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The new synthesis of substituted 3-(aryl)-1-tosyl-1*H*-pyrazole

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Abstract: The zwitterions generated from dialkyl acetylenedicarboxylate and pyridine or isoquinoline react with tosyl hydrazones to afford substituted 3-(aryl)-1-tosyl-1*H*-pyrazole.

Keywords: Tosyl hydrazone; Isoquinoline; Pyridine; Dialkyl acetylenedicarboxylate; Pyrazole**.**

Introduction

Pyrazole is found widely as a core structure in a large variety of compounds that exhibite important biological properties such as antiviral, analgesic, antimicrobial, anti-hypertensive, anti-inflammatory, hypoglycemix and antitumor [1-7]. It is convenient to synthesize substituted pyrazoles by the intermolecular [3+2] cycloaddition of 1,3-dipoles with alkynes or condensation of hydrazine with 1,3-diketones or their equivalents [8-11]. However, several papers have repoeted the synthesis of substituted pyrazoles on solide phase or by using a one-pot process with high efficiency [12-14]. We recently communicated diasteroselective and regioselective multicomponent synthesis of these compounds [15,16].

Results and discussion

We followed the same strategy and started our synthetic program from tosyl hydrazone, which is special starting material of this system. Herein, we now describe an efficient, novel, and highly simple peocedure for the direct synthesis of dialkyl 3-(aryl)-1-tosyl-1*H*-pyrazoles 3 from dialkyl acetylenedicarboxylates 1 and tosyl hydrazones 2 in the presence of isoquinoline or pyridine at room temperature in good yields (Scheme **1**).

The products were characterized on the basis of spectroscopic data. The IR spectrum of compound **3a** clearly shows absorbtion characteristic of ester carbonyl group at 1730 cm^{-1}, and for sulfonyl group at 1196 and 1274 cm^{-1}. The ^1H NMR spectrum exhibited three sharp singlets at 2.43, 3.62, and 3.73 for methyl group and the methoxycabonyl group protons, respectively. The presence of the doublet and multiblet signal in the range of 7.34-7.92 ppm for aromatic moiety and molecular ion peak *m/z* at 414 in the mass spectrum confirm the proposed structure as dimethyl 1-[(4-methylphenyl)sulfonyl]-3-phenyl-1H-pyrazole-3,4-dicarboxylate. The ^{13}C NMR signals for the two carbonyl groups were absorved at 162.5 and 163.2 ppm.

A mechanistic rationalization for the reaction is provided in scheme **2**. The target compounds **3** result from initial addition of isoquinoline to dialkyl acetylenedicarboxylate 1 (1,3-dipole 4) and subsequent protonation of this 1:1 adduct by tosyl hydrazone 2, followed by attack of the nitrogen atom of the anion of 2 to cation 5 to generate 6, which is converted into substituted pyrazole by elimination of H_2 and isoquinoline from intermediate 7.

Conclusion

A novel, versatile, three-component reaction is uncovered, which leads to pyrazole derivatives. The

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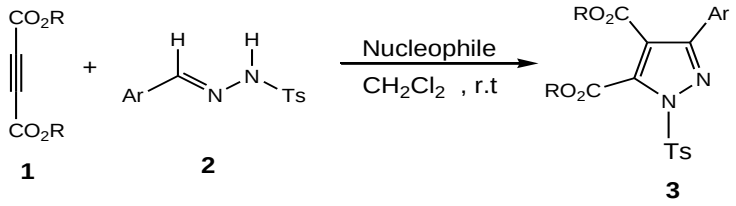
reaction is suitable for the generation of a library with high structural and functional diversity. Further investigations aimed at defining the scope and limitations of the reaction are in progress.



3	R	Ar	Nu	Yield %
a	Me	Ph	isoquinoline	80
a	Me	Ph	pyridine	87
b	Me	4-MeC_6H_4	isoquinoline	78
b	Me	4-MeC_6H_4	pyridine	80
c	Me	4-ClC_6H_4	isoquinoline	78
c	Me	4-ClC_6H_4	pyridine	83
d	Et	Ph	isoquinoline	84
d	Et	Ph	pyridine	75
e	Et	4-MeC_6H_4	isoquinoline	80
e	Et	4-MeC_6H_4	pyridine	79
f	Et	4-ClC_6H_4	isoquinoline	82
f	Et	4-ClC_6H_4	pyridine	78

Scheme 1. Reaction of dialkyl acetylenedicarboxylates with tosyl hydrazones in the presence of isoquinoline or pyridine at rt.

Experimental

Material and methods:

Mp: *Electrothermal-9100* apparatus; uncorrected. IR Spectra: *Shimadzu IR-460* spectrometer. ^{1}H- and ^{13}C-NMR spectra: Bruker DRX-400 AVANCE instrument; in $CDCl_3$ at 400.1 and 100.6 MHz, resp.; □ in ppm, *J* in Hz. EI-MS (70 eV): Finnigan-MAT-8430 Mass spectrometer, in *m/z*. Elemental analyses (C, H, N) were performed with a Heraeus CHN-O-Rapid analyzer. All chemicals were used as-received from the appropriate suppliers.

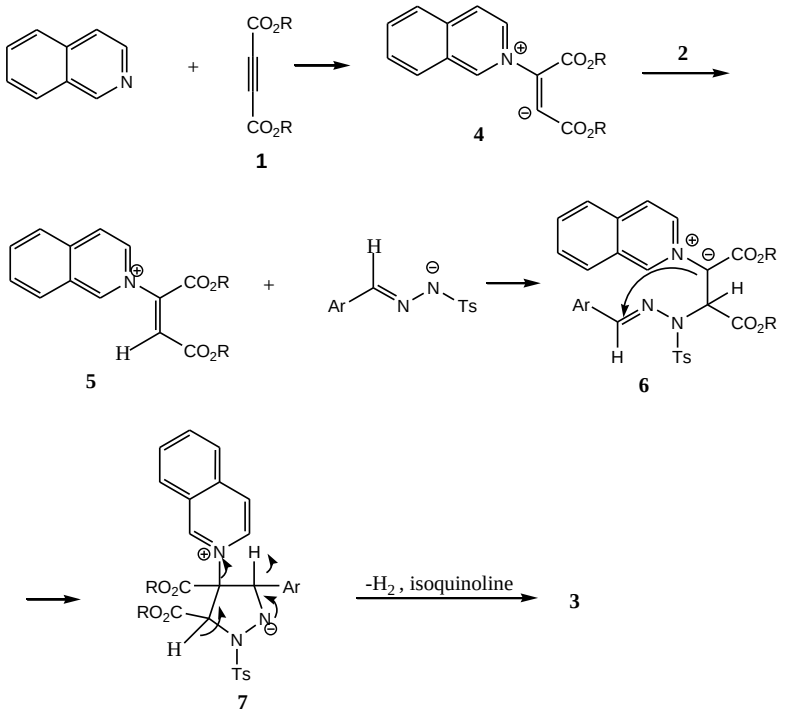
General procedure:

To a mixture of isoquinoline or pyridine (1 mmol) and tosyl hydrazone (1mmol) in 3 ml dichloromethane was added a solution of dialkyl acetylenedicarboxylate (1mmol) in 2 ml CH_2Cl_2 under -5 to 0 °C temperature. On completion of the reaction (15h), as indicated by the TLC of the reaction mixture, the solvent was evaporated using a rotary evaporator. The resulting residue was purified by silica gel column chromatography (6:1 hexane/ethyl acetate) and recrystallized from diethyl ether to afford crystalline product.

Dimethyl 1-[(4-methylphenyl)sulfonyl]-3-phenyl-1H-pyrazole-4,5-dicarboxylate (3a):

Yellow powder, yield: 0.33 g (80%), m.p. 124-126°C. IR (KBr) (ν_{max}/cm^{-1}): 2948, 1730, 1444, 1347, 1274, 1196, 1031, 769, 680, 568 cm^{-1}. ^{1}H NMR: 2.43 (s, 3 H, Me), 3.62 (s, 3 H, MeO), 3.73 (s, 3 H, MeO), 7.34 (m, 5 H, 5 CH), 7.59 (m, 2 H, 2 CH), 7.92 (d, ^3J = 8.40 Hz, 2 H, 2 CH). ^{13}C NMR: 21.6 (Me), 52.5 (MeO), 53.2 (MeO), 127.4 (2 CH), 128.5 (2 CH), 128.9 (2 CH), 129.1 (2 CH), 130.1 (CH), 133.1 (C), 133.6 (C), 134.4 (C), 135.2 (C), 143.0 (C), 144.2 (C), 162.5 (C=O), 163.2 (C=O). EI-MS: 414 (M^+, 3), 229 (100), 201 (75), 155 (35), 91 (90), 77 (40), 65 (30).

Anal. Calcd for $C_{20}H_{18}N_2O_6S$ (414.43): C 57.96, H 4.38, N 6.76%. Found: C 56.47, H 4.89, N 6.16 %.



Scheme 2. Proposed mechanism for the reaction of dialkyl acetylenedicarboxylate with tosyl hydrazone in the presence of isoquinoline.

Dimethyl 3-(4-methylphenyl)-1-[4-methylphenyl) sulfonyl] -1H-pyrazole-4,5-dicarboxylate (3b):

Yellow powder, yield: 0.33 g (78%), m.p. 147-148 °C. IR (KBr) (ν_{max}/cm^{-1}): 2981, 1715, 1453, 1342, 1245, 1159, 1053, 810, 668, 582 cm^{-1}. ^{1}H NMR: 2.35 (s, 3 H, Me), 2.43 (s, 3 H, Me), 3.60 (s, 3 H, MeO), 3.73 (s, 3 H, MeO), 7.16 (d, ^3J = 7.95 Hz, 2 H, 2 CH), 7.31 (d, ^3J = 8.30 Hz, 2 H, 2 CH), 7.47 (d, ^3J = 7.95 Hz, 2 H, 2 CH), 7.91 (d, ^3J = 8.30 Hz, 2 H, 2 CH). ^{13}C NMR: 21.4 (Me), 21.6 (Me), 52.5 (MeO), 53.21 (MeO), 127.4 (2 CH), 128.9 (2 CH), 129.0 (2 CH), 129.3 (2 CH), 130.9 (C), 133.3 (C), 134.3 (C), 135.3 (C), 140.5 (C), 143.4 (C), 144.1 (C), 162.6 (C=O), 163.3 (C=O). EI-MS: 428 (M$^+$, 3), 243 (100), 215 (86), 155 (30), 91 (90), 77 (40), 65 (25). Anal. Calcd for $C_{21}H_{20}N_2O_6S$ (428.45): C 58.87, H 4.70, N 6.54%. Found: C 59.54, H 5.12, C 6.14 %.

Dimethyl 3-(4-chlorophenyl)-1-[4-methylphenyl) sulfonyl]-1H-pyrazole-4,5-dicarboxylate (3c):

Yellow powder, yield: 0.37 g (83%), m.p. 122-124 °C. IR (KBr) (ν_{max}/cm^{-1}): 2937, 1737, 1441, 1359, 1266, 1186, 1039, 674, 568 cm^{-1}. ^{1}H NMR: 2.45 (s, 3 H, Me), 3.65 (s, 3 H, MeO), 3.75 (s, 3 H, MeO), 7.28 (d, ^3J = 7.40 Hz, 2 H, 2 CH), 7.34 (d, ^3J = 8.40 Hz, 2 H, 2 CH), 7.52 (d, ^3J = 7.40 Hz, 2 H, 2 CH), 7.91 (d, ^3J = 8.40 Hz, 2 H, 2 CH). ^{13}C NMR: 21.7 (Me), 52.6 (MeO), 53.3 (MeO), 128.5 (2 CH), 128.8 (2 CH), 128.9 (2 CH), 129.1 (2 CH), 132.1 (C), 133.0 (C), 134.6 (C), 135.0 (C), 136.0 (C), 141.5 (C), 144.4 (C), 162.4 (C=O), 163.1 (C=O). EI-MS: 448 (M$^+$, 2), 263 (100), 235 (85), 111 (40), 91 (95), 65 (32). Anal. Calcd for $C_{20}H_{17}ClN_2O_6S$ (448.87): C 53.52, H 3.82, N 6.24 %. Found: C 54.24, H 3.27, N 6.01%.

Diethyl 1-[(4-methylphenyl)sulfonyl]-3-phenyl-1H-pyrazole-4,5-dicarboxylate (3d):

Yellow powder, yield: 0.33 g (75%), m.p. 131-134°C. IR (KBr) (ν_{max}/cm^{-1}): 2935, 1735, 1452, 1341, 1292, 1175, 1021, 675, 582 cm^{-1}. ^{1}H NMR: 1.09 (t, ^3J = 7.20 Hz, 3 H, Me), 1.29 (t, ^3J = 7.20 Hz, 3 H, Me), 2.41 (s, 3 H, Me), 4.32 (q, ^3J = 7.20 Hz, 2 H, CH_2O), 4.40 (q, ^3J = 7.20 Hz, 2 H, CH_2O), 7.42 (m, 5 H, 5 CH), 7.55 (m, 2 H, 2 CH), 7.95 (d, ^3J = 8.20 Hz, 2 H, 2 CH). ^{13}C NMR: 13.9 (Me), 14.1 (Me), 21.7 (Me), 61.4 (CH_2O), 61.6 (CH_2O), 126.8 (2 CH), 128.0 (2 CH), 128.6 (2 CH), 129.4 (2 CH), 130.2 (CH), 133.0 (C), 133.5 (C), 134.5 (C), 135.3 (C), 143.1 (C), 144.1 (C), 162.7 (C=O), 163.9 (C=O). EI-MS: 442 (M$^+$+1, 80), 257 (100), 215 (90), 155 (25), 91 (93), 77 (38), 65

(28). Anal. Calcd for $C_{22}H_{22}N_2O_6S$ (442.48): C 59.72, H 5.01, N 6.33%. Found: C 60.12, H 5.12, C 6.14 %.

Diethyl 3-(4-methylphenyl)-1-[4-methylphenyl) sulfonyl]-1H-pyrazole-4,5-dicarboxylate (3e):

Yellow powder, yield: 0.36 g (80%), m.p. 125-128 °C. IR (KBr) (ν_{max}/cm^{-1}): 2985, 1710, 1472, 1363, 1231, 1125, 1018, 653, 573 cm^{-1}. ^{1}H NMR: 1.02 (t, ^3J = 7.20 Hz, 3 H, Me), 1.24 (t, ^3J = 7.20 Hz, 3 H, Me), 2.37 (s, 3 H, Me), 2.43 (s, 3 H, Me), 4.06 (q, ^3J = 7.20 Hz, 2 H, CH_2O), 4.22 (q, ^3J = 7.20 Hz, 2 H, CH_2O), 7.17 (d, ^3J = 8.02 Hz, 2 H, 2 CH), 7.28 (d, ^3J = 8.10 Hz, 2 H, 2 CH), 7.48 (d, ^3J = 8.02 Hz, 2 H, 2 CH), 7.94 (d, ^3J = 8.10 Hz, 2 H, 2 CH). ^{13}C NMR: 13.7 (Me), 13.8 (Me), 21.5 (Me), 21.6 (Me), 61.9 (CH_2O), 62.4 (CH_2O), 127.3 (2 CH), 128.9 (2 CH), 129.0 (2 CH), 129.3 (2 CH), 130.9 (C), 133.2 (C), 134.2 (C), 135.4 (C), 140.4 (C), 143.4 (C), 144.0 (C), 162.1 (C=O), 163.0 (C=O). EI-MS: 456 (M^+, 3), 271 (100), 229 (80), 155 (28), 91 (85), 77 (45), 65 (30). Anal. Calcd for $C_{23}H_{24}N_2O_6S$ (456.51): C 60.51, H 5.30, N 6.14%. Found: C 59.34, H 5.16, C 6.34 %.

Diethyl 3-(4-chlorophenyl)-1-[4-methylphenyl) sulfonyl]-1H-pyrazole-4,5-dicarboxylate (3f):

Yellow powder, yield: 0.37 g (78%), m.p. 145-147 °C. IR (KBr) (ν_{max}/cm^{-1}): 2980, 1717, 1468, 1358, 1258, 1160, 1029, 813, 663, 564 cm^{-1}. ^{1}H NMR: 1.06 (t, ^3J = 7.20 Hz, 3 H, Me), 1.25 (t, ^3J = 7.20 Hz, 3 H, Me), 2.44 (s, 3 H, Me), 4.09 (q, ^3J = 7.20 Hz, 2 H, CH_2O), 4.21 (q, ^3J = 7.20 Hz, 2 H, CH_2O), 7.30 (d, ^3J = 7.45 Hz, 2 H, 2 CH), 7.40 (d, ^3J = 8.40 Hz, 2 H, 2 CH), 7.52 (d, ^3J = 7.45 Hz, 2 H, 2 CH), 7.92 (d, ^3J = 8.40 Hz, 2 H, 2 CH). ^{13}C NMR: 13.7 (Me), 13.8 (Me), 21.6 (Me), 61.9 (CH_2O), 62.6 (CH_2O), 128.4 (2 CH), 128.8 (2 CH), 128.9 (2 CH), 129.1 (2 CH), 132.2 (C), 133.0 (C), 134.8 (C), 135.2 (C), 135.9 (C), 141.5 (C), 144.3 (C), 161.8 (C=O), 162.8 (C=O). EI-MS: 476 (M^+, 3), 277 (100), 244 249 (80), 138 (25), 111 (45) 91 (90), 65 (35). Anal. Calcd for $C_{22}H_{21}ClN_2O_6S$ (476.92): C 55.40, H 4.44, N 5.87 %. Found: C 56.08, H 3.89, N 6.12%.

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