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one-pot SYNTHESIS OF PYRROLO-[3,4-*d*]ISOXAZOLINE-4,6-DIONES *via* NITRILE OXIDES

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1,3-Dipolar cycloaddition of nitrile oxides generated in situ in the presence of variously substituted N-arylmaleimides and N-benzylmaleimide provides new pyrrolo[3,4-d]izoxazoline-4,6-diones in good yields. The whole procedure could be performed in a practical and efficient one-pot operation. All the cycloadducts were isolated in excellent yields and identified by spectral studies.

Keywords: maleimides, nitrile oxides, regiospecific 1,3-dipolar cycloaddition.

The 1,3-dipolar cycloaddition is an important and versatile method for the construction of five-membered heterocycles [1–3]. Nitrile oxides are an important class of 1,3-dipolar species of propargyl-allenyl type [4–6]. Since 1973 we have reported many syntheses of various heterocycles using 1,3-dipolar cycloaddition (see, for example, our last publications [7, 8], the former containing a rather complete bibliography). As an extention of our studies on 1,3-dipolar cycloaddition, in this communication we describe the *one-pot* synthesis of new pyrrolo-[3,4-*d*]isoxazoline-4,6-diones from the reaction of nitrile oxides and variously substituted N-arylmaleimides and N-benzylmaleimide. A series of seven maleimides has been prepared. These maleimides are evaluated as potential dipolarophiles for 1,3-dipolar cycloadditions, as having electron-releasing and electron-withdrawing substituents as well as one-atom spacer between nitrogen and the aryl ring.

Variously substituted N-arylmaleimides **3a**–**f** [9] and N-benzylmaleimide **3g** [10] have been prepared by an identical procedure as reported in the literature. The 1,3-dipolar cycloadditions of these maleimides with nitrile oxides prepared *in situ* by dehydrohalogenation of the corresponding aldoximes **1** and **2** [11–13] in the presence of chloramine T [14], were carried out in refluxing ethanol and led directly to the corresponding pyrrolo-[3,4-*d*]isoxazoline-4,6-diones **4a**–**g** and **5a**–**g** on workup (Table 1). On the basis of IR spectrum, ^{1}H NMR and mass-spectral studies, all the new products were identified as 5-aryl- or 5-benzyl-substituted 3-(3',4'-methylenedioxyphenyl)-3a,4,6,6a-tetrahydro-4H,6H-pyrrolo[3,4-*d*]isoxazoline-4,6-diones and 3-(3'-nitrophenyl)-3a,4,6,6a-tetrahydro-4H,6H-pyrrolo[3,4-*d*]isoxazoline-4,6-diones.

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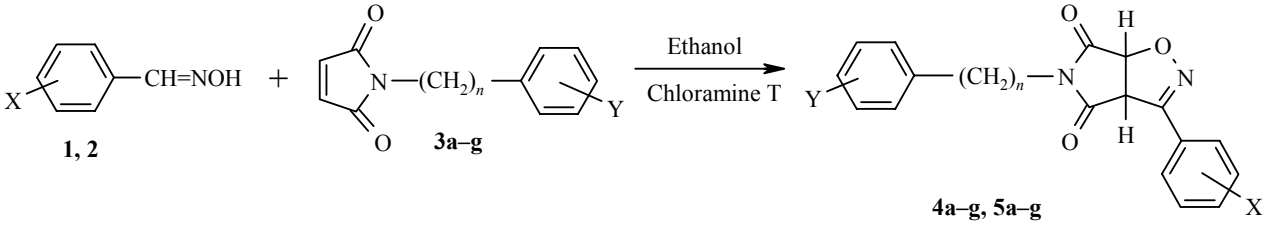
The cycloadditions of nitrile oxides proved to be highly regio- and stereospecific, leading to a single *cis* isomer. The IR spectra of the cycloadducts showed a strong absorption band around 1765–1795 cm^{-1} and a weak absorption band around 1717–1732 cm^{-1} corresponding to carbonyl functions of an imide moiety. The ^1H NMR spectra showed two doublets at δ 4.81–5.20 and 5.58–5.72 assigned to H-3a and H-6a, respectively. The coupling constant of the coupled protons is around 9–10 Hz showing the *cis* addition.



To conclude, the products were obtained in good yields with no side reaction, as no other product has been isolated. The substituents at the N-aryl part of the N-arylmaleimides have very little influence on the reaction rate, but one atom spacer between the nitrogen and the aryl part of N-benzylmaleimide increases it considerably (Table 1).

EXPERIMENTAL

Melting points were determined on a Gallenkamp equipment and are uncorrected. IR spectra were recorded in nujol on a Perkin-Elmer Spectrum RX-I series FT IR spectrophotometer at the Department of Chemistry, Punjabi University, Patiala. ^1H NMR spectra were recorded on a Bruker AC-300F (300 MHz) spectrometer in $CDCl_3$ using TMS as internal standard. Mass spectra were obtained on a VG-70-S mass spectrometer (70 eV) by SAIF, Punjab University, Chandigarh.

TABLE 1. Preparation of isoxazoline-4,6-diones **4** and **5**

Products	X	Y	*n*	Refluxing time, min	Yield, %*
4a	3,4-OCH_2O	H	0	120	73
4b	3,4-OCH_2O	4-Me	0	100	72
4c	3,4-OCH_2O	4-OMe	0	90	78
4d	3,4-OCH_2O	4-OEt	0	90	72
4e	3,4-OCH_2O	4-Cl	0	90	80
4f	3,4-OCH_2O	4-NO_2	0	110	65
4g	3,4-OCH_2O	H	1	20*[2]	71
5a	3-NO_2	H	0	150	72
5b	3-NO_2	4-Me	0	130	75
5c	3-NO_2	4-OMe	0	130	79
5d	3-NO_2	4-OEt	0	120	78
5e	3-NO_2	4-Cl	0	140	71
5f	3-NO_2	4-NO_2	0	160	69
5g	3-NO_2	H	1	30*[2]	72

* Isolated yield.

*[2] Refluxing time for the reactions involving N-benzylmaleimide as a dipolarophile.

Preparation of 4a–g, 5a–g. (General Method). In a 250 ml round bottom flask fitted with reflux condensor, a mixture of aldoxime (0.01 mol), maleimide (0.01 mol), and chloramine T (0.01 mol) in ethanol (100 ml) was refluxed with stirring for the appropriate time (Table 1). Sodium chloride formed in the reaction was filtered off and washed with ethanol. The filtrate and washings were concentrated under reduced pressure, and the residue was extracted with CH_2Cl_2. The extract was first washed with distilled water and then with 1N aqueous NaOH and dried over anhydrous Na_2SO_4. The solvent was evaporated under vaccum, and the viscous residue was crystallized.

3-(3,4-Methylenedioxyphenyl)-5-phenyl-3a,4,6,6a-tetrahydro-4H,6H-pyrrolo[3,4-*d*]isoxazoline-4,6-dione (**4a**). Mp 188–190°C. IR spectrum, ν, cm^{-1}: 1786, 1719 (>C=O), 930 (C–O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 4.87 (1H, d, *J* = 9.7, H-3a); 5.61 (1H, d, *J* = 9.7, H-6a); 6.02 (2H, s, OCH_2O); 6.85–7.54 (8H, m, H arom.). Mass spectrum, *m/z*: 336 $[M]^+$. Found, %: C 64.51; H 3.43; N 8.39. $C_{18}H_{12}N_2O_5$. Calculated, %: C 64.28; H 3.57; N 8.33.

3-(3,4-Methylenedioxyphenyl)-5-(4-tolyl)-3a,4,6,6a-tetrahydro-4H,6H-pyrrolo-[3,4-*d*]isoxazoline-4,6-dione (**4b**). Mp 193–195°C. IR spectrum, ν, cm^{-1}: 1784, 1718 (>C=O), 929 (C–O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.29 (3H, s, CH_3); 4.93 (1H, d, *J* = 9.8, H-3a); 5.68 (1H, d, *J* = 9.8, H-6a); 6.01 (2H, s, OCH_2O); 6.84–7.35 (7H, m, H arom.). Mass spectrum, *m/z*: 349 $[M]^+$. Found, %: C 65.20; H 4.03; N 8.08. $C_{19}H_{14}N_2O_5$. Calculated, %: C 65.14; H 4.00; N 8.00.

5-(4-Methoxyphenyl)-3-(3,4-methylenedioxyphenyl)-3a,4,6,6a-tetrahydro-4H,6H-pyrrolo[3,4-*d*]isoxazoline-4,6-dione (**4c**). Mp 195–197°C. IR spectrum, ν, cm^{-1}: 1784, 1721 (>C=O), 928 (C–O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.85 (3H, s, OCH_3); 4.81 (1H, d, *J* = 9.7, H-3a); 5.59 (1H, d, *J* = 9.7, H-6a); 6.02 (2H, s, OCH_2O); 6.89–7.84 (7H, m, H arom.). Mass spectrum, *m/z*: 365 $[M]^+$. Found, %: C 62.10; H 3.92; N 7.53. $C_{19}H_{14}N_2O_6$. Calculated, %: C 62.29; H 3.82; N 7.65.

5-(4-Ethoxyphenyl)-3-(3,4-methylenedioxyphenyl)-3a,4,6,6a-tetrahydro-4H,6H-pyrrolo[3,4-d]isoxazoline-4,6-dione (**4d**). Mp 191–192°C. IR spectrum, ν, cm^{-1}: 1779, 1718 (>C=O), 929 (C–O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.42 (3H, t, *J* = 9.3, $OCH_2C\underline{H}_3$); 4.05 (2H, q, *J* = 9.2, $OC\underline{H}_2CH_3$); 4.82 (1H, d, *J* = 9.7, H-3a); 5.62 (1H, d, *J* = 9.7, H-6a); 6.02 (2H, s, OCH_2O); 6.89–8.69 (7H, m, H arom.). Mass spectrum, *m/z*: 369 $[M]^+$. Found, %: C 63.21; H 4.27; N 7.21. $C_{20}H_{16}N_2O_6$. Calculated, %: C 63.15; H 4.21; N 7.36.

5-(4-Chlorophenyl)-3-(3,4-methylenedioxyphenyl)-3a,4,6,6a-tetrahydro-4H,6H-pyrrolo[3,4-*d*]isoxazoline-4,6-dione (**4e**). Mp 198–201°C. IR spectrum, ν, cm^{-1}: 1780, 1720 (>C=O), 929 (C–O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 4.89 (1H, d, *J* = 9.2, H-3a); 5.66 (1H, d, *J* = 9.2, H-6a); 6.02 (2H, s, OCH_2O); 6.84–7.99 (7H, m, arom.). Mass spectrum, *m/z*: 370 $[M]^+$. Found: C 58.01; H 2.82; N 7.43. $C_{18}H_{11}ClN_2O_5$. Calculated, %: C 58.29; H 2.96; N 7.55.

3-(3,4-Methylenedioxyphenyl)-5-(4-nitrophenyl)-3a,4,6,6a-tetrahydro-4H,6H-pyrrolo[3,4-*d*]isoxazoline-4,6-dione (**4f**). Mp 196–199°C. IR spectrum, ν, cm^{-1}: 1780, 1732 (>C=O), 931 (C–O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 4.90 (1H, d, *J* = 9.7, H-3a); 5.68 (1H, d, *J* = 9.7, H-6a); 6.02 (2H, s, OCH_2O); 6.85–8.01 (7H, m, H arom.). Mass spectrum, *m/z*: 381 $[M]^+$. Found, %: C 56.20; H 2.73; N 11.07. $C_{18}H_{11}N_3O_7$. Calculated, %: C 56.69; H 2.88; N 11.02.

5-Benzyl-3-(3,4-methylenedioxyphenyl)-3a,4,6,6a-tetrahydro-4H,6H-pyrrolo[3,4-*d*]isoxazoline-4,6-dione (**4g**). Mp 186–188°C. IR spectrum, ν, cm^{-1}: 1780, 1721 (>C=O), 929 (C–O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 4.59 (2H, s, CH_2 benzyl); 4.85 (1H, d, *J* = 9.4, H-3a); 5.66 (1H, d, *J* = 9.4, H-6a); 6.01 (2H, s, 2H, OCH_2O); 6.93–7.41 (8H, m, H arom.). Mass spectrum, *m/z*: 350 $[M]^+$. Found, %: C 65.01; H 3.97; N 7.95. $C_{19}H_{14}N_2O_5$. Calculated, %: C 65.14; H 4.00; N 8.00.

3-(3-Nitrophenyl)-5-phenyl-3a,4,6,6a-tetrahydro-4H,6H-pyrrolo[3,4-*d*]isoxazoline-4,6-dione (**5a**). Mp 240°C. IR spectrum, ν, cm^{-1}: 1790, 1718 (>C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 4.81 (1H, d, *J* = 9.2, H-3a); 5.67 (1H, d, *J* = 9.2, H-6a); 7.21–7.45 (9H, m, H arom.). Mass spectrum, *m/z*: 337 $[M]^+$. Found, %: C 60.53; H 3.10; N 12.51. $C_{17}H_{11}N_3O_5$. Calculated, %: C 60.21; H 3.26; N 12.46.

3-(3-Nitrophenyl)-5-(4-tolyl)-3a,4,6,6a-tetrahydro-4H,6H-pyrrolo[3,4-*d*]isoxazoline-4,6-dione (**5b**). Mp 180–182°C. IR spectrum, ν, cm^{-1}; 1795, 1717 (>C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.37 (3H, s, CH_3); 4.98 (1H, d, *J* = 9.7, H-3a); 5.72 (1H, d, *J* = 9.7, H-6a); 7.11–8.93 (8H, m, H arom.). Mass spectrum, *m/z*: 351 $[M]^+$. Found, %: C 61.62; H 3.62; N 11.81. $C_{18}H_{13}N_3O_5$. Calculated, %: C 61.53; H 3.70; N 11.96.

5-(4-Methoxyphenyl)-3-(3-nitrophenyl)-3a,4,6,6a-tetrahydro-4H,6H-pyrrolo[3,4-*d*]isoxazoline-4,6-dione (**5c**). Mp 203–205°C. IR spectrum, ν, cm^{-1}: 1780, 1720 (>C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.93, (3H, s, OCH_3); 5.06 (1H, d, *J* = 9.7, H-3a); 5.68 (1H, d, *J* = 9.7, H-6a); 7.01–8.27 (8H, m, H arom.). Mass spectrum, *m/z*: 367 $[M]^+$. Found, %: C 57.01; H 3.68; N 11.56.$C_{18}H_{13}N_3O_6$. Calculated, %: C 56.69; H 3.54; N 11.44.

5-(Ethoxyphenyl)-3-(3-nitrophenyl)-3a,4,6,6a-tetrahydro-4H,6H-pyrrolo[3,4-d]isoxazoline-4,6-dione (**5d**). Mp 195–198°C. IR spectrum, ν, cm^{-1}: 1772, 1720 (>C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.41 (3H, t, *J* = 9.3, $OCH_2C\underline{H}_3$); 4.06 (2H, q, *J* = 9.3, $OC\underline{H}_2CH_3$); 4.91 (1H, d, *J* = 9.3, H-3a); 5.67 (1H, d, *J* = 9.3, H-6a); 6.95–8.73 (8H, m, H arom.). Mass spectrum, *m/z* (I_{rel}): 381 $[M]^+$. Found, %: C 59.50; H 3.76; N 11.08. $C_{19}H_{15}N_3O_6$. Calculated, % C 59.84; H 3.93; N 11.02.

5-(4-Chlorophenyl)-3-(3-nitrophenyl)-3a,4,6,6a-tetrahydro-4H,6H-pyrrolo[3,4-*d*]isoxazoline-4,6-dione (**5e**). Mp 207–209°C. IR spectrum, ν, cm^{-1}: 1780, 1724 (>C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 4.89 (1H, d, *J* = 9.4, H-3a); 5.58 (1H, d, *J* = 9.4, H-6a); 7.04–8.15 (8H, m, H arom.). Mass spectrum, *m/z*: 371 (^{35}Cl) $[M]^+$. Found, %: C 54.68; H 2.81; N 11.38. $C_{17}H_{10}ClN_3O_5$. Calculated, %: C 54.91; H 2.69; N 11.30.

3-(3-Nitrophenyl)-5-(4-nitrophenyl)-3a,4,6,6a-tetrahydro-4H,6H-pyrrolo[3,4-*d*]isoxazoline-4,6-dione (**5f**). Mp 229–231°C. IR spectrum, ν, cm^{-1}: 1789, 1720 (>C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 4.91 (1H, d, *J* = 9.45, H-3a); 5.67 (1H, d, *J* = 9.45, H-6a); 6.91–8.02 (8H, m, H arom.). Mass spectrum, *m/z*: 382 $[M]^+$. Found, %: C 53.21; H 2.50; N 18.67. $C_{17}H_{10}N_5O_7$. Calculated, %: C 53.40; H 2.61; N 18.32.

5-Benzyl-3-(3-nitrophenyl)-3a,4,6,6a-tetrahydro-4H,6H-pyrrolo[3,4-*d*]isoxazoline-4,6-dione (**5g**). Mp 203–205°C. IR spectrum, ν, cm^{-1}: 1765, 1709 (>C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 4.59 (2H, s, CH_2); 5.20 (1H, d, *J* = 9.7, H-3a); 5.66 (1H, d, *J* = 9.7, H-6a); 7.28–8.82 (9H, m, H arom.). Mass spectrum, *m/z*: 352 $[M]^+$. Found: C 61.20; H 3.68; N 11.72. $C_{18}H_{13}N_3O_5$. Calculated, %: C 61.53; H 3.70; N 11.96.

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