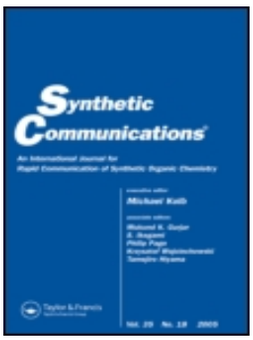

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Dong Ju Jeon , Dong Wook Yu , Kyeong Yeol Yun & Eung K. Ryu

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SYNTHESIS OF NEW 4-BENZOYL-5-HYDROXY-3-TRIFLUOROMETHYLPYRAZOLE DERIVATIVES *VIA* [1,3] REARRANGEMENTS OF BENZOYL GROUP USING *tert*-BUTYLLITHIUM

Dong Ju Jeon, Dong Wook Yu, Kyeong Yeol Yun, and Eung K. Ryu*

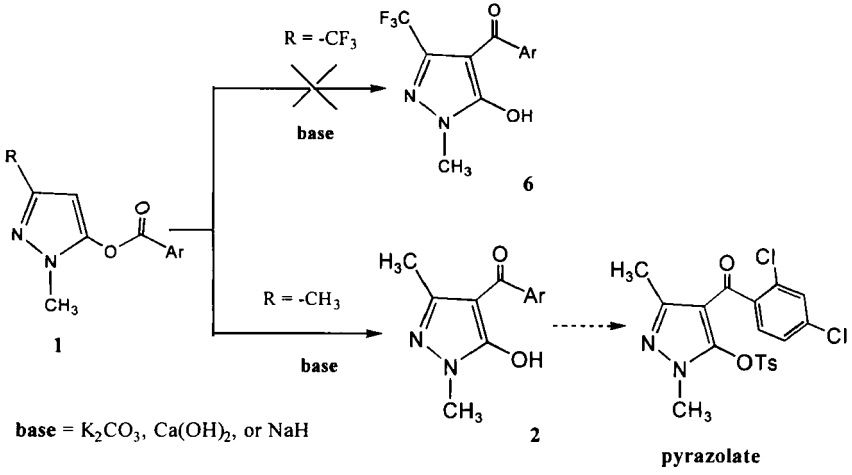
Korea Research Institute of Chemical Technology, P. O. Box 107, Yusong, Taejon 305-600, Korea

Abstract. The 4-benzoyl-3-trifluoromethyl-5-*p*-toluenesulfonyloxypyrazole derivatives (**7a - c**) were synthesized by a new procedure involving rearrangement of the benzoyl groups in 5-benzoyloxy-4-bromo-3-trifluoromethylpyrazole derivatives (**5a - c**) to 4-benzoyl-5-hydroxy-3-trifluoromethylpyrazoles (**6a - c**) *via* lithium-bromide exchange using *tert*-butyllithium.

4-Benzoyl-5-hydroxy-3-methylpyrazole derivatives (**2**) have recently received much interest as potent herbicidal agents. 4-(2,4-Dichlorobenzoyl)-3-methyl-5-*p*-toluenesulfonyloxypyrazole, known as *pyrazolate*[1], has an especially useful herbicidal effect in paddy rice. In search of new pesticides, we have explored modifications of *pyrazolate,* and especially the 3-trifluoromethyl-pyrazole derivatives (**7**), as target molecules.

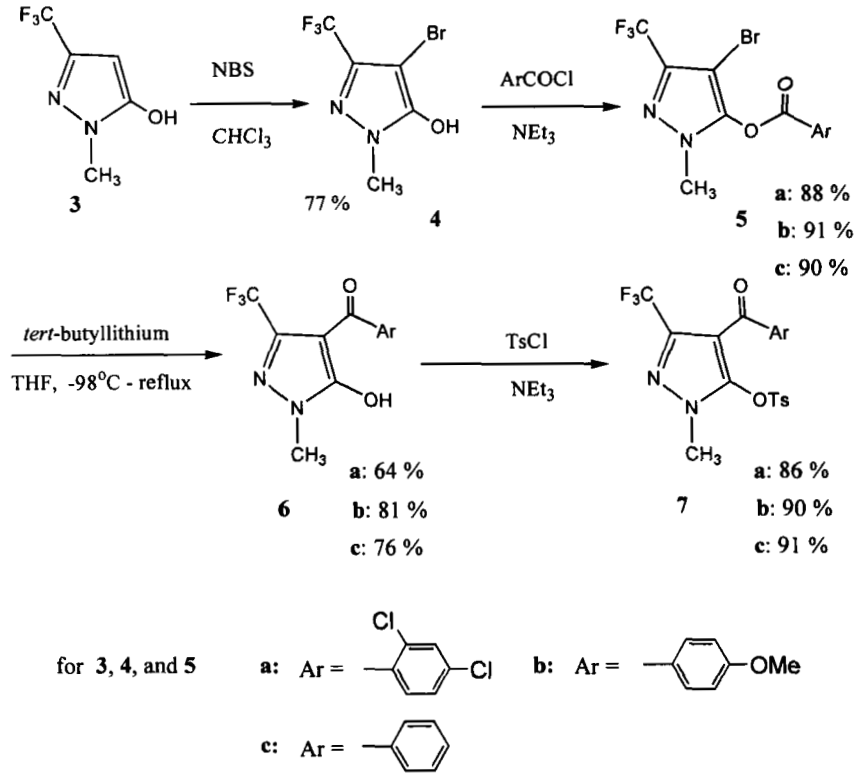
*To whom correspondence should be addressed.

4-Benzoyl-5-hydroxy-3-methylpyrazole derivatives (**2**) can usually be prepared by [1.3] rearrangements of 5-benzoyloxy-3-methylpyrazoles (**1**, R = CH_3).[1,2] When we attempted rearrangements of 5-benzoyloxy-3-trifluoromethyl-pyrazole derivatives (**1**, R = CF_3), we failed to obtain the desired 4-benzoyl-5-hydroxy-3-trifluoromethylpyrazoles (**6**) even under drastic conditions using bases such as K_2CO_3, $Ca(OH)_2$ or NaH (Scheme 1). It became apparent that 5-benzoyloxy-3-trifluoromethylpyrazole derivatives are inert to benzoyl rearrangement by bases, presumably due to the strong electron-withdrawing effect of the trifluoromethyl group.



Scheme 1

However, when we turned our attention to conduct the carbanion-mediated rearrangements of benzoyl groups in 5-benzoyloxy-4-bromo-3-trifluoromethyl-pyrazole derivatives (**5**) to 4-benzoyl-5-hydroxy-3-trifluoromethylpyrazoles (**6**)



Scheme 2

via lithium-bromide exchange using *tert*-butyllithium, we found that the benzoyl group rearranged smoothly to the C-4 position in good yields as shown in Scheme 2. To the best of our knowledge, [1.3] shifts of benzoyl groups *via* lithium-anion intermediates in heterocyclic systems have not been studied.[3]

5-Hydroxy-3-trifluoromethylpyrazole was brominated by NBS at -5 °C for 1h to afford the brominated pyrazole (**4**). The brominated product **4** was benzoylated and then treated with *tert*-butyllithium followed by heating to reflux for 3h to afford the 4-benzoyl-5-hydroxy-3-trifluoromethylpyrazoles (**6**) in good

yields (**Scheme 2**). The rearranged products were easily separable by silica gel column chromatography or recrystallization in yields as listed in **Scheme 2**.

All of the rearranged products **6** were easily distinguished from the corresponding reactants **5** by the ^{1}H NMR and IR spectra. In the IR spectra of compounds **6**, the broad band at around 3300 cm^{-1} was attributed to the hydroxy absorption, and carbonyl bands were shown at 1636 cm^{-1} in **6a**, 1623 cm^{-1} in **6b** and 1630 cm^{-1} in **6c**, respectively.[4]

The compounds **7** as target molecules could be prepared by tosylation of compounds **6**, which was confirmed by their spectra. The MS of compounds **7a** and **7b** showed the molecular ion peaks at m/z, 454 in **7a** and 424 in **7c** respectively, and IR spectra of **7** showed absorptions at 1365 and 1154 cm^{-1} in **7a**, 1356 and 1141 cm^{-1} in **7b**, 1370 and 1172 cm^{-1} in **7c**, respectively, due to the sulfonate absorptions.

In summary, we have developed the [1,3] rearrangement of benzoyl groups in 5-benzoyloxy-4-bromo-3-trifluoromethylpyrazole derivatives (**5a - c**) *via* lithium-bromide exchange with *tert*-butyllithium for the synthesis of 4-benzoyl-3-trifluoromethyl-5-*p*-toluenesulfonyloxypyrazole derivatives (**7a - c**).

EXPERIMENTALS

Melting points were measured in capillary tubes with a Thomas-Hoover capillary melting point apparatus and uncorrected. IR spectra were recorded on a Shimadzu IR-435 spectrophotometer. ^{1}H NMR spectra were obtained with a Varian GEMINI-200. All chemical shifts are reported in ppm downfield from internal tetramethylsilane and coupling constants are given in Hz. Mass spectra

were obtained on a Shimadzu GCMS-QP 1000 mass spectrometer. Chromatographic separations were carried out on a silica gel column (Merck silica gel 60).

Preparation of 4-bromo-1-methyl-5-hydroxypyrazole (4): To a stirred solution of 1-methyl-5-hydroxypyrazole (4.5 g, 27 mmol) in chloroform was added slowly NBS (5.8 g, 33 mmol) under cooling with an ice-bath with stirring for 1h. The mixture was washed twice with water, dried over magnesium sulfate, filtered and evaporated to give a yellow solid. It was washed with *n*-hexane to obtained a colorless solid (5.1 g, 77 %). mp 289 - 292 °C; ^{1}H NMR (acetone-d_6) δ 3.70 (3H, s, -CH_3), 3.15 (1H, brs, -OH); IR (KBr, cm^{-1}) 3500, 1600 , 1577; MS (70eV) m/z (rel. intensity) 246 (M^++1, 46.9), 245 (M^+, 38.3), 225 (10.9), 165 (9.5), 121 (15.3).

Preparation of 4-bromo-5-(2,4-dichlorobenzoyl)oxy-1-methyl-3-trifluoromethylpyrazole (5a); General Procedure: To a stirred solution of **4** (1 g, 4.1 mmol) in chloroform was added slowly 2,4-dichlorobenzoyl chloride (0.6 mL, 4.5 mmol) and then, dropped triethylamine (0.6 mL, 4.5 mmol) under cooling with an ice-bath. The mixture was stirred at that temperature and then at room temperature for 1h, respectively. The reaction mixture was washed twice with water and brine. The organic layers were combined, dried over magnesium sulfate, filtered and evaporated to give a crude solid. It was washed with *n*-hexane and further purified by silica gel column chromatography to obtained **5a** as a colorless solid (1.5 g, 88 %); mp 78 - 80 °C; ^{1}H NMR ($CDCl_3$) δ 8.15 - 7.42 (3H, m, Ar), 3.85 (3H, s, -CH_3); IR (KBr, cm^{-1}) 1770 , 1588; MS (70eV) m/z (rel. intensity) 401(1.2), 400 (1.6), 399 (3.8), 331 (2.0), 330 (1.6), 329 (5.7), 246 (1.8), 245 (4.4), 177 (91.6), 176 (72.6), 175 (100).

4-Bromo-5-(4-methoxybenzoyl)oxy-1-methyl-3-trifluoromethylpyrazole (5b): yield, 91 %; mp 118 - 120 °C; ^{1}H NMR ($CDCl_3$) δ 8.19 (2H, d, J = 9Hz, Ar), 7.04 (2H, d, J = 9Hz, Ar), 3.94 (3H, s, -OCH_3), 3.81 (3H, s, -CH_3); IR (KBr, cm^{-1}) 1736 , 1595; MS (70eV) m/z (rel. intensity) 291 (12.4), 263 (16.4), 262

(52.1), 234 (29.7), 183 (46.0), 182 (52.8), 136 (12.5), 135 (100), 109 (10.0), 108 (25.8).

4-Bromo-5-benzoyloxy-1-methyl-3-trifluoromethylpyrazole (5c): yield, 90 %; mp 289 - 292 °C; ^{1}H NMR ($CDCl_3$) δ 8.19 - 7.50 (5H, m, Ar), 3.80 (3H, s, -CH_3); IR (KBr, cm^{-1}) 1766 , 1601; MS (70eV) m/z (rel. intensity) 331(2.4), 329 (2.1), 251 (3.6), 250 (1.1), 245 (1.3), 244 (0.9), 243 (1.3), 165 (1.5), 155 (1.4), 122 (1.2), 121 (2.8), 120 (2.0), 106 (39.3), 105 (100), 104 (38), 77 (100).

Preparation of 4-(2,4-dichlorobenzoyl)-1-methyl-5-hydroxy-3-trifluoromethylpyrazole (6a); General Procedure: To a stirred solution of **5a** (0.5 g, 1.2 mmol) in dry THF was dropped 1.7M *tert*-butyllithium (0.8 mL, 1.4 mmol) at -98 °C by cooling with a bath of liquid nitrogen-methanol mixture. After stirring for 10 min at that temperature, the solution was allowed to room temperature with stirring and then refluxed for 3h. The mixture was cooled by an ice-bath and then quenched with a saturated NH_4Cl water solution, followed by extraction with ethylacetate. The organic layers were combined, washed twice with brine, dried over magnesium sulfate, filtered and evaporated to give a crude solid. It was washed with *n*-hexane and further purified by silica gel column chromatography to obtained **6a** as a yellow solid (0.26 g, 64 %); mp 150 - 152 °C; ^{1}H NMR ($CDCl_3$) δ 8.35 (1H, brs, D2O exchangeable, -OH), 8.00 (1H, d, J = 8 Hz, Ar), 7.54 (1H, d, J = 2 Hz, Ar), 7.36 (1H, dd, J = 8 Hz and 2 Hz, Ar), 3.79 (3H, s, -CH_3); IR (KBr, cm^{-1}) 3424, 1636 , 1595; MS (70eV) m/z (rel. intensity) 330 (9.0), 311 (5.6), 310 (15.9), 291 (12.0), 290 (37.9), 239 (11.7), 219 (11.8), 173 (7.8), 172 (5.0), 158 (11.2), 157 (12.2).

4-(4-Methoxybenzoyl)-1-methyl-5-hydroxy-3-trifluoromethylpyrazole (6b): yield, 81 %; mp 155 - 157 °C; ^{1}H NMR (MeOH-d_4) δ 7.73 (2H, d, J = 9 Hz, Ar), 6.94 (2H, d, J = 9 Hz, Ar), 3.81 (3H, s, -OCH_3), 3.65 (3H, s, -CH_3); IR (KBr, cm^{-1}) 3205, 1623, 1604; MS (70eV) m/z (rel. intensity) 301 (M^++1, 4.8), 300 (M^+, 9.5), 261 (1.5), 199 (1.9), 198 (4.4), 135 (41.6), 108 (100).

4-Benzoyl-1-methyl-5-hydroxy-3-trifluoromethylpyrazole (6c): yield, 76 %; mp 210 - 212 °C;^{1}H NMR (MeOH-d_4) δ 7.41 - 7.31 (5H, m, Ar), 3.40 (3H, s, -

CH_3); IR (KBr, cm^{-1}) 3435, 1630, 1611; MS (70eV) m/z (rel. intensity) 270 (M^+, 12.6), 250 (28.9), 240 (20.8), 231 (52.5), 230 (21.1), 192 (10.3), 105 (100).

Preparation of 4-(2,4-dichlorobenzoyl)-1-methyl-5-(*p*-toluenesulfonyl)oxy-3-trifluoromethylpyrazole (7a): General Procedure: To a stirred solution of **6a** (0.2 g, 0.6 mmol) in THF was added slowly triethylamine (0.1 mL, 0.7 mmol) and then droppwise a solution of *p*-toluenesulfonylchloride (0.12 g, 0.7 mmol) in THF. The mixture was stirred at room temperature during overnight. Ethylacetate was added and washed twice with water and brine. The organic layers were combined, dried over magnesium sulfate, filtered and evaporated. The crude product was purified by silica gel column chromatography to give **7a** as a colorless solid (0.25 g, 86 %); mp 114 - 116 °C; ^1H NMR ($CDCl_3$) δ 7.60 - 7.23 (7H, m, Ar), 3.74 (3H, s, $-CH_3$), 2.50 (3H, s, $-OCH_3$); IR (KBr, cm^{-1}) 1649 , 1605, 1365, 1154; MS (70eV) m/z (rel. intensity) 459 (6.0), 458 (2.9), 457 (14.2), 303 (1.3), 283 (2.1), 177 (1.8), 176 (1.3), 175 (8.8), 173 (18.5), 172 (13.9)157 (2.3), 156 (4.7), 155 (48.7), 154 (38.3), 147 (3.4), 146 (3.50, 145 (7.8). *Anal.* Calcd for $C_{19}H_{13}Cl_2F_3N_2O_4S$: C, 46.26; H, 2.66; N, 5.68. Found: C, 45.97; H, 2.94; N, 5.89.

4-(4-Methoxybenzoyl)-1-methyl-5-(*p*-toluenesulfonyl)oxy-3-trifluoromethylpyrazole (7b): yield, 90 %; mp 133 - 135 °C; ^1H NMR ($CDCl_3$) δ 7.50 (2H, d, J = 9 Hz, Ar), 7.43 (2H, d, J = 9 Hz, Ar), 7.17 (2H, d, J = 9 Hz, Ar), 6.84 (2H, d, J = 9 Hz, Ar), 3.93 (3H, s, $-OCH_3$), 3.89 (3H, s, $-CH_3$), 2.40 (3H, s, $-CH_3$); IR (KBr, cm^{-1}) 1633 , 1579, 1356, 1141; MS (70eV) m/z (rel. intensity) 455 (M^++1, 6.5), 454 (M^+, 15.6), 300 (2.5), 271 (6.5), 262 (9.5), 155 (74.0), 154 (68.1). *Anal.* Calcd for $C_{20}H_{17}F_3N_2O_5S$: C, 52.86; H, 3.77; N, 6.16. Found: C, 52.99; H, 4.04; N, 5.89.

4-Benzoyl-1-methyl-5-(*p*-toluenesulfonyl)oxy-3-trifluoromethylpyrazole (7c): yield, 91 %; mp 136 - 137 °C; ^1H NMR ($CDCl_3$) δ 7.56 -7.11 (8H, m, Ar), 3.93 (3H, s, $-OCH_3$), 2.40 (3H, s, $-CH_3$); IR (KBr, cm^{-1}) 1657 , 1603, 1370, 1172; MS (70eV) m/z (rel. intensity) 425 (M^++1, 2.1), 424 (M^+, 7.1), 270 (1.5), 241 (1.1), 192 (1.5), 173 (1.5), 155 (76.0), 154 (60.1). *Anal.* Calcd for $C_{19}H_{15}F_3N_2O_4S$: C, 53.77; H, 3.56; N, 6.60. Found: C, 53.99; H, 3.84; N, 6.39.

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4. Although the wavenumbers of carbonyl absorption in compounds **6** and **7** are lower than usual carbonyl groups in the IR spectra, these values are in good agreement with those reported for the other 4-benzoylpyrazoles, see reference 1(**a**).

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