hz) -$CH_2CH_3$, 3.83 (3H, s) -$OCH_3$, 4.45 (2H, q, J = 7 Hz) -$CH_2CH_3$, 6.89 (2H, d, J = 9 Hz), 6.96 (1H, d, J = 8 Hz) 7.04 (1H, s) pyrazole-H, 7.23 (2H, d, J = 9 Hz), 7.35 (1H, q, J = 8 Hz), 7.38 (1H, s) |
| 15B | Cl | Cl | $OCH_3$ | 1.29 (3H, t, J = 7 Hz) -$CH_2CH_3$, 3.86 (3H, s) -$OCH_3$, 4.26 (2H, q, J = 7 Hz) -$CH_2CH_3$, 6.98 (2H, d, J = 9 Hz), 7.27 (1H, s) pyrazole-*H*, 7.39 (2H, d, J = 9 Hz) 7.48 (1H, d, J = 8 Hz), 7.69 (1H, d, J = 8 Hz), 7.99 (1H s) |

[a] all spectra were taken using deuteriochloroform as solvent.

Table IV

Melting Points and Combustion Analysis on Lithium Ethyl Aroylpruvates

| Compound | MP °C | Theoretical | Found |
|---|---|---|---|
| 1 | 278-281 dec | C, 55.30 H, 3.87 | C, 54.90 H, 4.01 |
| 2 | 270-272 dec | C, 65.01 H, 5.16 | C, 64.71 H, 5.30 |
| 3 | 244-247 dec | C, 60.95 H, 5.12 | C, 60.83 H, 4.88 |
| 5 | 293-294 dec | C, 58.75 H, 5.28 | C, 58.46 H, 5.43 |
| 6 | 264-265 dec | C, 59.03 H, 4.13 | C, 58.97 H, 4.07 |
| 7 | 235-237 dec | C, 66.15 H, 5.95 | C, 65.99 H, 5.74 |
| 8 | 251-253 dec | C, 48.85 H, 3.07 | C, 48.83 H, 2.97 |

Lithium Ethyl 4-Methoxybenzoylpyruvate **3**.

Lithium hexamethyldisilazide (1.2 molar, 208 mℓ, 0.25 mole) was added to anhydrous ether (1 liter). The solution was then cooled to −78° under a nitrogen atmosphere. After 15 minutes, 4-methoxyacetophenone (37.5 g, 0.25 mole) in anhydrous ether (200 mℓ) was added and stirred for 30 minutes at −78°. Diethyl oxalate (36.5 g, 0.25 mole) in anhydrous ether (200 mℓ) was added at once. The solution was then allowed to warm to room temperature. After stirring for an additional 2 hours at room temperature, a solid began to form. Stirring was discontinued and the mixture was allowed to settle overnight. The solid was filtered to afford the title compound, 52 g, 81% of a pale yellow solid, mp 244-247°. A second crop of 9 g, 14%, mp 243-246° was isolated from the mother liquors. Recrystallization from acetone afforded **3** as a pale yellow solid, mp 244-247°; ir (potassium bromide): 1707 $cm^{-1}$, 1622, 1599; $^1H$ nmr (DMSO-$d_6$): δ 1.25 (t, 3H, J = 8 Hz), 3.8 (s, 3H), 4.14 (q, 2H, J = 8 Hz), 6.40 (s, 1H); 6.95 (d, 2H, J = 9 Hz), 7.81 (d, 2H, J = 9 Hz); ms: (DCI) m/e 257 ($M^+$).

*Anal.* Calcd. for $C_{13}H_{13}O_5Li$: C, 60.95; H, 5.12. Found: C, 60.83; H, 4.88.

General Procedure for the Synthesis of 4-Carboethoxy-1,5-diphenylpyrazoles.

A. The desired lithium benzoylpyruvate and substituted phenylhydrazine hydrochloride (0.25 mole each) were combined in 100% ethanol (2 liters) and stirred for 16 hours. The reaction mixture was then concentrated to ½ volume. At this time, crystallization occurred to give most of the desired 1,5-pyrazole. The mother liquors were concentrated and flash chromatographed on silica gel to isolate the remaining 1,5-isomer and the 1,3-isomer. Recrystallization from ethyl acetate/hexane afforded analytically pure samples.

B. The desired lithium ethyl benzoylpyruvate and phenylhydrazine hydrochloride (0.5 moles each) were combined in 100% ethanol (400 mℓ) and stirred for 16 hours. The reaction mixture was then concentrated to a brown residue. The residue was chromatographed on silica gel (Hexane/20% ethyl acetate). The 1,5-isomer was the more polar and was isolated by concentration and crystallization from ethyl acetate/hexane to afford between 70 and 91% yield. The 1,3-isomers were also isolated for comparison.

Table V

Melting Points and Combustion Analysis on Ethyl 1,5-Diarylpyrazole-3-carboxalates

| Compound | MP °C | Theoretical | Found |
|---|---|---|---|
| 9 | 124-125 | C, 71.41 H, 5.99 N, 8.33 | C, 71.13 H, 6.16 N, 8.36 |
| 10 | 105-107 | C, 63.95 H, 4.80 N, 7.85 | C, 63.72 H, 4.96 N, 7.60 |
| 11 | 97-98 | C, 68.17 H, 5.72 N, 7.95 | C, 68.39 H, 5.75 N, 7.87 |
| 12 | oil | C, 67.04 H, 5.03 N, 8.23 | C, 67.18 H, 5.06 N, 8.19 |
| 13 | 112-114 | C, 71.97 H, 6.32 N, 7.99 | C, 71.98 H, 6.54 N, 7.82 |
| 14 | 160-163 | C, 65.96 H, 5.79 N, 7.32 | C, 65.64 H, 5.85 N, 7.30 |
| 15 | 167-168 | C, 58.32 H, 4.12 N, 7.16 | C, 58.16 H, 4.02 N, 7.02 |
| 16 | 68-71 | C, 70.79 H, 5.63 N, 8.69 | C, 70.59 H, 5.40 N, 8.51 |
| 17 | oil | C, 71.41 H, 5.99 N, 8.33 | C, 71.20 H, 6.16 N, 8.16 |
| 18 | 118-120 | C, 63.96 H, 4.80 N, 7.85 | C, 63.99 H, 4.73 N, 7.74 |
| 19 | 129-130 | C, 63.96 H, 4.80 N, 7.85 | C, 64.03 H, 4.61 N, 7.81 |
| 20 | 95-98 | C, 67.05 H, 5.03 N, 8.23 | C, 67.01 H, 5.16 N, 8.28 |

Ethyl 3-(4-Methoxybenzoyl)-2-oxopropanoate-2-(4-chlorophenyl)-hydrazone **21**.

Lithium ethyl 2-(4-methoxybenzoyl)-2-oxopropanoate (2.56 g, 0.01 moles) and 2-chlorophenylhydrazine hydrochloride (1.79 g, 0.01 moles) were combined in 100% ethanol (135 m*l*). The solution was stirred for 2 hours at room temperature. At this point a precipitate formed which was filtered and dried *in vacuo* to afford a yellow solid, 3.25 g, 87%, mp 89-92°; ir (potassium bromide): 3240 $cm^{-1}$, 1678, 1658, 1598; $^1H$ nmr (deuteriochloroform): $\delta$ 1.38 (3H, t, J = 7 Hz), 3.87 (3H, s), 4.33 (2H, q, J = 7 Hz), 4.35 (2H, s)-CO-C$H_2$C=N-, 6.93 (1H, dd, J = 8 Hz), 6.96 (2H, d, J = 9 Hz), 7.24 (1H, dd, J = 8 Hz), 7.3 (1H, d, J = 8 Hz), 7.66 (1H, d, J = 8 Hz), 8.21 (2H, d, J = 9 Hz), 10.43 (1H, s)=N-N*H*-Ph-Cl; ms: (DCI) m/e 375 ($MH^+$).

*Anal.* Calcd. fr $C_{19}H_{19}ClN_2O_4$: C, 60.88; H, 5.11; N, 7.47. Found: C, 60.48; H, 5.11; N, 7.17.

The hydrazone can be readily converted in quantitative yield to compound **19** by heating it at reflux in methanol for 2 hours. No 1,3-isomer could be detected in the mother liquors after reflux for 2 hours.

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[5] Small quantities (0-2%) of the ethyl 2-ethoxy-3-benzoyl-2-propenoate, the enol ethyl ether of the benzoyl pyruvates, were isolated from the mother liquors.

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