NEW SYNTHESIS OF TRIAZOLO[5,1-a] AND [3,4-a]ISOINDOLES BY INTERNAL ELECTROCYCLISATION OF DISUBSTITUTED TRIAZOLIUM YLIDES

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Abstract

This paper reports the synthesis of triazolo[5,1-a] and [3,4-a]isoindoles by an internal electrocyclisation of disubstituted triazolium ylides having as structural subunit a tricyanophenyl group. The intermediate formation of a dihydrotriazoloisoindole has been proved.

Keywords: triazoloisoindoles, disubstituted triazolium ylides, electrocyclisation

Introduction

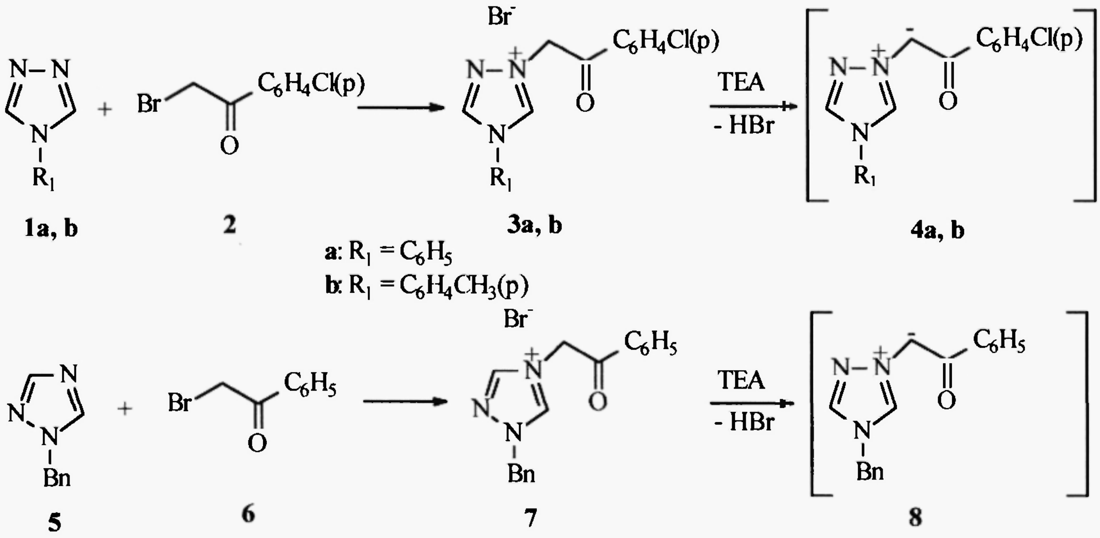
Fused heterocycles containing a triazole ring, have become a point of interest for synthetic chemists and biologists because of their unusual structures and wide range of biological and medicinal properties (1). The *N*-aryl-1,2,4-triazole derivatives have been found to display potent biological activity such as cardiotonic (2) and antidiuretic (3).

The stable disubstituted triazolium ylides containing the subunit 2,4,6-trinitrophenyl (also named picryl) give in presence of piperidine the corresponding 1*H*-[1,2,4]triazolo[3,4-a]isoindoles by elimination of nitrous acid (4).

In the present paper we extend the synthesis of triazoloisoindoles replacing the picryl chloride by 2,4,6-tricyanobromobenzene. The objective is to generalise the synthesis of triazoloisoindoles thus, to enlarge the series of these derivatives as potential pharmaceutical products after their subsequent functionalization.

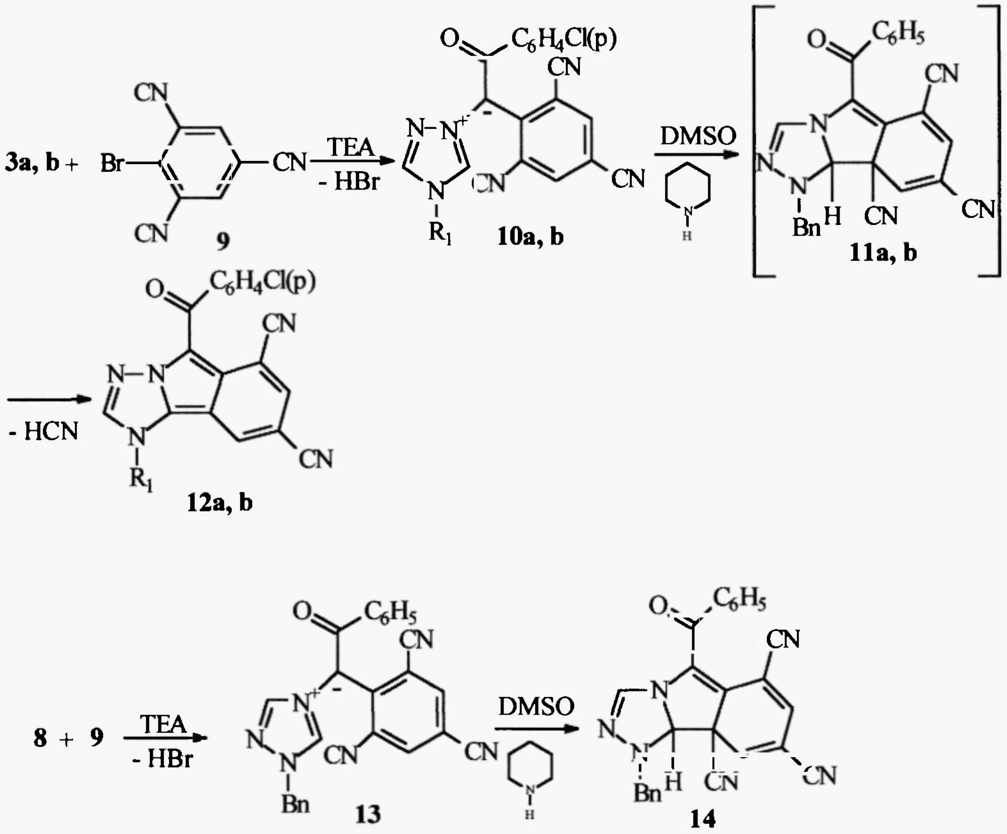
Results and Discussion

The monosubstituted triazolium ylides **4a-b** have been obtained (scheme 1) "in situ" using the "salt method" (5). Thus, the 4-substituted 1,2,4 triazoles **1** react with 4-substituted-2-bromo acetophenones **2** and **6**, giving the corresponding triazolium salts **3**. These salts in the presence of triethylamine (TEA) form the unstable monosubstituted triazolium ylides **4a-b** and **8**. Similarly, 1-benzyl-1,2,4-triazole **5** react with **6** to give the salt **7** and then the ylide **8**.



Scheme 1

Analogously, a mixture of salt **3** or **7** and 2,4,6-tricyanobromobenzene **9** dissolved in chloroform in presence of TEA give the stable disubstituted triazoliumbenzoyl-2,4,6-tricycanophenylmethylides **10** and **13** (Scheme 2).



Scheme2

All ylide synthesis have been performed at 0-5°C, in the dark and under argon in order to avoid the decomposition of the monosubstituted triazolium ylides, caused by cleavage of the N^+-C^- bond (6) or by 3+3 cycloaddition dimerisation (7). The disubstituted triazolium ylides **10** and **13** dissolved in DMSO containing piperidine at room temperature after 2-4h provided the triazolo[5,1-a] **12** or triazolo[3,4-a] **14** isoindoles, in fairly good yields.

The structures of the new compounds have been established by ^{1}H nmr, ir and ms spectra. All molecular ion peaks have been observed in ms spectra. In the ^{1}H nmr spectra, the proton in the 5 position (δ = 10.83-11.15 ppm) of disubstituted triazolium ylides **10** and **13** disappears when these compounds are transformed into the isoindole derivatives **12a,b** and **14**. In the case of triazolium ylide **13**, the dihydroisoindole derivative **14** (salt form) has been separated and characterised in the same experimental conditions. The formation of adducts **11 a,b** and **14** may be take place by internal electrocyclisation of the corresponded disubstituted triazolium ylides **10 a,b** and **13** respectively(8). In the last case, a lower aromatization energie of the cycloadduct **14** could explained the lack of the elimination of HCN.

Experimental

^{1}H nmr spectra were recorded on a Bruker AM-250 spectrometer with trimethylsilane as internal standard. Chemical shifts are given in ppm. Mass spectra were taken on a platform II Micromass apparatus using Electrospray ionisation. Ir spectra were recorded on a Perkin Elmer 2000 spectrometer. The melting points were uncorrected and registered on a Kofler bank and on an Electrothermal 9100 apparatus. Wolf laboratories, Clichy, performed elemental analyses. For column chromatography SDS silica gel 60 (70-200 μm) was used. Chloroform and acetone were freshly distilled over CaH_2 and K_2CO_3 respectively. Dry glassware for moisture-sensitive reactions were obtained by oven drying and assembly under Ar. An inert atmosphere was obtained with a stream of Ar and glassware use in experiments was equipped with rubber septa. The reagent transfer was performed by syringe techniques.

General procedure for the synthesis of disubstituted ylides 10a, b and 13.

In a 200 mL two-necked flask equipped with a reflux condenser, a dropping funnel and a magnetically stirrer, 2.59 mmol of salt **4a, b** or **8** was dissolved in 40 mL of dried chloroform. Next, 2.59 mmol of **9** dissolved in 20 mL of dried chloroform were added. The reaction mixture was cooled at 0-5°C in an ice-water bath. A solution of 7.7 mmol of triethylamine in 15 mL of dried chloroform was added dropwise overe for 10 minutes while stirring. The reaction mixture was maintained under argon and exclusion of light, for 3 hours. The chloroform was removed on a rotary evaporator. The crude triazolium ylide was obtained as a red-violet solid. The pure product was separated by column chromatography on silica gel using a mixture of petroleum ether – acetone (1/1) as eluent.

4-chlorobenzoyl-4-phenyl-[1,2,4]triazol-1-ium-2,4,6-tricyanophenylmethylide 10a

This compound was isolated as orange crystals in 58 % yield; mp 200°C; ir (potassium bromide): 2356 (C=N), 1653 (C=O), 1599, 1558 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 7.34 (s, 1H, H aromatic), 7.64-7.77 (m, 8H, H aromatic), 8.35 (s, 2H, H aromatic), 9.83 (s, 1H, CH=N), 11.15 (s, 1H, CH=N$^+$); ms (ES$^+$): m/z= 451 (M+H)$^+$.

4-chlorobenzoyl-4-(4-tolyl)-[1,2,4]-triazol-1-ium-2,4,6-tricyanophenylmethylide 10b

This compound was isolated as orange crystals in 62 % yield; mp 140°C; ir (potassium bromide): 2280 (C=N), 1653 (C=O), 1600, 1521 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 2.52 (s, 3H, CH_3), 7.18-7.30 (m, 4H, H aromatic), 7.42-7.51 (m, 4H, H aromatic), 7.88 (s, 2H, H aromatic), 8.41 (s, 1H, CH=N), 10.89 (s, 1H, CH=N$^+$); ms (ES$^+$): m/z= 465 (M+H)$^+$.

1-benzyl-1*H*-[1,2,4]triazol-4-iumbenzoyl-2,4,6-tricyanophenylmethylide 13

This compound was isolated as orange crystals in 60 % yield; mp 99°C; ir (potassium bromide): 2230 (C≡N), 1698 (C=O), 1596, 1579 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 5.49 (s,2H, CH_2), 7.21-7.49 (m, 10H, H aromatic), 7.66 (s, 2H, H aromatic), 8.27 (s, 1H, CH=N), 9.78 (s, 1H, CH=N$^+$); ms (ES$^+$): m/z= 429 (M+H)$^+$.

General procedure for the synthesis of isoindoles derivatives 12a, b and 14.

In a solution of 0.9 mmol of ylide **10a, b** or **13** dissolved in 8 mL of DMSO adds 0.2 mL of piperidine. The mixture is stirring 2 hours at room temperature, under argon, without light. A net colour change form red-violet to red-orange has been observed. The reaction mixture is treated with 3*N* acetic acid solution until the solid formation. The solid is filtered and washed with water. The crude solid was refluxed in ethanol in an oil bath for 2 hours with magnetic stirring. The final pure product is obtained after filtration.

5-(4-chlorobenzoyl)-6,8-dicyano-1-phenyl-1*H*-1,2,4-triazolo[5,1-a]isoindole 12a

This compound was isolated as orange crystals in 68 % yield; mp 125°C; ir (potassium bromide): 2242 (C≡N), 1690 (C=O), 1592, 1560 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 7.09-7.17 (m, 1H, H aromatic), 7.31-7.42 (m, 2H, H aromatic), 7.62 (d, *J* = 8.5, 2H, H aromatic), 7.76 (d, *J* = 8.5, 2H, H aromatic), 8.00 (d, *J* = 8.5, 2H, H aromatic), 8.51 (s, 1H, H aromatic), 8.73 (s, 1H, H aromatic), 10.31 (s, 1H, CH=N); ms (ES$^+$): m/z= 424 (M+H)$^+$. Anal. Calcd. For $C_{24}H_{12}ClN_5O$: C, 68.33; H, 2.87; N, 16.30. Found C, 68.41; H, 2.92; N, 16.14.

5-(4-chlorobenzoyl)-6,8-dicyano-1-(4-tolyl)-1*H*-1,2,4-triazolo[5,1-a]isoindole 12b

This compound was isolated as orange crystals in 66 % yield; mp 160°C; ir (potassium bromide): 2231 (C≡N), 1687 (C=O), 1591, 1554 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 2.42 (s, 3H, CH_3), 7.16 (d, *J* = 8.5, 2H, H aromatic), 7.41 (d, *J* = 8.5, 2H, H aromatic), 7.71 (d, *J* = 8.2, 2H, H aromatic), 7.98 (d, *J* = 8.2, 2H, H aromatic), 8.32 (s, 1H, H aromatic), 8.45 (s, 1H, H aromatic), 10.23 (s, 1H, CH=N); ms (ES$^+$): m/z= 438 (M+H)$^+$. Anal. Calcd. For $C_{25}H_{14}ClN_5O$: C, 68.89; H, 3.24; N, 16.07. Found C, 68.58; H, 3.22; N, 16.01.

1-benzyl-5-benzoyl-6,8,9a-tricyano-9a,9b-dihydro-1*H*-[1,2,4]triazolo[3,4-a]isoindol-1-ium acetate 14

This compound was isolated as red-orange crystals in 90 % yield; mp 245°C; ir (potassium bromide): 2234 (C≡N), 1692 (C=O), 1582, 1550 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 6.18 (br.s, 3H, CH_2 + CH), 7.29-7.54 (m, 10H, H aromatic), 8.01 (s, 1H, H aromatic), 8.89 (s, 1H, H aromatic), 10.31 (s, 1H, H aromatic), 11.61 (s, 1H, N+-H); ms (ES$^+$): m/z= 429 (M+H)$^+$. Anal. Calcd. For $C_{26}H_{17}N_6O$: C, 72.89; H, 3.76; N, 16.61. Found C, 73.02; H, 3.37; N, 16.22.

Conclusion

The disubstituted triazolium ylides **10a, b** and **13** give the new corresponding triazoloisoindole derivatives **12a, b** and **14** by an internal electrocyclisation, respectively. The Yields in synthesis of disubstituted triazolium ylides **10a, b** and **13** are 58-62% , those in synthesis of triazoloisoindoles are of 66-90%. The structures off all new synthesised compounds have been established by elemental analysis, mass spectra, ir spectra and ^{1}H nmr spectra.

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Received on October 7, 2002.