Synthesis of Some New Substituted Ethanone Hydrazones Containing 1*H*-1,2,4-triazole and Thiazole

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Three new thiosemicarbazones have been synthesized by condensation reaction of 2-bromo-1-arylethanones with thiosemicarbazide, which reacted with various 2-bromo-1-arylethanones in ethanol under refluxing to give a series of substituted ethanone hydrazone derivatives. Their structures were confirmed by elemental analysis, IR, ^{1}H NMR, and MS spectra.

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Introduction.

In recent years, there has been increasing interest in synthesis of heterocyclic compounds that have biological and commercial importance. 1,2,4-Triazols are biological interesting molecules and their chemistry is receiving considerable attention due to antihypertensive, antifungal and antibacterial properties [1-4]. In addition, many heterocycles containing the thiazole ring are associated with a particularly wide range of biological properties, including antiprotozoal [5] and anticonvulsant activity [6], as well as a depressant effect on the central nervous system [7]. Moreover, it is frequently present in the tuberculostically active drugs [8], in addition to its use as mildew-preventing agent [9]. Therefore, compounds containing both 1,2,4-triazole and thiazole moieties are expected to possess potential biological activities. For this reason, synthesis of compounds of 1-aryl-2-(1*H*-1,2,4-triazol-1-yl)ethanone (4-aryl-1,3-thiazol-2-yl)hydrazone derivatives that contain 1,2,4-triazol and thiazol in the molecule are very interesting. The title compounds were prepared according to the Scheme 1.

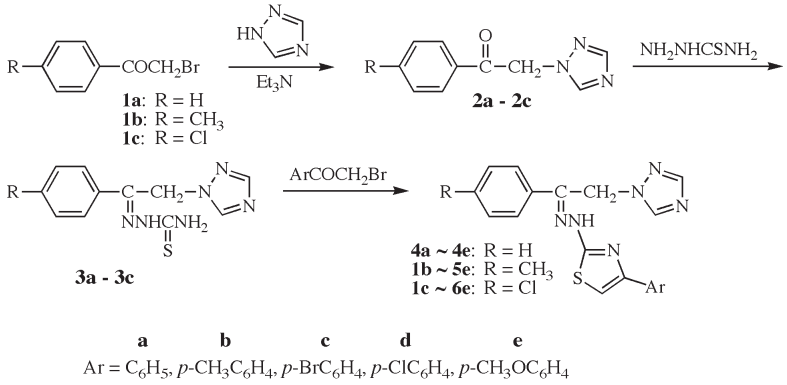
Results and Discussion.

Substituted 2-bromo-1-arylethanones **1a-1c** and substituted 1-aryl-2-(1*H*-1,2,4-triazol-1-yl) ethanones **2a-2c** were obtained according to the literature [10-11]. The treatment of **2a-2c** with thiosemicarbazide in the presence of acetic acid yielded three new thiosemicarbazones **3a-3c**. Condensation of **3a-3c** with various 2-bromo-1-arylethanones in anhydrous ethanol under reflux gave a series of substituted ethanone hydrazone derivatives.

The behaviour of thiocarbamoyl functional group in thiosemicarbazone towards phenacyl bromide was investigated. Literature [12] reported three sets of experimental conditions used to the reaction of thiosemicarbazone with phenacyl bromide: thermal, sonication and microwave irradiation. All the three sets of experimental conditions included using pyridine as catalyst. In the literature [13] it was reported that thiosemicarbazone reacted with phenacyl bromide in absolute ethanol in the presence of fused sodium acetate at room temperature. We treated the thiosemicarbazones **3a-3c** with phenacyl bromide in anhydrous ethanol under reflux to give corresponding compounds in good yields without using any catalyst.

The structures of intermediates **3a-3c** were substantiated by elemental analyses and IR. The infrared spectra of compounds **3a-3c** revealed in each case, absorption bands in the regions 3395-3215 cm^{-1}, 1613-1604 cm^{-1}, and 1276-1275 cm^{-1} corresponding to N-H, C=N, and C=S respectively. The structures of title comounds have been confirmed by elemental analysis, IR, ^{1}H NMR and MS. The infrared spectra of these compounds show C=C/C=N

Scheme 1



absorption bands between 1610-1482 cm^{-1} and showed a broad band at 3118-3104 cm^{-1} due to N-H group absorption. In the nuclear magnetic resonance spectra, title compounds exhibited broad singlet between δ12.05-11.90 ppm due to N-H protons, the signal for triazole C_5-H and triazole C_3-H appeared at δ 8.78-8.71 ppm, δ 8.03-7.92 ppm respectively, the presence of multiplet signal at δ 6.96-7.87 ppm was assigned to the aromatic protons and thiazole-H, the methylene absorption bands appeared as a singlet at δ 5.71-5.79. In MS spectra, molecular ion peaks of all title compounds were obtained from EI-MS, but the intensities of molecular ion peaks were very weak, The presence of M+2 peaks are characteristic for the compound having chlorine or bromine atoms.

EXPERIMENTAL

Melting points were recorded on a Mettler FP-5 capillary melting point apparatus and are uncorrected. Elemental analyses were recored on a Perkin-Elmer 2400 elemental analyser. IR spectra were measured as potassium bromide pellet on a Biorad FT-40 spectrophotometer. ^{1}H NMR spectra were recorded on a Varian Inova-400 spectrometer using tetramethylsilane as an internal reference. Mass spectra were performed on a VG ZAB-HS spectrometer (EI, 70 eV).

General Procedure for the Preparation of Thiosemicarbazones (**3a-3c**).

A mixture of 1-phenyl-2-(1*H*-1,2,4-triazol-1-yl)ethanone (**2a**) (0.01 mol), thiosemicarbazide (0.01 mol), ethanol (16 ml), H_2O (4 ml) and acetic acid (4 ml) was refluxed for 4 hours, then allowed to cool. The solid product was collected and recrystallized from anhydrous ethanol to give **3a** as white solid.

1-Phenyl-2-(1*H*-1,2,4-triazol-1-yl)ethan-1-one Thiosemicarbazone (**3a**).

This compound was obtained as a white solid, yield (76.2%), m.p. 152-154 ˚C; ir (potassium bromide): ν 3390, 3279, 3226 (NH_2, NH), 1613 (C=N), 1275 (C=S) cm^{-1}.

Anal. Calcd. for $C_{11}H_{12}N_6S$: C, 50.75; H, 4.65; N, 32.28. Found: C, 50.72; H, 4.67; N, 4.61.

1-(4-Methylphenyl)-2-(1*H*-1,2,4-triazol-1-yl)ethan-1-one Thiosemicarbazone (**3b**).

This compound was obtained as a white solid, yield (74.5%), m.p. 195-196 ˚C; ir (potassium bromide): ν 3395, 3280, 3215 (NH_2, NH), 1604 (C=N), 1276 (C=S) cm^{-1}.

Anal. Calcd. for $C_{12}H_{14}N_6S$: C, 52.54; H, 5.14; N, 30.63; Found: C, 50.52; H, 5.16; N, 30.69.

1-(4-Chlorophenyl)-2-(1*H*-1,2,4-triazol-1-yl)ethan-1-one Thiosemicarbazone (**3c**).

This compound was obtained as a white solid, yield (76.2%), m.p. 207-208 ˚C; ir (potassium bromide): ν 3393, 3286, 3220 (NH_2, NH), 1605 (C=N), 1272 (C=S) cm^{-1}.

Anal. Calcd. for $C_{11}H_{11}ClN_6S$: C, 44.82; H, 3.76; N, 28.51. Found: C, 44.85; H, 3.75; N, 28.48.

General Procedure for the Preparation of Substituted Ethanone Hydrazones **4a-4c**, **5a-5c** and **6a- 6c**.

A mixture of 0.001 mol 1-phenyl-2-(1*H*-1,2,4-triazol-1-yl)ethan-1-one thiosemicarbazone (**3a**) and 0.001 mol 2-bromo-1-phenylethanone was refluxed in 20 ml anhydrous ethanol for 0.5 hours, the solid product appeared in refluxing process and was collected after cooling. The product was recrystallized from DMF/EtOH to give **4a** as yellow solid.

1-Phenyl-2-(1*H*-1,2,4-triazol-1-yl)ethanone (4-Phenyl-1,3-thiazol-2-yl)hydrazone (**4a)**.

This compound was obtained as a yellow solid, (81.5%), m.p. 200-201 ˚C; ir (potassium bromide): ν 3114 (N-H), 1603 , 1568, 1490 (C=C, C=N) cm^{-1}; ^{1}H nmr (400 MHz, DMSO-d_6): δ 11.95 (s, 1H, NH), 8.71 (s, 1H, triazole C_5-H), 7.92 (s, 1H, triazole C_3-H), 7.31-7.87 (m, 11H, ArH + thiazole -H), 5.71 (s, 2H, CH_2); ms: (EI) m/z: 360 (M^+, 1.10), 278 (24.12), 175 (11.28), 104 (31.26), 103 (100), 82 (24.73), 77 (36.32).

Anal. Calcd. for $C_{19}H_{16}N_6S$: C 63.31; H 4.48; N 23.23. Found: C 63.34; H 4.46; N 23.27.

1-Phenyl-2-(1*H*-1,2,4-triazol-1-yl)ethanone [4-(4-Methylphenyl)-1,3-thiazol-2-yl]hydrazone (**4b**).

This compound was obtained as a yellow solid, yield (84.1%), m.p. 218-219 ˚C; ir (potassium bromide): ν 3116 (N-H), 1607, 1572, 1492 (C=C, C=N) cm^{-1}; ^{1}H nmr (400 MHz, DMSO-d_6): δ 11.90 (s, 1H, NH), 8.72 (s, 1H, triazole C_5-H), 7.93 (s, 1H, triazole C_3-H), 7.29-7.85 (m, 10H, ArH + thiazole -H), 5.72 (s, 2H, CH_2), 2.38 (s, 3H, CH_3); ms: (EI) m/z: 374 (M^+, 1.27), 292 (20.69), 174 (12.65), 104 (34.72), 103 (100), 82 (15.62), 77 (34.16).

Anal. Calcd. for $C_{20}H_{18}N_6S$: C 64.15; H 4.48; N 22.43. Found: C 64.13; H 4.46; N 22.46.

1-Phenyl-2-(1*H*-1,2,4-triazol-1-yl)ethanone [4-(4-Bromophenyl)-1,3-thiazol-2-yl]hydrazone (**4c**).

This compound was obtained as a yellow solid, yield (86.3%), m.p. 202-203 ˚C; ir (potassium bromide): ν 3109 (N-H), 1601, 1578,, 1492, (C=C, C=N) cm^{-1}; ^{1}H nmr (400 MHz, DMSO-d_6): δ 12.01 (s, 1H, NH), 8.75 (s, 1H, triazole C_5-H), 7.95 (s, 1H, triazole C_3-H), 7.15-7.80 (m, 10H, ArH + thiazole -H), 5.74 (s, 2H, CH_2); ms: (EI) m/z: 438 (M^+, 1.50), 440 (M^++2, 1.42), 356 (4.87), 358 (5.01), 174 (23.57), 104 (17.31), 103 (100), 82 (11.28), 77 (36.50).

Anal. Calcd. for $C_{19}H_{15}BrN_6S$: C 51.95; H 3.44; N 19.13. Found: C 51.92; H 3.45; N 19.09.

1-Phenyl-2-(1*H*-1,2,4-triazol-1-yl)ethanone [4-(4-Chlorophenyl)-1,3-thiazol-2-yl]hydrazone (**4d**).

This compound was obtained as a yellow solid, yield (80.9%), m.p. 204-206 ˚C; ir (potassium bromide): ν 3112 (N-H), 1603, 1565, 1502, (C=C, C=N) cm^{-1}; ^{1}H nmr (400 MHz, DMSO-d_6): δ 12.03 (s, 1H, NH), 8.73 (s, 1H, triazole C_5-H), 7.99 (s, 1H, triazole C_3-H), 7.10-7.82 (m, 10H, ArH + thiazole -H), 5.72 (s, 2H, CH_2); ms: (EI) m/z: 394 (M^+, 1.55), 396 (M^++2, 0.51), 312 (11.74), 314 (3.92), 174 (25.32), 104 (20.12), 103 (100), 82 (13.65), 77 (35.21).

Anal. Calcd. for $C_{19}H_{15}ClN_6S$: C 57.79; H 3.83; N 21.28. Found C: 57.81; H 3.81; N 21.24.

1-Phenyl-2-(1*H*-1,2,4-triazol-1-yl)ethanone [4-(4-Methoxyphenyl)-1,3-thiazol-2-yl]hydrazone (**4e**).

This compound was obtained a s yellow solid, yield (80.2%), m.p. 190-192 ˚C; ir (potassium bromide): ν 3116 (N-H), 1605, 1574, 1495, (C=C, C=N) cm^{-1}; ^1H nmr (400 MHz, DMSO- d_6): δ 11.98 (s, 1H, NH), 8.75 (s, 1H, triazole C_5-H), 7.93 (s, 1H, triazole C_3-H), 6.98-7.81 (m, 10H, ArH + thiazole -H), 5.73 (s, 2H, CH_2), 3.94 (s, 3H, OCH_3); ms: (EI) m/z: 390 (M^+, 1.34), 308 (28.46), 174 (25.12), 104 (19.67), 103 (100), 82 (12.96), 77 (30.26).

Anal. Calcd. for $C_{20}H_{18}N_6OS$: C 61.52; H 4.65; N 21.52. Found: C 61.55; H 3.63; N 24.49.

1-(4-Methylphenyl)-2-(1*H*-1,2,4-triazol-1-yl)ethanone (4-Phenyl-1,3-thiazol-2-yl)hydrazone (**5a**).

This compound was obtained as a yellow solid, yield (82.3%), m.p. 219-221 ˚C; ir (potassium bromide): ν 3118 (N-H), 1610, 1560, 1502 (C=C, C=N) cm^{-1}; ^1H nmr (400 MHz, DMSO-d_6): δ 11.92 (s, 1H, NH), 8.75 (s, 1H, triazole C_5-H), 8.03 (s, 1H, triazole C_3-H), 7.30-7.82 (m, 10H, ArH + thiazole -H), 5.75 (s, 2H, CH_2), 2.39 (s, 3H, CH_3); ms: (EI) m/z: 374 (M^+, 1.27), 292 (15.64), 175 (27.13), 118 (32.16), 117 (100), 82 (18.34), 77 (35.25).

Anal. Calcd. for $C_{20}H_{18}N_6S$: C 64.15; H 4.84; N 22.44. Found: C 64.12; H 4.86; N 22.45.

1-(4-Methylphenyl)-2-(1*H*-1,2,4-triazol-1-yl)ethanone [4-(4-Methylphenyl)-1,3-thiazol-2-yl]hydrazone (**5b**).

This compound was obtained as a yellow solid, yield (83.5%), m.p. 222-224 ˚C; ir (potassium bromide): ν 3116 (N-H), 1606, 1573, 1495 (C=C, C=N) cm^{-1}; ^1H nmr (400 MHz, DMSO-d_6): δ 11.93 (s, 1H, NH), 8.76 (s, 1H, triazole C_5-H), 8.01 (s, 1H, triazole C_3-H), 7.26-7.83 (m, 9H, ArH + thiazole -H), 5.76 (s, 2H, CH_2), 2.40 (s, 3H, CH_3), 2.37 (s, 3H, CH_3); ms: (EI) m/z: 388 (M^+, 1.45), 306 (16.47), 174 (26.87), 118 (35.21), 117 (100), 82 (21.62), 77 (30.96).

Anal. Calcd. for $C_{21}H_{20}N_6S$: C 64.93; H 5.19; N 21.63. Found: C 64.95; H 5.16; N 21.66.

1-(4-Methylphenyl)-2-(1*H*-1,2,4-triazol-1-yl)ethanone [4-(4-Bromophenyl)-1,3-thiazol-2-yl]hydrazone (**5c**).

This compound was obtained a a yellow solid, yield (86.1%), m.p. 208-210 ˚C; ir (potassium bromide): ν 3110 (N-H), 1608, 1571,, 1502, (C=C, C=N) cm^{-1}; ^1H nmr (400 MHz, DMSO-d_6): δ 11.96 (s, 1H, NH), 8.78 (s, 1H, triazole C_5-H), 8.02 (s, 1H, triazole C_3-H), 7.12-7.80 (m, 9H, ArH + thiazole -H), 5.78 (s, 2H, CH_2), 2.39 (s, 3H, CH_3); ms: (EI) m/z: 452 (M^+, 1.32), 454 (M^++2, 1.29), 370 (6.14), 372 (6.28), 174 (38.65), 118 (26.75), 117 (100), 82 (27.41), 77 (28.92).

Anal. Calcd. for $C_{20}H_{17}BrN_6S$: C 52.99; H 3.78; N 18.54. Found: C 52.94; H 3.76; N 18.57.

1-(4-Methylphenyl)-2-(1*H*-1,2,4-triazol-1-yl)ethanone [4-(4-Chlorophenyl)-1,3-thiazol-2-yl]hydrazone (**5d**).

This compound was obtained as a yellow solid, yield (84.9%), m.p. 211-212 ˚C; ir (potassium bromide): ν 3112 (N-H), 1606, 1579, 1505, (C=C, C=N) cm^{-1}; ^1H nmr (400 MHz, DMSO-d_6): δ 11.98 (s, 1H, NH), 8.72 (s, 1H, triazole C_5-H), 7.95 (s, 1H, triazole C_3-H), 7.08-7.84 (m, 9H, ArH + thiazole -H), 5.79 (s, 2H, CH_2), 2.38 (s, 3H, CH_3); ms: (EI) m/z: 408 (M^+, 1.15), 410 (M^++2, 0.38), 326 (12.47), 328 (4.15), 174 (26.59), 118 (28.25), 117 (100), 82 (15.32), 77 (30.15).

Anal. Calcd. for $C_{20}H_{17}ClN_6S$: C 58.75; H 4.19; N 20.55. Found: C 58.76; H 4.16; N 20.58.

1-(4-Methylphenyl)-2-(1*H*-1,2,4-triazol-1-yl)ethanone [4-(4-Methoxyphenyl)-1,3-thiazol-2-yl]hydrazone (**5e**).

This compound was obtained as a yellow solid, yield (81.2%), m.p. 212-213 ˚C; ir (potassium bromide): ν 3114 (N-H), 1601, 1562, 1498, (C=C, C=N) cm^{-1}; ^1H nmr (400 MHz, DMSO-d_6): δ 11.90 (s, 1H, NH), 8.74 (s, 1H, triazole C_5-H), 8.01 (s, 1H, triazole C_3-H), 6.96-7.85 (m, 10H, ArH + thiazole -H), 5.76 (s, 2H, CH_2), 3.95 (s, 3H, OCH_3), 2.38 (s, 3H, CH_3); ms: (EI) m/z: 404 (M^+, 1.24), 322 (27.45), 174 (29.65), 118 (21.32), 117 (100), 82 (15.65), 77 (29.17).

Anal. Calcd. for $C_{21}H_{20}N_6OS$: C 62.36; H 4.98; N 20.78. Found: C 62.38; H 4.97; N 20.80.

1-(4-Chlorophenyl)-2-(1*H*-1,2,4-triazol-1-yl)ethanone (4-Phenyl-1,3-thiazol-2-yl)hydrazone (**6a**).

This compound was obtained as a yellow solid, yield (80.2%), m.p. 224-226 ˚C; ir (potassium bromide): ν 3106 (N-H), 1608, 1573, 1491 (C=C, C=N) cm^{-1}; ^1H nmr (400 MHz, DMSO-d_6): δ 12.03 (s, 1H, NH), 8.75 (s, 1H, triazole C_5-H), 7.95 (s, 1H, triazole C_3-H), 7.31-7.87 (m, 10H, ArH + thiazole -H), 5.78 (s, 2H, CH_2); ms: (EI) m/z: 394 (M^+, 1.40), 396 (M^++2, 0.46), 312 (11.35), 314 (3.79), 175 (18.32), 138 (29.15), 137 (100), 82 (26.35), 77 (36.41).

Anal. Calcd. for $C_{19}H_{15}ClN_6S$: C 57.79; H 3.83; N 21.28. Found: C 57.83; H 3.81; N 21.25.

1-(4-Chlorophenyl)-2-(1*H*-1,2,4-triazol-1-yl)ethanone [4-(4-Methylphenyl)-1,3-thiazol-2-yl]hydrazone. (**6b**).

This compound was obtained as a yellow solid, yield (84.3%), m.p. 215-216 ˚C; ir (potassium bromide): ν 3112 (N-H), 1602, 1570, 1489 (C=C, C=N) cm^{-1}; ^1H nmr (400 MHz, DMSO-d_6): δ 12.01 (s, 1H, NH), 8.72 (s, 1H, triazole C_5-H), 7.98 (s, 1H, triazole C_3-H), 7.10-7.82 (m, 9H, ArH + thiazole -H), 5.76 (s, 2H, CH_2), 2.38 (s, 3H, CH_3); ms: (EI) m/z: 408 (M^+, 1.35), 410 (0.44), 326 (12.64), 328 (4.21), 174 (18.73), 138 (32.15), 137 (100), 82 (26.91), 77 (31.25).

Anal. Calcd. for $C_{20}H_{17}ClN_6S$: C 58.75; H 4.19; N 20.55. Found: C 58.72; H 4.20; N 20.52.

1-(4-Chlorophenyl)-2-(1*H*-1,2,4-triazol-1-yl)ethanone [4-(4-Bromophenyl)-1,3-thiazol-2-yl]hydrazone. (**6c**).

This compound was obtained a s yellow solid, yield (87.1%), m.p. 227-228 ˚C; ir (potassium bromide): ν 3109 (N-H), 1605, 1573, 1494, (C=C, C=N) cm^{-1}; ^1H nmr (400 MHz, DMSO-d_6): δ 12.05 (s, 1H, NH), 8.76 (s, 1H, triazole C_5-H), 7.96 (s, 1H, triazole C_3-H), 7.09-7.84 (m, 9H, ArH + thiazole -H), 5.74 (s, 2H, CH_2); ms: (EI) m/z: 472 (M^+, 1.24), 474 (M^++2, 0.41), 390 (12.39), 392 (9.65), 174 (16.37), 138 (30.16), 137 (100), 82 (28.14), 77 (33.74).

Anal. Calcd. for $C_{19}H_{14}BrClN_6S$: C 48.16; H 2.98; N 17.74. Found: C 48.18; H 2.95; N 17.76.

1-(4-Chlorophenyl)-2-(1*H*-1,2,4-triazol-1-yl)ethanone [4-(4-Chlorophenyl)-1,3-thiazol-2-yl]hydrazone (**6d**).

This compound was obtained as a yellow solid, yield (82.6%), m.p. 229-230 ˚C; ir (potassium bromide): ν 3111 (N-H), 1609, 1575, 1497, (C=C, C=N) cm^{-1}; ^1H nmr (400 MHz, DMSO-d_6): δ 12.03 (s, 1H, NH), 8.78 (s, 1H, triazole C_5-H), 7.93 (s, 1H, triazole C_3-H), 7.05-7.79 (m, 10H, ArH + thiazole -H), 5.71 (s, 2H,

CH_2); ms: (EI) m/z: 428 (M^+, 1.16), 430 (M^++2, 0.39), 346 (12.38), 348 (4.12), 174 (17.84), 138 (29.28), 137 (100), 82 (26.39), 77 (34.58).

Anal. Calcd. for $C_{19}H_{14}Cl_2N_6S$: C 53.15; H 3.29; N 19.57. Found: C 53.18; H 3.28; N 19.56.

1-(4-Chlorophenyl)-2-(1*H*-1,2,4-triazol-1-yl)ethanone [4-(4-Methoxyphenyl)-1,3-thiazol-2-yl]hydrazone (**6e**).

This compound was obtained as a yellow solid, yield (83.9%), m.p. 209-211 ˚C; ir (potassium bromide): ν 3104 (N-H), 1608, 1571, 1482, (C=C, C=N) cm^{-1}; ^1H nmr (400 MHz, DMSO-d_6): δ 11.98 (s, 1H, NH), 8.72 (s, 1H, triazole C_5-H), 7.94 (s, 1H, triazole C_3-H), 6.97-7.81 (m, 9H, ArH + thiazole -H), 5.72 (s, 2H, CH_2), 3.94 (s, 3H, OCH_3); ms: (EI) m/z: 424 (M^+, 1.36), 426 (M^++2, 0.45), 342 (12.62), 344 (4.20), 174 (24.32), 138 (35.28), 137 (100), 82 (23.96), 77 (31.07).

Anal. Calcd. for $C_{20}H_{17}ClN_6OS$: C 56.53; H 4.03; N 19.78. Found: C 56.50; H 4.05; N 19.76.

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