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# Cycloaddition of Bis-1,3-dipolar Reagents to 1,3-Diarylprop-2-en-1-ones

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ABSTRACT: *Bis pyrazolines and isoxazolines were prepared by 1,3-dipolar cycloaddition of benzene-1,3/1,4-dicarboxaldehyde dihydrazones and dioximes to 1,3-diaryl-prop-2-en-1-ones.* © 2003 Wiley Periodicals, Inc. Heteroatom Chem 14:379–383, 2003; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.10169

## INTRODUCTION

Pyrazolines and isoxazolines have gained importance in recent years because of their wide applications as chemotherapeutic agents. Amongst various methods available for their syntheses, the 1,3-dipolar cycloaddition of nitrile imines and nitrile oxides to dipolarophiles has gained importance [1]. In fact, we have examined the addition of nitrile imines and nitrile oxides generated from araldehyde phenylhydrazones and araldoximes to bifunctional olefins and also bis olefinic systems [2]. The former are generated by the dehydrogenation of araldehyde phenylhydrazones and araldoximes with chloramine-T [3]. However, there are no reports, to our knowledge, about the use of bis dipoles on dipolar reagents in 1,3-dipolar cycloaddition reactions. In continuation of our study, the present paper deals with the reaction of 1,3/1,4-benzenedicarbaldehyde dihydrazones and dioximes with 1,3-diarylprop-2-en-1-one to get a new type of bis heterocycles.

## RESULTS AND DISCUSSION

The reaction of 1 mol of benzene-1,4-dicarboxaldehyde dihydrazone (**1**) with 2 mol of 1,3-diarylprop-2-en-1-one (**3**) was carried out in the presence of chloramine-T in refluxing AcOH. The solid separated after 12 h was identified as 3,3′-(1,4-phenylene)bis[1,5-diaryl-4-aroyl-2-pyrazoline] (**4**) by $^1$H NMR spectra (Scheme 1). A similar reaction of 1 mol of benzene-1,4-dicarboxaldedhyde dioxime (**2**) with 2 mol of **3** in the presence of chloramine-T in refluxing AcOH gave 3,3′-(1,4-phenylene)bis[5-aryl-4-aroyl-2-isoxazoline] (**5**). Compounds **4a** and **5a** showed two doublets $\delta_H$ 6.54, 6.61 (d, 5-H) and 5.89, 5.94 (d, 4H) with a coupling constants $J = 6.8$ and 7.0 Hz, respectively, in their $^1$H NMR spectra. The IR spectra ($\nu$, cm$^{-1}$) of **4** and **5** exhibited absorption bands in the region 1558–1590 cm$^{-1}$ (C=N) and 1670–1689 cm$^{-1}$ (C=O). Likewise, the cycloaddition was carried out between 1 mol of benzene-1,3-dicarboxaldehyde dihydrazone (**8**) and 2 mol of **3** in the presence of chloramine-T in acetic acid (Scheme 2). The solid was separated after 15 h and identified as 3,3′-(1,3-phenylene)bis[1,5-diaryl-4-aroyl-2-pyrazoline] (**10**) by $^1$H NMR spectra. Similarly the reaction of 1 mol of benzene-1,3-dicarboxaldehyde dioxime (**8**) with 2 mol of **3** in the presence of chloramine-T in acetic acid resulted 3,3′-(1,3-phenylene)bis[5-aryl-4-aroyl-2-isoxazoline] (**11**). The $^1$H NMR spectra of compounds **10a** and **11a** showed two doublets $\delta_H$ 6.45, 6.53 (d, 5-H)

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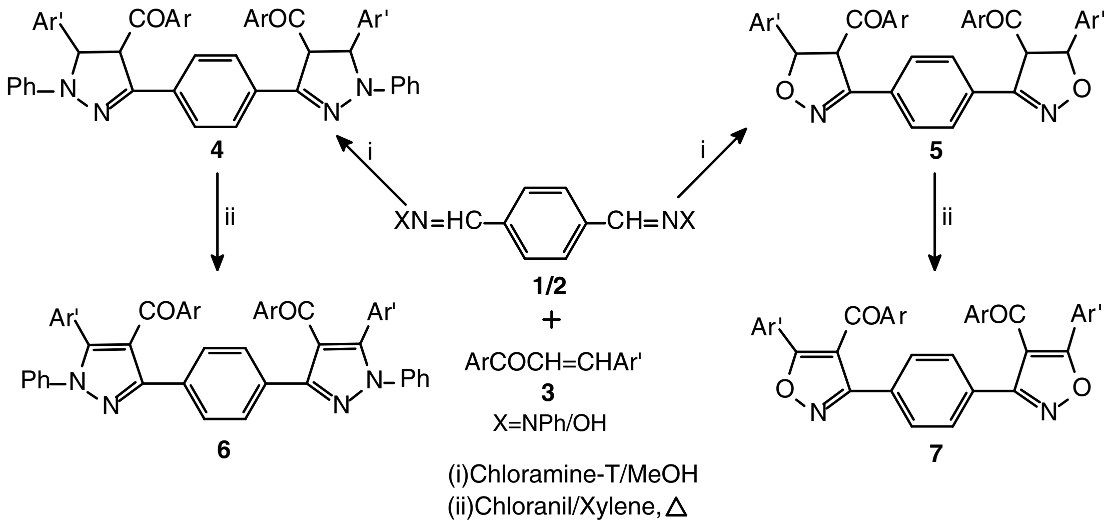
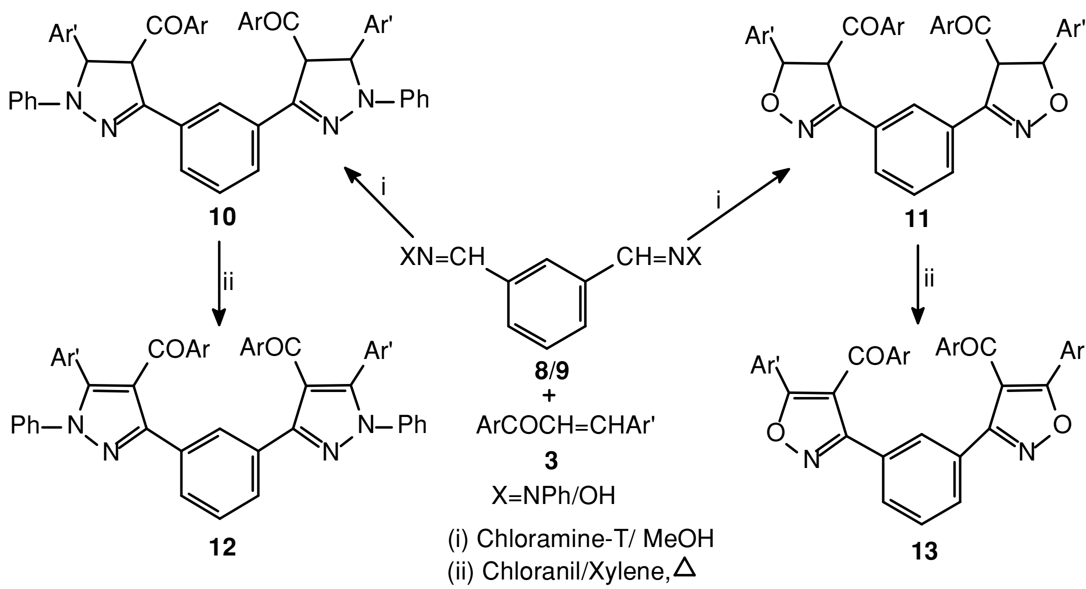


| | Ar | Ar' |
|---|---|---|
| **a** | Ph | Ph |
| **b** | Ph | 4-MePh |
| **c** | Ph | 4-ClPh |
| **d** | 4-MePh | Ph |
| **e** | 4-ClPh | Ph |

SCHEME 1



| | Ar | Ar' |
|---|---|---|
| **a** | Ph | Ph |
| **b** | Ph | 4-MePh |
| **c** | Ph | 4-ClPh |
| **d** | 4-MePh | Ph |
| **e** | 4-ClPh | Ph |

SCHEME 2

and 5.65, 5.73 (d, 4H) with a coupling constants $J = 6.1$ and 5.8 Hz respectively. The IR spectra ($\nu$, cm$^{-1}$) of **10** and **11** exhibited absorption bands in the region 1568–1594 cm$^{-1}$ (C=N) and 1674–1693 cm$^{-1}$ (C=O). The dehydrogenation of **4, 5, 10**, and **11** with chloranil in xylene resulted 3,3′-(1,4-phenylene)bis[1,5-diaryl-4-aroylpyrazole] (**6**)/3,3′-(1,4-phenylene)bis[5-aryl-4-aroylisoxazole] (**7**)/3,3′-(1,3-phenylene)bis[1,5-diaryl-4-aroylpyrazole] (**12**)/3,3′-(1,3-phenylene)bis[5-aryl-4-aroylisoxazole] (**13**). The absence of two doublets at $\delta_H$ 6.41–6.62 and 5.61–5.81 in their $^1$H NMR spectra supports their formation (physical data of compounds **4–6** and **7–13** is given in Table 1; $^1$H NMR data of compounds **4–7** and **10–13** is given in Table 2).

However, similar reaction with benzene-1,2-dicarboxaldehyde dihydrazone/dioxime **3** was failed. This may be due to the steric hindrance. In conclusion, a new class of bis pyrazolines and bis isoxazolines have been prepared by 1,3-dipolar cycloaddition reaction of bis dipoles to dipolarophiles.

## *EXPERIMENTAL*

Melting points were determined in open capillaries on a Mel-Temp apparatus and are uncorrected. The

**TABLE 1** Physical Data of Compounds **4–6** and **7–13**

| | | | | *Found%*[a] | | |
|---|---|---|---|---|---|---|
| *Compound* | *m.p. (°C)* | *Yield (%)* | *Mol. Formula (Mol. wt.)* | *C* | *H* | *N* |
| **4a** | 165–166 | 61 | $C_{50}H_{38}N_4O_2$ (726.88) | 82.84 (82.62) | 5.39 (5.27) | 7.84 (7.71) |
| **4b** | 172–133 | 60 | $C_{52}H_{42}N_4O_2$ (754.93) | 82.91 (82.73) | 5.51 (5.61) | 7.58 (7.42) |
| **4c** | 149–150 | 65 | $C_{50}H_{36}Cl_2N_4O_2$ (795.77) | 75.33 (75.47) | 4.50 (4.56) | 7.21 (7.04) |
| **4d** | 156–157 | 62 | $C_{52}H_{42}N_4O_2$ (754.93) | 82.59 (82.73) | 5.73 (5.61) | 7.28 (7.42) |
| **4e** | 164–165 | 63 | $C_{50}H_{36}Cl_2N_4O_2$ (795.77) | 75.68 (75.47) | 4.45 (4.56) | 7.16 (7.04) |
| **5a** | 139–140 | 64 | $C_{38}H_{28}N_2O_4$ (576.65) | 79.29 (79.15) | 5.01 (4.89) | 4.72 (4.86) |
| **5b** | 142–143 | 66 | $C_{40}H_{32}N_2O_4$ (604.70) | 79.61 (79.45) | 5.43 (5.33) | 4.52 (4.63) |
| **5c** | 147–148 | 68 | $C_{38}H_{26}Cl_2N_2O_4$ (645.55) | 70.61 (70.70) | 4.16 (4.06) | 4.24 (4.33) |
| **5d** | 134–135 | 64 | $C_{40}H_{32}N_2O_4$ (604.70) | 79.64 (79.45) | 5.28 (5.33) | 4.52 (4.63) |
| **5e** | 144–145 | 63 | $C_{38}H_{26}Cl_2N_2O_4$ (645.55) | 70.61 (70.70) | 4.14 (4.06) | 4.24 (4.33) |
| **6a** | 168–169 | 67 | $C_{50}H_{34}N_4O_2$ (722.85) | 83.26 (83.08) | 4.86 (4.74) | 7.87 (7.75) |
| **6b** | 188–189 | 61 | – | – | – | – |
| **6c** | 196–197 | 66 | – | – | – | – |
| **6d** | 172–173 | 65 | $C_{52}H_{38}N_4O_2$ (750.90) | 83.36 (83.18) | 4.98 (5.10) | 7.38 (7.46) |
| **6e** | 214–216 | 68 | – | – | – | – |
| **7a** | 143–145 | 63 | $C_{38}H_{24}N_2O_4$ (572.62) | 79.58 (79.70) | 4.14 (4.22) | 4.78 (4.89) |
| **7b** | 158–160 | 66 | – | – | – | – |
| **7c** | 140–142 | 68 | – | – | – | – |
| **7d** | 169–170 | 65 | $C_{40}H_{28}N_2O_4$ (600.67) | 80.14 (80.00) | 4.77 (4.70) | 4.51 (4.66) |
| **7e** | 171–172 | 62 | – | – | – | – |
| **10a** | 134–135 | 61 | $C_{50}H_{38}N_4O_2$ (726.88) | 82.84 (82.62) | 5.39 (5.27) | 7.54 (7.71) |
| **10b** | 129–131 | 63 | $C_{52}H_{42}N_4O_2$ (754.93) | 82.91 (82.73) | 5.51 (5.61) | 7.58 (7.42) |
| **10c** | 159–160 | 61 | $C_{52}H_{36}Cl_2N_4O_2$ (795.77) | 75.68 (75.47) | 4.44 (4.56) | 7.21 (7.04) |
| **10d** | 146–145 | 64 | $C_{52}H_{42}N_4O_2$ (754.93) | 82.96 (82.73) | 5.53 (5.61) | 7.26 (7.42) |
| **10e** | 168–170 | 62 | $C_{52}H_{36}Cl_2N_4O_2$ (795.77) | 75.68 (75.47) | 4.67 (4.86) | 7.16 (7.04) |
| **11a** | 125–126 | 61 | $C_{38}H_{28}N_2O_4$ (576.65) | 78.95 (79.15) | 4.97 (4.89) | 4.68 (4.86) |
| **11b** | 118–119 | 62 | $C_{40}H_{32}N_2O_4$ (604.70) | 79.31 (79.45) | 5.39 (5.33) | 4.48 (4.63) |
| **11c** | 131–132 | 61 | $C_{38}H_{26}Cl_2N_2O_4$ (645.55) | 70.91 (70.70) | 3.96 (4.06) | 4.24 (4.33) |
| **11d** | 141–143 | 61 | $C_{40}H_{32}N_2O_4$ (604.70) | 79.24 (79.45) | 5.38 (5.33) | 4.75 (4.63) |
| **11e** | 121–122 | 63 | $C_{38}H_{26}Cl_2N_2O_4$ (645.55) | 69.81 (70.70) | 3.96 (4.06) | 4.24 (4.33) |
| **12a** | 204–205 | 66 | $C_{50}H_{34}N_4O_2$ (722.85) | 83.26 (83.08) | 4.86 (4.74) | 7.94 (7.75) |
| **12b** | 186–187 | 62 | – | – | – | – |
| **12c** | 201–203 | 63 | – | – | – | – |
| **12d** | 199–200 | 69 | – | – | – | – |
| **12e** | 211–213 | 67 | $C_{50}H_{32}Cl_2N_4O_2$ (791.74) | 76.01 (75.85) | 4.12 (4.07) | 6.95 (7.07) |
| **13a** | 194–195 | 66 | $C_{38}H_{24}N_2O_4$ (572.62) | 79.91 (79.70) | 4.31 (4.22) | 5.02 (4.89) |
| **13b** | 167–168 | 67 | – | – | – | – |
| **13c** | 182–183 | 70 | – | – | – | – |
| **13d** | 178–179 | 69 | – | – | – | – |
| **13e** | 186–187 | 71 | $C_{38}H_{22}Cl_2N_2O_4$ (641.51) | 71.04 (71.15) | 3.54 (3.45) | 4.48 (4.36) |

[a] Values in parentheses represent calculated values.

TABLE 2 $^1$H NMR Spectral Data for **4–7** and **10–13**

| *Product* | $\delta\,^1H$ *in ppm (J in Hz)* |
|---|---|
| **4a** | 7.09–8.14 (m, 34H, Ar-H), 6.54 (d, $J = 6.8$, 2H, H-5), 5.89 (d, $J = 6.8$, 2H, H-4). |
| **4b** | 7.08–8.14 (m, 32H, Ar-H), 6.51 (d, $J = 6.8$, 2H, H-5), 5.87 (d, $J = 6.8$, 2H, H-4), 2.38 (s, 6H, H–$CH_3$). |
| **4c** | 7.09–8.18 (m, 32H, Ar-H), 6.56 (d, $J = 7.0$, 2H, H-5), 5.91 (d, $J = 7.0$, 2H, H-4). |
| **4d** | 7.04–8.16 (m, 32H, Ar-H), 6.51 (d, $J = 6.9$, 2H, H-5), 5.89 (d, $J = 6.9$, 2H, H-4), 2.43 (s, 6H, H–$CH_3$). |
| **5a** | 7.14–8.25 (m, 24H, Ar-H), 6.61 (d, $J = 7.0$, 2H, H-5), 5.94 (d, $J = 7.0$, 2H, H-4). |
| **5b** | 7.11–8.23 (m, 22H, Ar-H), 6.58 (d, $J = 7.0$, 2H, H-5), 5.92 (d, $J = 7.0$, 2H, H-4), 2.45 (s, 6H, H–$CH_3$). |
| **5c** | 7.10–8.25 (m, 22H, Ar-H), 6.62 (d, $J = 7.1$, 2H, H-5), 5.93 (d, $J = 7.1$, 2H, H-4). |
| **5d** | 7.11–8.24 (m, 22H, Ar-H), 6.60 (d, $J = 7.1$, 2H, H-5), 5.89 (d, $J = 7.1$, 2H, H-4), 2.41 (s, 6H, H–$CH_3$). |
| **6a** | 7.20–8.19 (m, 34H, Ar-H). |
| **6b** | 7.18–8.12 (m, 32H, Ar-H), 2.32 (s, 6H, H–$CH_3$). |
| **6c** | 7.08–8.17 (m, 32H, Ar-H). |
| **6d** | 7.06–8.10 (m, 32H, Ar-H), 2.43 (s, 6H, H–$CH_3$). |
| **7a** | 7.14–8.25 (m, 24H, Ar-H). |
| **7b** | 7.01–8.13 (m, 22H, Ar-H), 2.38 (s, 6H, H–$CH_3$). |
| **7c** | 7.10–8.25 (m, 22H, Ar-H). |
| **7d** | 7.14–8.24 (m, 22H, Ar-H), 2.39 (s, 6H, H–$CH_3$). |
| **10a** | 7.16–8.08 (m, 34H, Ar-H), 6.45 (d, $J = 6.1$, 2H, H-5), 5.65 (d, $J = 6.1$, 2H, H-4). |
| **10b** | 7.14–8.06 (m, 32H, Ar-H), 6.48 (d, $J = 5.9$, 2H, H-5), 5.75 (d, $J = 5.9$, 2H, H-4), 2.51 (s, 6H, H–$CH_3$). |
| **10c** | 7.12–8.02 (m, 32H, Ar-H), 6.48 (d, $J = 6.0$, 2H, H-5), 5.65 (d, $J = 6.0$, 2H, H-4). |
| **10e** | 7.04–7.98 (m, 32, Ar-H), 6.46 (d, $J = 6.1$, 2H, H-5), 5.62 (d, $J = 6.1$, 2H, H-4). |
| **11a** | 6.98–7.81 (m, 24H, Ar-H), 6.53 (d, $J = 5.8$, 2H, H-5), 5.73 (d, $J = 5.8$, 2H, H-4). |
| **11b** | 7.01–7.81 (m, 22H, Ar-H), 6.50 (d, $J = 5.8$, 2H, H-5), 5.61 (d, $J = 5.8$, 2H, H-4), 2.42 (s, 6H, H–$CH_3$). |
| **11c** | 6.89–7.78 (m, 22H, Ar-H), 6.52 (d, $J = 5.8$, 2H, H-5), 5.68 (d, $J = 5.8$, 2H, H-4). |
| **11d** | 7.01–7.85 (m, 22H, Ar-H), 6.49 (d, $J = 5.8$, 2H, H-5), 5.64 (d, $J = 6.0$, 2H, H-5), 2.36 (s, 6H, H–$CH_3$). |
| **12a** | 7.06–7.98 (m, 34H, Ar-H). |
| **12b** | 7.14–8.06 (m, 32H, Ar-H), 2.50 (s, 6H, H–$CH_3$). |
| **12c** | 7.10–8.12 (m, 32H, Ar-H). |
| **12e** | 7.14–8.04 (m, 32, Ar-H). |
| **13a** | 6.99–7.91 (m, 24H, Ar-H). |
| **13b** | 7.01–7.81 (m, 22H, Ar-H), 2.42 (s, 6H, H–$CH_3$). |
| **13c** | 6.92–7.89 (m, 22H, Ar-H). |
| **13d** | 7.10–7.98 (m, 22H, Ar-H), 2.33 (s, 6H, H–$CH_3$). |

purity of the compounds was checked by TLC (silica gel H, BDH, ethyl acetate/hexane, 1:3). The IR spectra were recorded on a Perkin-Elmer grating infrared spectrophotometer (model 337) in KBr pellets. The $^1$H NMR spectra were recorded in $CDCl_3$/DMSO-$d_6$ on a Varian EM-360 spectrometer (300 MHz) with TMS as an internal standard. The elemental analyses were performed at Indian Institute of Science, Bangalore, India. The 1,3-diarylprop-2-en-1-one and benzene-1,4-dicarboxaldehyde dihydrazone and dioxime were prepared according to the literature procedure [4].

### *3,3′-(1,4-Phenylene)bis[1,5-diaryl-4-aroyl-2-pyrazoline](***4***)/3,3′-(1,4-Phenylene)bis[5-aryl-4-aroyl-2-isoxazoline](***5***)*

To a mixture of benzene-1,4-dicarboxaldedhyde dihydrazone/dioxime (**1/2**) (10 mmol) and 1,3-diarylprop-2-ene-1-one (**3**) (20 mmol) in AcOH (10 ml), chloramine-T (20 mmol) in AcOH (10 ml) was added and refluxed for 12–14 h. Salts formed were filtered off. The solvent was removed under vacuum and the solid obtained was recrystallized from acetic acid to get pure **4/5**.

### *3,3′-(1,3-Phenylene)bis[1,5-diaryl-4-aroyl-2-pyrazoline](***10***)/3,3′-(1,3-Phenylene)bis[5-aryl-4-aroyl-2-isoxazoline](***11***)*

To a solution of benzene-1,3-dicarboxaldehyde dihydrazone/dioxime (**8/9**) (10 mmol) and 1,3-diarylprop-2-ene-1-one (**3**) (20 mmol) in AcOH (10 ml), chloramine-T (20 mmol) in AcOH (10 ml) was added and refluxed for 18–20 h. The salts formed, if any, were removed by filtration. The contents were poured onto crushed ice. The solid separated was filtered and dried. It was recrystallized from acetic acid to obtain pure **10/11**.

### *Dehydrogenation of* **4/5/10/11**

A mixture of **4/5/10/11** (10 mmol) and chloranil (11 mmol) in xylene (20 ml) was refluxed for 20–22 h. The organic layer was washed with 1 N NaOH and water and dried (anhydrous $Na_2SO_4$). The solvent was removed under reduced pressure. The solid obtained was purified by recrystallization from AcOH to provide **6/7/12/13**, respectively.

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