A Novel Regioselective *t*-Butylation as Applied to the Synthesis of 5-Cyano-1-(1,1-dimethylethyl)-*N*-methyl-1*H*-pyrazole-4-carboxamide

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The title compound was synthesized in a regiocontrolled way from 5-cyano-1*H*-pyrazole-4-carboxylic acid, ethyl ester (**5**) with isobutylene, *p*-toluenesulfonic acid and methylamine.

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In a continuing search for useful pesticides, Beck and Lynch reported the synthesis of 5-cyano-1-(1,1-dimethylethyl)-*N*-methyl-1*H*-pyrazole-4-carboxamide (**7**) [1] which was found to have excellent herbicidal activity in corn [2]. In this paper we report a more economic alternate synthesis of **7** *via* a novel regioselective *t*-butylation reaction from readily available precursors (Scheme I).

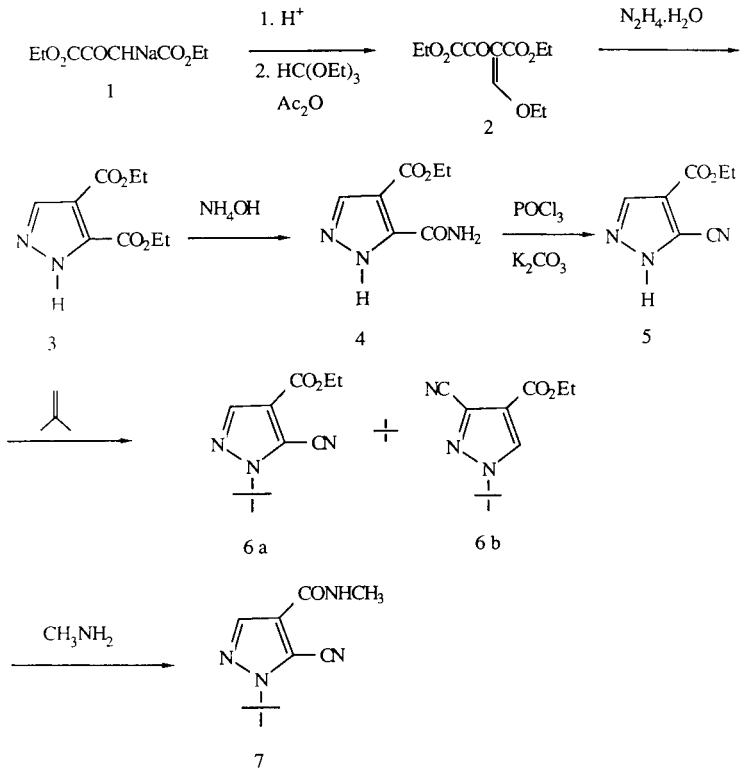
The key step of our strategy involved in the preparation of **5** and its subsequent selective *t*-butylation was to introduce the crucial *t*-butyl group at the N-1 position of the pyrazole nucleus. The most successful alkylation was achieved with isobutylene (2 equivalents) and *p*-toluenesulfonic acid monohydrate in acetonitrile in a parr bottle at 80-85° for 24 hours. This reaction proceeded smoothly to give 84% yield of product in which **6a** predominated **6b** by a ratio greater than 90:1 as measured by hplc. Several other Lewis acids were also examined in this reaction, and the results are shown in Table I.

Table I

Lewis Acids	Isomer Ratio (**6a**:**6b**) HPLC
$ZnCl_2$	10:1
$AlCl_3$	1:99
$SnCl_4$	1:2
BF_3 etherate	1:23

The synthesis of **4** outlined in Scheme I was chosen to be developed and modeled after the general process published by Jones [3-4]. Diethyl (ethoxymethylene)oxalacetate **2** was prepared by the condensation of diethyl oxalacetate obtained from the corresponding sodium salt

Scheme I



7

1 with triethyl orthoformate and acetic anhydride. Reaction of **2** with hydrazine hydrate provided the desired pyrazole diester **3** which was not isolated, but was reacted with ammonium hydroxide to afford **4**. Treatment of **4** with phosphorus oxychloride and potassium carbonate in acetonitrile gave the corresponding pyrazole cyano ester **5**, which was not isolated, but was reacted with isobutylene and *p*-toluenesulfonic acid monohydrate in acetonitrile to provide the desired *t*-butylpyrazole cyano ester **6**. Finally, the solution containing **6** was reacted with 40% aqueous methylamine to produce **7** in 62% yield from **4**. In order to secure the definitive proof of structure **7**, the structural dimensions have been ascertained by means of X-ray crystallography and were shown to be identical with those of product prepared by Beck and Lynch [1].

In conclusion, we have developed an inexpensive, efficient method for the direct introduction of a *t*-butyl group regioselectively to the pyrazole nucleus. The generality of this approach, which not only provides access to the *t*-butyl pyrazole but also is the strategy to provide other N-1 alkyl substituted pyrazoles. The results of the application of this methodology will be the subject of future publication.

EXPERIMENTAL

5-Cyano-1*H*-4-pyrazolecarboxylic Acid, Ethyl Ester (**5**).

To a suspension containing 96.8 g (94.5% pure, 0.5 mole) of **4** [3-4] and 35.0 g (0.33 mole) of sodium carbonate in 500 ml of acetonitrile was added 75 ml (0.8 mole) of phosphorus oxychloride. The mixture was refluxed for 90 minutes and cooled to room temperature and filtered. The solvent was removed *in vacuo*, and water (500 ml) was added. The solid was collected and dried at 40° *in vacuo*, to afford 76.8 g (93%) of **5**, mp 148-150°; ^{1}H nmr (300 MHz, DMSO-d_6, tetramethylsilane): δ 1.3 (t, 3H, CH_3, J = 7 Hz), 4.3 (q, 2H, CH_2, J = 7 Hz), 8.65 (s, 1H, CH).

Anal. Calcd. for $C_7H_7N_3O_2$: C, 50.91; H, 4.27; N, 25.44. Found: C, 51.09; H, 4.23; N, 25.30.

5-Cyano-1-(1,1-dimethylethyl)-1*H*-pyrazole-4-carboxylic Acid, Ethyl Ester (**6**).

A cold mixture (dry ice/acetone) containing 8.3 g (0.05 mole) of **5**, 10 ml (0.1 mole) of isobutylene and 3.1 g (0.015 mole) of *p*-toluenesulfonic acid monohydrate in 100 ml of acetonitrile was placed in a parr bottle, stirred and was gradually heated to reflux. The solution was refluxed for 18 hours, cooled, and excess isobutylene was slowly vented. The solvent was removed *in vacuo*. The material was dissolved in 200 ml of diethyl ether which was washed successively with water, saturated sodium bicarbonate and brine solutions and dried with magnesium sulfate. The solvent was removed *in vacuo* to yield 8.4 g (84%) of oil **6**; ^{1}H nmr (300 MHz, DMSO-d_6, tetramethylsilane): δ 1.3 (t, 3H, CH_3, J = 7 Hz), 1.72 (s, 9H, *t*-butyl), 4.3 (q, 2H, CH_2, J = 7 Hz).

Anal. Calcd. for $C_{11}H_{15}N_3O_2$: C, 59.71; H, 6.83; N, 18.99. Found: C, 59.50; H, 6.57; N, 18.84.

5-Cyano-1-(1,1-dimethylethyl)-*N*-methyl-1*H*-pyrazole-4-carboxamide (**7**).

To a suspension containing 18.3 g (0.1 mole) of **4** and 4.1 g (0.033 mole) of potassium carbonate in 100 ml of acetonitrile was added 7 ml (0.075 mole) of phosphorus oxychloride. The mixture was refluxed for 4 hours and cooled to room temperature and filtered. To the cold filtrate (dry ice/acetone) in a parr bottle was added 20 ml (0.2 mole) of isobutylene and 6.3 g (0.033 mole) of *p*-toluenesulfonic acid monohydrate. The mixture was gradually heated to reflux and was refluxed for 18 hours, cooled and excess isobutylene was slowly vented. The reaction mixture was filtered and the solvent was removed *in vacuo* to afford an oil which was dissolved in 50 ml of methanol and 48 ml of aqueous methylamine. The resulting solution was stirred at room temperature for 18 hours. The solvent was removed *in vacuo*, and water (150 ml) was added. The solid was collected to yield 12.8 g (62%) of **7**, mp 158-160°, lit mp 163-165° [1].

Anal. Calcd. for $C_{10}H_{14}N_4O$: C, 58.24; H, 6.84; N, 27.17. Found: C, 58.38; H, 6.71; N, 26.96.

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REFERENCES AND NOTES

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