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Ester *tert*-butoxycarbonylhydrazones **2** were reacted with some carboxylic acid hydrazides to give 4-*tert*-butoxycarbonylamino-3,5-dialkyl-4*H*-1,2,4-triazoles **3-6**. Treatment of **3-5** with 6 *N* hydrochloric acid under mild conditions resulted in the formation of 4-amino-3,5-dialkyl-4*H*-1,2,4-triazole hydrochlorides **7-9** in good yields. Compound **7a** was converted to the free 4-amino compound **10a** upon treatment with ethanolic sodium ethoxide solution.

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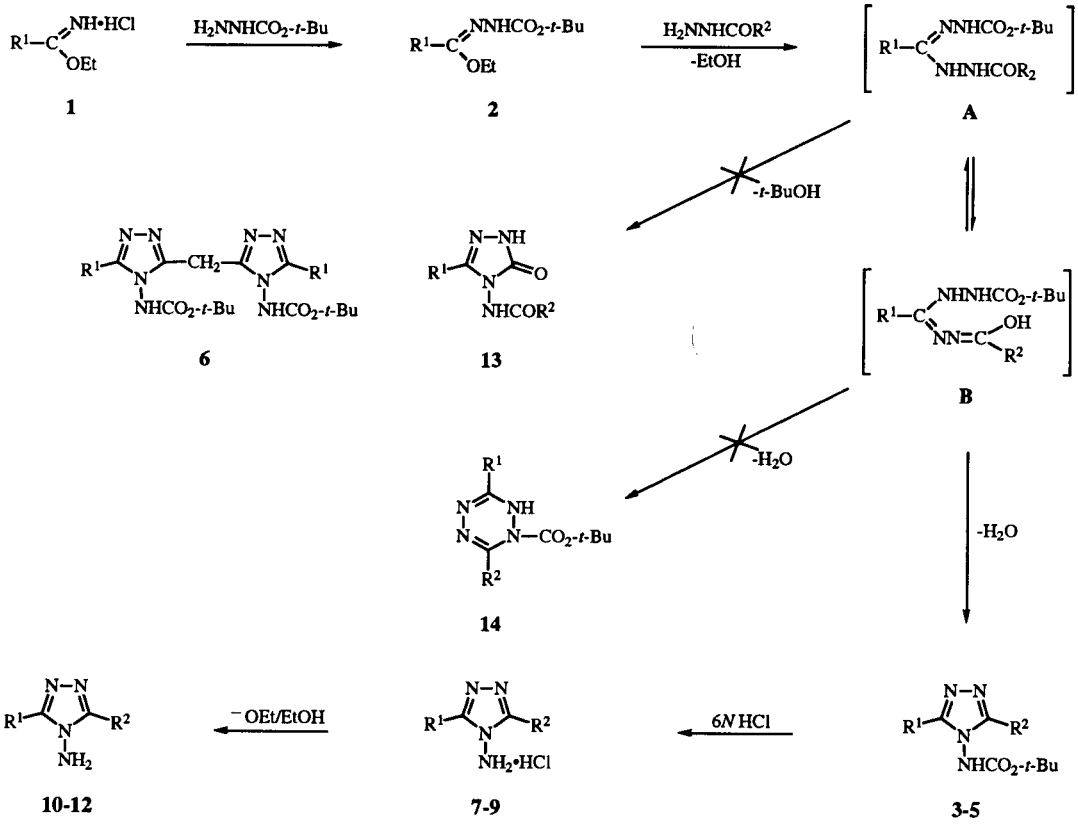
In order to synthesize 4-amino-3,5-dialkyl-4*H*-1,2,4-triazoles three general methods have been developed. One of these methods involves the reaction of carboxylic acids and their functional derivatives with hydrazine hydrate at a high temperature [1-3]. In the other method, the treatment of diacylhydrazines with hydrazine leads to the formation of this type amino compounds with lower yields [1,3,4]. But, in the condensation of nitriles with hydrazine, higher yields of these compounds have been obtained when the reaction mixture contained sulfur or a sulfurcontaining compound [5-13]. In general, symmetrical substituted 4-amino-3,5-dialkyl-4*H*-1,2,4-triazoles have been prepared by using the three methods and only a few of unsymmetrically substituted 4-amino-3,5-dialkyl-4*H*-1,2,4-triazoles have been reported in the literature.

Scheme 1




| | $R^2$ | | $R^1$ |
|---|---|---|---|
| **3,7,10** | Methyl | **a** | Methyl |
| **4,8,11** | 3-Pyridyl | **b** | Ethyl |
| **5,9,12** | 4-Pyridyl | **c** | Benzyl |
| | | **d** | 4-Chlorobenzyl |
| | | **e** | Phenyl |

Furthermore, it has been reported that the last type compounds are considerably more difficult to synthesize [7]. But, we now report a general and convenient method for the synthesis of this type unsymmetrically substituted compounds.

Ester *tert*-butoxycarbonyl hydrazones **2** are recently synthesized compounds by the reactions of alkyl imidate hydrochlorides **1** with *tert*-butyl carbazate [14]. The reactions of **2** leading to the formation of 4,5-dihydro-1*H*-1,2,4-triazol-5-ones with ammonia, primary amines and hydrazine have been studied [14]. In the present study, compounds **2** were treated with some acylhydrazines such as acetic-, nicotinic-, isonicotinic and malonic acid hydrazides and 3-alkyl-4-*tert*-butoxy-

Table 1

Physical Data of Compounds **3-10**

| Compound No. | Yield (%) | Mp (°C) (recrystallization solvent) | Molecular Formula (Molecular Weight) | Analysis (%) Calcd./Found | | |
|---|---|---|---|---|---|---|
| | | | | C | H | N |
| **3a** | 43 | 163-164 | $C_9H_{16}N_4O_2$ | 50.93 | 7.60 | 26.40 |
| | | (ethyl acetate) | (212.25) | 50.86 | 7.77 | 26.74 |
| **3b** | 32 | 141-142 | $C_{10}H_{18}N_4O_2$ | 53.08 | 8.02 | 24.76 |
| | | (isobutyl acetate) | (226.28) | 52.90 | 8.29 | 25.07 |
| **3c** | 35 | 114-115 | $C_{15}H_{20}N_4O_2$ | 62.48 | 6.99 | 19.43 |
| | | (ethyl acetate) | (288.34) | 62.27 | 7.20 | 19.49 |
| **3e** | 38 | 160-162 | $C_{14}H_{18}N_{14}O_2 \cdot H_2O$ | 57.52 | 6.90 | 19.17 |
| | | (ethanol/ethyl acetate) | (292.33) | 57.88 | 7.00 | 19.26 |
| **4a** | 34 | 154-156 | $C_{13}H_{17}N_5O_2 \cdot H_2O$ | 53.23 | 6.53 | 23.88 |
| | | (ethanol/ethyl acetate) | (293.32) | 53.08 | 6.67 | 23.61 |
| **4b** | 44 | 147-148 | $C_{14}H_{19}N_5O_2$ | 58.11 | 6.62 | 24.21 |
| | | (benzene) | (289.33) | 58.42 | 6.70 | 23.93 |
| **4c** | 46 | 97-98 | $C_{19}H_{21}N_5O_2$ | 64.94 | 6.02 | 19.93 |
| | | (ethyl acetate) | (351.40) | 64.84 | 6.04 | 20.13 |
| **4d** | 47 | 166-167 | $C_{19}H_{20}ClN_5O_2$ | 59.14 | 5.22 | 18.15 |
| | | (benzene) | (385.85) | 59.19 | 5.04 | 17.84 |
| **5a** | 49 | 150-152 | $C_{13}H_{17}N_5O_2 \cdot H_2O$ | 53.23 | 6.53 | 23.88 |
| | | (ethanol/ethyl acetate) | (293.32) | 53.51 | 6.52 | 23.67 |
| **5c** | 47 | 161-162 | $C_{19}H_{21}N_5O_2$ | 64.94 | 6.02 | 19.93 |
| | | (ethyl acetate) | (351.40) | 65.25 | 5.88 | 20.05 |
| **5d** | 34 | 176- 177 | $C_{19}H_{20}ClN_5O_2$ | 59.14 | 5.22 | 18.15 |
| | | (ethyl acetate) | (385.85) | 59.40 | 5.25 | 18.24 |
| **6a** | 34 | 198-199 | $C_{17}H_{28}N_8O_4$ | 49.99 | 6.91 | 27.43 |
| | | (chloroform/ethyl acetate) | (408.46) | 50.16 | 7.11 | 27.67 |
| **6c** | 23 | 163-164 | $C_{29}H_{36}N_8O_4$ | 62.13 | 6.47 | 19.99 |
| | | (acetone) | (560.65) | 61.94 | 6.27 | 19.90 |
| **7a** | 70 | 223-225 | $C_4H_9ClN_4$ | 32.33 | 6.10 | 37.70 |
| | | (ethanol/ethyl acetate) | (148.59) | 32.28 | 6.08 | 37.95 |
| **7b** | 65 | 163-165 | $C_5H_{11}ClN_4$ | 36.93 | 6.82 | 34.45 |
| | | (ethanol/ethyl acetate) | (162.62) | 36.60 | 7.08 | 34.70 |
| **7c** | 68 | 194-196 | $C_{10}H_{13}ClN_4$ | 53.45 | 5.83 | 24.93 |
| | | (ethanol/ethyl acetate) | (224.69) | 53.16 | 5.81 | 25.23 |
| **7e** | 67 | 169-171 | $C_9H_{11}ClN_4$ | 51.31 | 5.26 | 26.59 |
| | | (ethanol/ethyl acetate) | (210.66) | 51.04 | 5.08 | 26.46 |
| **8a** | 83 | 173-175 | $C_8H_{10}ClN_5$ | 45.40 | 4.76 | 33.09 |
| | | (ethanol/ethyl acetate) | (211.65) | 45.64 | 4.86 | 33.43 |
| **8b** | 84 | 160-162 | $C_9H_{12}ClN_5$ | 47.90 | 5.36 | 31.03 |
| | | (ethanol/ethyl acetate) | (225.68) | 48.12 | 5.26 | 31.26 |
| **9a** | 92 | 278-280 | $C_8H_{10}ClN_5$ | 45.40 | 4.76 | 33.09 |
| | | (ethanol) | (211.65) | 45.70 | 4.72 | 33.27 |
| **9c** | 84 | 241-243 | $C_{14}H_{14}ClN_5$ | 58.44 | 4.90 | 24.34 |
| | | (ethanol) | (287.75) | 58.19 | 4.77 | 24.32 |
| **9d** | 90 | 243-245 | $C_{14}H_{13}Cl_2N_5$ | 52.19 | 4.07 | 21.74 |
| | | (ethanol) | (322.19) | 52.34 | 4.07 | 21.93 |
| **10a** | 46 | 196-197 [a] | $C_4H_8N_4$ | 42.84 | 7.19 | 49.97 |
| | | (ethanol/ethyl acetate) | (112.09) | 42.80 | 7.24 | 50.10 |

[a] Lit [1] mp 196.5-197.5°.

carbonylamino-5-methyl-4*H*-1,2,4-triazoles **3**, 3-alkyl-4-*tert*-butoxycarbonylamino-5-(3-pyridyl)-4*H*-1,2,4-triazoles **4**, 3-alkyl-4-*tert*-butoxycarbonylamino-5-(4-pyridyl)-4*H*-1,2,4-triazoles **5** and di-(3-alkyl-4-*tert*-butoxycarbonylamino-4*H*-1,2,4-triazol-5-yl) methanes **6** were obtained, respectively. In case of monoacylhydrazines, the reaction course is shown in Scheme 1. But, the expected compounds **13** were not isolated.

It is plausible to take into consideration of the formation of isomeric 1,2-dihydro-1,2,4,5-tetrazines **14** instead of 4-amino-4*H*-1,2,4-triazoles **3-5**. But instability of a type **14** structure at elevated reaction temperatures [7] and the hydrolysis of the compounds obtained to give **7-9** reveals the impossibility of the formation of type 14 compounds. However, a further reliable basis is $^1$H-nmr spectra in order to differentiate of 1,2-dihydro-1,2,4,5-tetrazines from 4-amino-4*H*-1,2,4-triazoles. Indeed, the appearance of the nitrogen protons of dihydrotetrazines at δ 8.69-9.13 has been reported [7-11]. But, the nitrogen protons of the obtained compounds appear at a lower field (δ 10.46-11.60) as expected from structures **3-5**.

It has been reported that the *tert*-butyl carbazates can be hydrolysed in acidic condition to give hydrazinium salts, differing from ethyl carbazates [15-16]. Indeed, compounds **3-5** were converted to 4-amino-3,5-dialkyl-4*H*-1,2,4-triazole hydrochlorides **7-9** in good yields when treating with 6*N*-hydrochloric acid under mild conditions. The formation of 4-amino-3,5-dialkyl-4*H*-1,2,4-triazoles **10-12** from the hydrochlorides **7-9** could be achieved by the treatment of equivalent amount of ethoxide anion/ethanol in absolute ethanol. As an example, compound **10a** was obtained from **7a** by using this route.

Table 2

$^1$H-NMR Data of Compounds **3-10**

| Compound No. | $^1$H-NMR, δ (ppm) [a] | | | | | |
|---|---|---|---|---|---|---|
| | $CH_3$ | $CH_3$ | $CH_2$ | Ar-H | NH | Other signals |
| **3a** | 1.65 (s, 9H, $3CH_3$) | 2.44 (s, 6H, $2CH_3$) | — | — | 11.60 (s, 1H) | — |
| **3b** | 1.53 (s, 9H, $3CH_3$) | 1.30 (t, 3H)<br>2.31 (s, 3H) | 2.70 (q, 2H) | — | 11.02 (s,1H) | — |
| **3c** | 1.45 (s, 9H, $3CH_3$) | 2.37 (s, 3H) | 4.10 (s, 2H) | 7.26 (s, 5H) | 10.62 (s, 1H) | — |
| **3e** | 1.60 (s, 9H, $3CH_3$) | 3.40 (s, 3H) | — | 7.32-7.85 (m, 5H) | 10.95 (s, 1H) | 2.37 (s, 2H, $H_2O$) [b] |
| **4a** | 1.58 (s, 9H, $3CH_3$) | 2.54 (s, 3H) | — | 7.60-9.18 (m, 4H) | 11.18 (s, 1H) | 3.60 (s, 2H, $H_2O$) [b] |
| **4b** | 1.48 (s, 9H, $3CH_3$) | 1.32 (t, 3H) | 2.83 (q, 2H) | 7.20-9.05 (m, 4H) | 11.22 (s, 1H) | — |
| **4c** | 1.41 (s, 9H, $3CH_3$) | — | 4.22 (s, 2H) | 7.06-9.07 (m, 9H) | 10.70 (s, 1H) | — |
| **4d** | 1.35 (s, 9H, $3CH_3$) | — | 4.04 (s, 2H) | 7.03-8.91 (m, 8H) | 10.70 (s, 1H) | — |
| **5a** | 1.60 (s, 9H, $3CH_3$) | 2.40 (s, 3H) | — | 7.65 (d, 2H)<br>8.60 (d, 2H) | 10.95 (s, 1H) | 3.40 (s, 2H, $H_2O$) [b] |
| **5c** | 1.32 (s, 9H, $3CH_3$) | — | 4.12 (s, 2H) | 6.93-7.32 (m, 5H)<br>7.65 (d, 2H)<br>8.50 (d, 2H) | 10.58 (s, 1H) | — |
| **5d** | 1.38 (s, 9H, $3CH_3$) | — | 4.02 (s, 2H) | 6.90-7.40 (m, 4H)<br>7.62 (d, 2H)<br>8.52 (d, 2H) | 10.48 (s, 1H) | — |
| **6a** | 1.51 (s, 18H, $6CH_3$) | 2.25 (s, 6H, $2CH_3$) | 3.96 (s, 2H) | — | 10.47 (s, 2H) | — |
| **6c** | 1.49 (s, 18H, $6CH_3$) | — | 3.98 (s, 4H, $2CH_2$)<br>4.13 (s, 2H) | 6.98-7.35 (m, 10H) | 10.46 (s, 2H) | |
| **7a** | 2.64 (s, 6H, $2CH_3$) | — | — | — | — | 4.85 (s, 3H, $NH_3^+$) |
| **7b** | 1.20 (t, 3H) | 2.40 (s, 3H) | 2.85 (q, 2H) | — | — | 4.60 (s, 3H, $NH_3^+$) |
| **7c** | 2.50 (s, 3H) | — | 4.30 (s, 2H) | 7.29 (s, 5H) | — | 4.75 (s, 3H, $NH_3^+$) |
| **7e** | 2.65 (s, 3H) | — | — | 7.40-8.20 (m, 5H) | — | 4.50 (s, 3H, $NH_3^+$) |
| **8a** | 2.85 (s, 3H) | — | — | 7.92-9.65 (m, 4H) | — | 4.90 (s, 3H, $NH_3^+$) |
| **8b** | 1.50 (t, 3H) | — | 3.15 (q, 2H) | 7.65-9.60 (m, 4H) | — | 4.75 (s, 3H, $NH_3^+$) |
| **9a** | 2.50 (s, 3H) | — | — | 8.44-8.84 (m, 4H) | — | 4.60 (s, 3H, $NH_3^+$) |
| **9c** | — | — | 4.44 (s, 2H) | 7.22-7.59 (m, 5H)<br>8.58 (d, 2H)<br>8.95 (d, 2H) | — | 4.80 (s, 3H, $NH_3^+$) |
| **9d** | — | — | 4.30 (s, 2H) | 7.05-7.45 (m, 4H)<br>8.54 (d, 2H)<br>8.90 (d, 2H) | — | 4.75 (s, 3H, $NH_3^+$) |
| **10a** | 2.37 (s, 6H, $2CH_3$) | — | — | — | — | 5.80 (s, 2H, $NH_2$) |

[a] The spectra were recorded in deuteriochloroform, **3a-c, 4b-d, 5a,c,d, 6c** and dimethyl sulfoxide-$d_6$ **3e, 4a, 6a, 7a-c,e, 8a,b, 9,a,c,d, 10a**.
[b] Exchanged with deuterium.

Table 3

IR and UV Data of Compounds **3-10**

| Compound No. | IR, ν ($cm^{-1}$) [a] $NH_3^+$ | NH | C=O | C=N | Substituted Arom. Ring | UV, $\lambda_{max}$ (nm)/ε x $10^{-3}$ (in ethanol) |
|---|---|---|---|---|---|---|
| **3a** | — | 3120 | 1725 | 1548 | — | 202 (1.09) |
| **3b** | — | 3085 | 1730 | 1540, 1505 | — | 274 (1.00) |
| **3c** | — | 3130 | 1720 | 1560, 1530 | 735, 690 | 258 (0.17), 207 (9.52) |
| **3e** [b] | — | 3070 | 1730 | 1540, 1500 | 770, 690 | 241 (11.49), 207 (9.05) |
| **4a** [c] | — | 3090 | 1735 | 1590, 1548 | — | 239 (9.17), 207 (7.25) |
| **4b** | — | 3080 | 1720 | 1580, 1565 | — | 240 (7.45), 203 (6.92) |
| **4c** | — | 3080 | 1732 | 1586, 1565 | 735, 695 | 241 (11.50), 208 (16.23) |
| **4d** | — | 3070 | 1718 | 1590, 1565 | 810 | 239 (10.35), 223 (14.62) |
| | — | | | | | 207 (12.90) |
| **5a** [d] | — | 3070 | 1730 | 1595, 1542 | — | 249 (9.88), 203 (7.34) |
| **5c** | — | 3060 | 1722 | 1598, 1520 | 730, 690 | 251 (11.00), 206 (13.31) |
| **5d** | — | 3090 | 1740 | 1598, 1532 | 830 | 250 (11.43), 222 (13.30) |
| | — | | | | | 204 (15.51) |
| **6a** | — | 3120 | 1755 | 1560, 1535 | — | 218 (3.20), 203 (6.45) |
| **6c** | — | 3110 | 1725 | 1520, 1595 | 690, 720 | 258 (0.32), 211 (16.52) |
| **7a** | 3242 | — | — | 1620 | — | 202 (1.00) |
| **7b** | 3260 | — | — | 1622, 1560 | — | 274 (0.99) |
| **7c** | 3260 | — | — | 1622, 1562 | 760, 738 | 258 (0.03), 208 (6.86) |
| **7e** | 3250 | — | — | 1620, 1540 | 745, 705 | 242 (13.73), 206 (14.24) |
| **8a** | 3275 | | | 1590, 1545 | — | 240 (10.19), 220 (10.10) |
| | | | | | | 203 (10.87) |
| **8b** | 3250 | — | — | 1605, 1568 | — | 243 (8.40), 208 (6.55) |
| **9a** | 3235 | | | 1642, 1582 | — | 256 (8.68), 203 (7.10) |
| **9c** | 3270 | — | — | 1624, 1590 | 732, 693 | 269 (8.27), 252 (8.81), |
| | | | | | | 213 (7.00), 207 (6.41) |
| **9d** | 3265 | — | — | 1640, 1610 | 768 | 256 (11.93), 221 (12.21) |
| | | | | | | 207 (12.53) |
| **10a** [e] | — | — | — | 1615 | — | — |

[a] Potassium bromide pellets. [b] 3410 (OH). [c] 3400 (OH). [d] 3420 (OH). [e] 3200, 3270 ($NH_2$).

## EXPERIMENTAL

Melting points were determined on a Büchi oil heated melting point apparatus and are uncorrected. Experimental data of compounds **3-10** are given in Table 1. The $^1$H-nmr spectra (δ, ppm) were recorded on a Varian 60A spectrometer using TMS as internal reference (Table 2). The ir spectra (ν, $cm^{-1}$) were run on a Perkin Elmer 377 spectrophotometer in potassium bromide discs (Table 3). The uv absorption spectra were measured between 200 and 400 nm with a Shimatzu-1201 spectrophotometer using 10 mm quartz cells. All the measurements were carried out with $1.10^{-5}$-$1.10^{-4}$ *M* ethanolic solutions (Table 3). The elemental analyses were performed on a Carlo Erba 1106 elemental analyzer. The starting compounds **2** were synthesized by routes previously reported [14]. The necessary chemicals were obtained from Fluka. Compounds **3e**, **4a** and **5a** were obtained as hydrate forms.

General Method for the Synthesis of Compounds **3-5**.

The corresponding ethyl carboxylate *tert*-butoxycarbonylhydrazone **2** (0.01 mole) was heated in an oil bath with acetic-, nicotinic- or isonicotinic acid hydrazide (0.01 mole) at 115-120°C for 2 hours. After cooling to room temperature, 2-3 ml of isobutyl acetate was added to the viscous reaction mixture. On cooling the mixture in deep freeze, a white solid appeared. This was recrystallized from an appropriate solvent to afford the desired compound.

Synthesis of Compounds **6a** and **6c**.

Compound **2a** or **2c** (0.01 mole) was heated in an oil bath with malonic acid dihydrazide (0.005 mole) at 110-115°C for 2 hours. After cooling to room temperature, 3-4 ml of ethyl acetate-petroleum ether (1:2) mixture was added to the viscous residue. On cooling the mixture in deep freeze, a white solid appeared. This crude product was recrystallized from an appropriate solvent to give **6a** or **6c**.

General Procedure for the Synthesis of Compounds **7-9**.

Hydrochloric acid (6*N*, 5 ml) was added dropwise to a solution of compound **3**, **4** or **5** (0.01 mole) in a minimum quantity of tetrahydrofuran. After heating on a steam bath for 15 minutes, the resulting solution was evaporated at 30-35°C under reduced pressure and dried *in vacuo*. The solid residue was recrystallized from an appropriate solvent to give the desired compound.

Preparation of Compound **10a**.

A sodium ethoxide solution prepared by dissolving of sodium (0.01 mole) in 20 ml of absolute ethanol was added to the solution of compound **7a** (0.01 mole) in 50 ml of absolute ethanol. After stirring at room temperature for 4 hours, the mixture was filtered. Evaporation of the filtrate at 30-35°C under reduced pressure gave crude product. Several recrystallizations of the residue from an appropriate solvent afforded pure compound **10a**.

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