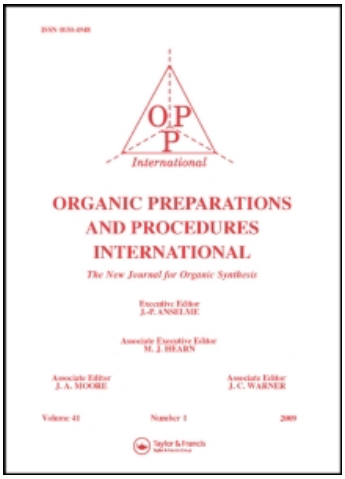

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ONE-POT SYNTHESIS OF NOVEL 10-ARYL[1,2,4]TRIAZOLO[3',4':2,3][1,3,4]-THIADIAZEPINO[6,7-*c*]QUINOLIN-6(5*H*)-ONES

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The newly reported 3,4-heteroannelated quinolin-2-ones are associated with a variety of pharmacological properties.[1] Due to high incidence of desirable pharmacological and physiological properties of these heterocycles, new synthetic methods to afford these heterocycles are gaining importance. Thiadiazepines and triazoles also contribute a wide range of therapeutically interesting drug candidates. Recent attempts were made to incorporate the 1,2,4-triazole nucleus into a wide variety of pharmacologically active compounds such as antihistamines, antianxiety agents and sedatives.[2] Thus, certain *s*-triazolobenzodiazepines like alprazolam, triazolam and adinazolam have been reported to have very high anxiolytic and hypnotic activities in humans.[3] In continuation of our interest in hitherto unknown 3,4-heteroannelated quinolin-2-ones[4] and , as a result of the importance of triazolodiazepines in the pharmacological field, the synthesis of the title compounds is reported in the present communication. For the synthesis of 10-aryl[1,2,4]triazolo[3',4':2,3][1,3,4]thiadiazepino-[6,7-*c*]quinolin-6(5*H*)-ones, 4-chloro-3-formylquinolin-2(1*H*)-ones (**1**)[5] and 5-aryl-4-amino-3-mercapto(4*H*)-1,2,4-triazoles (**2**)[6] were selected as the suitable starting materials.

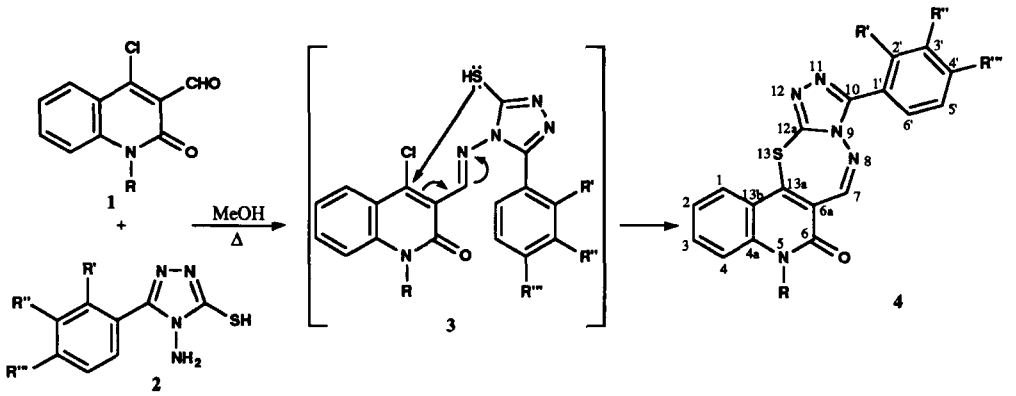
As an illustrative example, the reaction of 1-methyl-4-chloro-3-formylquinolin-2-one (**1a**) with an equimolar quantity of 5-*o*-tolyl-4-amino-3-mercapto-(4*H*)-1,2,4-triazole (**2b**) in refluxing methanol furnished a single compound in 95% yield (mp. 280-282°). The mass spectrum of the compound displayed a molecular ion peak at m/z 373 (95%) and a M+2 peak at 375 (4%). The IR spectrum (KBr) revealed stretching frequencies due to N-C=O and C=N groups at 1630 and 1600 cm^{-1}. The ^1H NMR spectrum ($CDCl_3$) displayed signals at δ 2.35 (s, 3H, Ar-CH_3), 3.75 (s, 3H, N-CH_3), 7.2-8.2 (m, 7H, arom), 8.45 (d, 1H, arom, J = 8.3 Hz, C^1-H) and 8.65 (s, 1H, CH=N). With the aid of above spectral data and elemental analysis, the structure of the compound has been assigned as 5-methyl-10-(2-methylphenyl)[1,2,4]triazolo[3',4':2,3][1,3,4]thiadiazepino[6,7-c]-quinolin-6(5*H*)-one (**4b**). The ^{13}C NMR spectrum of this compound was recorded, and the assignments are presented in Table 3.

The reaction involves the nucleophilic addition of -NH_2 group of 5-aryl-4-amino-3-mercapto-(4*H*)-1,2,4-triazole (**2**) to the carbonyl group of 4-chloro-3-formylquinolin-2(1*H*)-ones, followed by

dehydration to afford the intermediate **3**. Nucleophilic attack of sulfur on the electron deficient carbon in intermediate **3**, and simultaneous ring closure leads to the formation of another intermediate from which the elimination of chloride ion results in the formation of title compounds **4**. Adopting the above procedure, fourteen other substituted 10-aryl[1,2,4]triazolo[3',4':2,3][1,3,4]thiadiazepino[6,7-*c*]quinolin-6(5*H*)-ones (**4b-o**) were synthesized in 70-95% yields. The structures assigned to these compounds (**4a-o**) are well supported by the spectral properties and elemental analysis. The mass fragmentation pattern of the compounds (**4a-o**) is similar, and the important ions, along with M^+ are presented in Table 1. ^{13}C-NMR spectra of compounds **4d** and **4j** were recorded, and the assignments are given in Table 3.

The reaction of **1a** and **2b** has been carried out in DMF in the presence of K_2CO_3 at room temperature and also in THF at room temperature. In both these cases, the same product **4b** was isolated, but in considerably lower yields (70, 75%). Therefore, the title compounds were synthesized by reacting **1** and **2** in refluxing methanol.

Scheme



a) R = Me. R' = R'' = R''' = H b) R = R' = Me, R'' = R''' = H c) R = Me, R' = NO_2, R'' = R''' = H
d) R = Me, R' = H, R'' = OMe, R''' = H e) R = Me, R' = R'' = H, R''' = OMe f) R = Et, R' = R'' = R''' = H
g) R = Et, R' = Me. R'' = R''' = H h) R = Et, R' = NO_2, R'' = R''' = H i) R = Et, R' = H, R'' = OMe, R''' = H
j) R = Et, R' = R'' = H, R''' = OMe k) R = Ph, R' = R'' = R''' = H l) R = Ph, R' = Me, R'' = R''' = H
m) R = Ph, R' = NO_2, R'' = R''' = H n) R = Ph, R' = H, R'' = OMe, R''' = H o) R = Ph, R' = R'' = H, R''' = OMe.

EXPERIMENTAL SECTION

Melting points reported are uncorrected and were determined in capillaries using a sulfuric acid bath. UV spectra were taken in methanol IR spectra were obtained in KBr and ^{1}H NMR were recorded in $CDCl_3$.

Synthesis of 10-Aryl[1,2,4]triazolo[3',4':2,3][1,3,4]thiadiazepino[6,7-*c*]quinolin-6(5*H*)-ones (4a-o). General Procedure. - To a solution of 4-chloro3-formylquinolin-2(1*H*)-one (**1**, 1 mmole) in absolute methanol (10 mL), an equimolar quantity of the appropriate 5-aryl-4-amino-3-mercapto-(4*H*)-1,2,4triazole (**2**, 1 mmole) was added and refluxed for 10-75 minutes. The title compounds sepa-

rated out from the reaction mixture as yellow-orange colored crystalline solids while hot. The reaction mixture was cooled, filtered, residue washed with little methanol and dried. The crude 10-aryl[1,2,4]triazolo[3',4':2,3][1,3,4]thiadiazepino[6,7-*c*]quinolin-6(5*H*)-ones (**4a-o**), thus obtained were crystallized from methanol:benzene (1:1) solvent mixture.

TABLE 1. Physical Constants of Compounds **4**

Compd	m.p. (°C)	Yield (%)	Elemental analysis (Found) C	H	N	EIMS m/z (%)
4a	290-292	80	63.47 (63.61)	3.67 (3.70)	19.49 (19.62)	359 (M^+100), 358 (30), 330 (5) 242 (30), 117 (5)
4b	280-282	95	64.38 (64.51)	4.06 (4.12)	18.78 (18.90)	373 (M^+95), 372 (20), 242 (20), 131 (100)
4c	282-284	90	56.49 (56.62)	2.91 (2.78)	20.76 (20.90)	—
4d	240-241	95	61.62 (61.45)	3.86 (3.93)	17.90 (17.77)	—
4e	250-251	95	61.67 (61.81)	3.80 (3.82)	17.93 17.78)	389 (M^+20), 388 (15), 357 (5), 242 (5), 147(5).
4f	248-250	80	64.37 (64.51)	4.03 (4.12)	18.79 (18.90)	373 (M^+100), 372 (20), 330 (5), 256 (30), 117 (10)
4g	250-252	95	65.06 (65.21)	4.41 (4.50)	18.08 (18.23)	387 (M^+80), 386 (15), 256 (20), 131 (100)
4h	307-309	70	57.42 (57.28)	3.31 (3.25)	20.06 (20.21)	—
4i	156-158	90	62.51 (62.37)	4.23 (4.31)	17.31 (17.25)	403 (M^+90), 402 (10), 256 (30), 147 (20)
4j	160-162	85	62.53 (62.61)	4.25 (4.32)	17.37 (17.51)	403 (M^+100), 402 (20), 256 (40), 147 (20)
4k	290-292	80	68.33 (68.51)	3.51 (3.48)	16.66 (16.70)	421 (M^+100), 330 (5), 304 (20), 117 (5)
4l	330-332	95	68.90 (68.83)	3.91 (3.85)	16.08 (16.09)	435 (M^+90), 304 (30), 131 (80)
4m	286-288	70	61.73 (61.91)	3.06 (3.10)	18.09 (18.20)	466 (M^+50), 304 (10), 162 (10)
4n	260-261	95	66.51 (66.36)	3.72 (3.63)	15.54 (15.71)	451 (M^+100), 304 (40), 147 (20)
4o	170-172	70	66.51 (66.45)	3.76 (3.81)	15.53 15.71)	—

TABLE 2. Spectral Data of Compounds **4**

Compd	IR cm^{-1}	UV λ_{max} (log ε)	^1H NMR δ ppm, J (Hz)
4a	1640 1600	473.1 (2.82), 375.2 (4.11), 305.4 (4.23), 241.0 (4.77)	3.7 (s, 3H), 7.0-8.2 (m, 9H, arom), 8.4 (s, 1H)
4b	1630 1600	472.6 (2.84), 321.1 (4.39), 236.3 (4.90)	2.35 (s, 3H), 3.75 (s, 3H), 7.2-8.2 (m, 7H, arom), 8.45 (d, 1H, arom, J = 8.3), 8.65 (s, 1H).
4c	1640 1600	472.8 (2.73), 385.8 (4.20), 375.5 (4.22), 229.3 (4.77) 210.4 (4.72)	3.75 (s, 3H), 7.2-8.2 (m, 7H, arom), 8.45 (d, 1H, arom, J = 8.3), 8.6 (s, 1H)
4d	1645 1600	473.1 (2.72), 375.4 (4.26), 297.9 (4.43), 231.5 (4.93)	3.7 (s, 3H), 3.85 (s, 3H), 7.0-7.8 (m, 7H, arom), 8.4 (d, 1H, J = 8), 8.7 (s, 1H).
4e	1640 1600	473.6 (2.64), 375.5 (4.08), 244.3 (4.67), 203.5 (4.75)	3.7 (s, 3H), 3.85 (s, 3H), 6.9-8.0 (m, 7H, arom), 8.3 (d, 1H, arom, J = 8), 8.6 (s, 1H).
4f	1620 1600	472.5 (2.62), 375.3 (4.21), 300.0 (4.53), 238.8 (4.51), 209.2 (4.80)	1.4 (t, 3H, J = 6.6), 4.25 (q, 2H, J = 6.6), 7.2-8.05 (m, 8H, arom), 8.3 (d, 1H, J = 8, arom), 8.6 (s, 1H).
4g	1640 1600	473.0 (2.64), 370.9 (4.45), 306.1 (4.53), 236.2 (4.62), 207.8 (4.79)	1.25 (t, 3H, J = 6.8), 2.25 (s, 3H), 4.25 (q, 2H, J = 6.8), 7.25-8.1 (m, 7H, arom), 8.5 (d, 1H, arom, J = 8.3), 8.6 (s, 1H).
4h	1640 1600	472.0 (2.95), 379.0 (4.21), 339.4 (4.22), 335.2 (4.23), 285.8 (4.32), 239.4 (4.85), 210.6 (4.74)	1.45 (t, 3H, J = 6.8), 4.4 (q, 2H, J = 6.8), 7.3-8.2 (m, 7H, arom), 8.4 (d, 1H, arom, J = 8.0), 8.85 (s, 1H).
4i	1640 1600	473.0 (2.62), 376.5 (4.42), 298.4 (4.58), 231.8 (4.82)	1.4 (t, 3H, J = 7.1), 3.9 (s, 3H), 4.4 (q, 2H, J = 7.1), 7.05-7.8 (m, 7H, arom), 8.45 (d, 1H, arom, J = 8.2), 8.8 (s, 1H)
4j	1630 1600	472.5 (2.73), 369.6 (4.31), 320.3 (4.34), 248.6 (4.90)	1.4 (t, 3H, J = 7.00), 3.88 (s, 3H), 4.38 (q, 2H, J = 7.00), 6.87-7.8 (m, 7H, arom), 8.4 (d, 1H, arom, J = 8.3), 8.8 (s, 1H)
4k	1645 1600	473.4 (2.62), 342.2 (4.22), 268.0 (4.44), 210.0 (4.77)	6.75-8.2 (m, 13H, arom), 8.4 (d, 1H, arom, J = 8), 8.8 (s, 1H).
4l	1645 1600	472.2 (2.66), 345.0 (4.31), 273.9 (4.31), 210.4 (4.88)	2.25 (s, 3H), 6.7-8.3 (m, 12H, arom), 8.5 (d, 1H, arom, J = 8.2), 8.8 (s, 1H)
4m	1645 1610	472.8 (2.99), 345.4 (4.15), 273.3 (4.35), 234.4 (4.65), 209.3 (4.60)	6.8-8.3 (m, 12H, arom), 8.5 (d, 1H, arom, J = 8.0), 8.85 (s, 1H).
4n	1650 1600	473.1 (2.73) , 345.9 (4.44), 275.5 (4.14), 235.9 (4.69), 210.0 (4.90)	3.95 (s, 3H), 6.75-8.2 (m, 12H, arom), 8.5 (d, 1H, arom, J = 8.3), 8.8 (s, 1H)
4o	1645 1610	473.4 (2.73), 340.2 (4.23), 275.6 (4.40), 234.6 (4.88), 201.2 (4.40)	3.85 (s, 3H), 6.7-8.2 (m, 12H, arom), 8.45 (d, 1H, arom, J = 8.2), 8.8 (s, 1H).

TABLE. 3. ^{13}C NMR Data of Compounds **4**

Compd	Solvent	δ ppm (assignments) J (Hz)
4b	TFA	21.17 (C-7'), 33.24 (C-8'), 119.58 (C-4), 122.54 (C-13b), 125.62 (C-l), 128.71 (C-2), 129.54 (C-6a), 130.65 (C-2'), 133.29 (C-6'), 134.51 (C-3, C-4'), 137.49 (C-5'), 139.54 (C-3'), 142.08 (C-1'), 143.55 (C-4a), 150.47 (C-13a), 152.64 (C-10), 157.34 (C-12a), 162.84 (C-6) and 165.68 (C-7).
4d	TFA	31.06 (q, J = 83.6, C-8'), 55.96 (q, J = 83.6, C-7'), 115.99 (d , J = 117.1, C-4'), 116.66 (d, J = 139.4, C-2'), 120.20 (s, C-13b), 121.36 (d, J = 117.1, C-6'), 122.87 (d, J = 125.5, C-4), 123.49 (s, C-1'), 126.56 (d, J = 139.4, C-l), 128.38 (d, J = 133.8, C-2), 128.79 (s, C-6a), 132.02 (d, J = 125.5, C-3), 137.36 (d, J = 125.5, C-5'), 141.20 (s, C-4a), 148.50 (s, C-13a), 150.16 (s, C-10), 153.04 (s, C-12a), 160.50 (s, C-3'), 163.30 (d, J = 139.4, C-7)
4j	DMSO-d_6	12.57 (C-9'), 37.41 (C-8'), 55.32 (C-7'), 114.19 (C-3', C-5'), 115.41 (C-4), 118.56 (C-13b), 121.19 (C-1), 127.66 (C-2), 128.0 (C-3, C-6'), 129.59 (C-2'), 134.25 (C-6a), 139.12 (C-1'), 144.26 (C-4a), 149.52 (C-13a), 150.12 (C-10), 152.20 (C-12a), 157.72 (C-4'), 160.21 (C-6), 160.94 (C-7).

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