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A SIMPLEAND CONVENIENT APPROACHFORTHE SYNTHESISOF SPIROPYRAZOLE DERIVATIVES*VIA* 1,3-DIPOLARCYCLOADDITIONREACTION

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Abstract:
One pot synthesis of 1,2,7,9-tetraazaspiro[4.5]dec-2-ene-6,8,10-trione derivatives is developed through the reaction of aromatic aldehydes, *N,N*-dimethyl babituric acid and hydrazonoyl chlorides in the presence of Et_3N in EtOH at room temprature. The advantages of this method are one pot and mild reaction condition, high yield, easy purification of products and relatively short reaction time.

Key words: Pyrazole; 1,3-Dipolar cycloaddition; Spirocompound; Nitrile imine

Introduction

1,3-Dipolar cycloaddition reactions are useful strategy for the synthesis of five membered heterocyclic compounds.[I] Among the various dipolar reagents, nitrile imine are widely used in 1,3-dipolar cycloaddition reactions leading to pyrazole, pyrazoline, pyrazolidine, etc.[II] Nitrile imines can be obtained easily by base treatment from hydrazonoyl chlorides.[III] Pyrazoles and their derivatives are an important class of heterocycles and play a key role in organic synthesis as well as biology. Numerous compounds containing pyrazole motif exhibit interesting properties such as antiviral, anti-inflammatory, antitumor, antibacterial and antipyretic activities.[IV-VII] Some pyrazole containing medicines like, Celebrex, Viagra and Acomplia are commercially available (Figure).

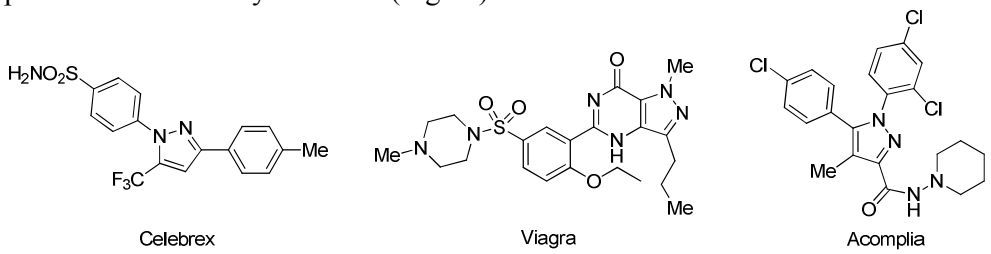
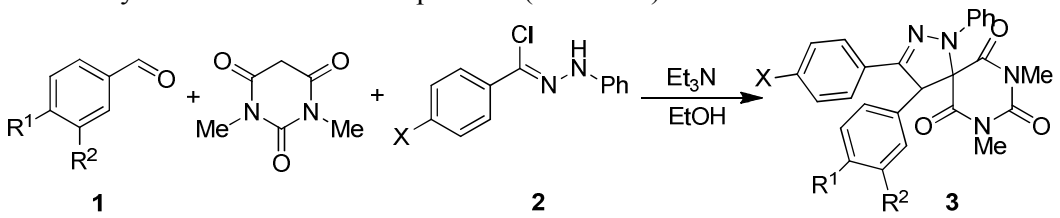


Figure Examples of some commercially available pyrazoles

In addition, a number of pyrazole derivatives are applied as biocides including acaricides, herbicides and fungicides.[VIII] On the other hand, spirocompounds have attracted much

attention due to their presence in a large number of biologically active molecules.[IX] Spiro-pyrazole derivatives have been discovered as cytotoxic, antimicrobial, anticonvulsant, antifungal and anticancer.[X]

Despite the importance of spiropyrazole scaffold, there are not many reports for the synthesis of these heterocycles in the literature.[XI-XII] Recently two-component reaction of 5-arylidene-1,3-dimethyl-2,4,6-pyrimidinetriones and nitrile imine for the synthesis of 1,2,7,9-tetraaza-spiro[4.5]dec-2-ene-6,8,10-triones has been reported.[XIII] Harsh reaction condition, using toxic organic solvent, tedious work up and generation of products in high temperature are disadvantages of this method. As a continue of our studies for the synthesis of various spiroheterocyclic compounds using multicomponent reaction,[XIV-XVI] herein, we reported a new and simple access for the preparation of spiropyrazole **3** through the reaction of aromatic aldehydes **1**, *N,N*-dimethyl barbituric acid and hydrazonoyl chlorides **2** in the presence of Et_3N as catalyst in EtOH at room temperature (Scheme 1).



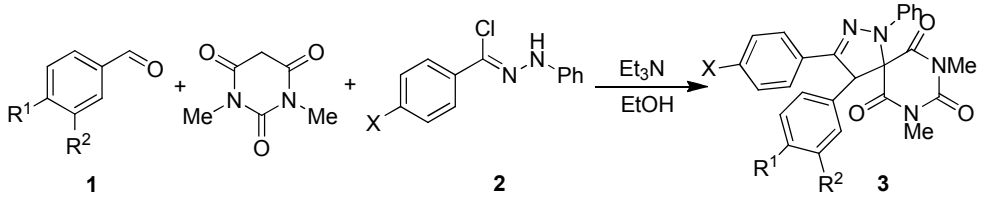
Scheme 1 Three Component Synthesis of Spiropyrazole**3**

Results and Discussion

Initially, the reaction was done by mixing 4-chlorobenzaldehyde **1a** (1mmol, R^1 = Cl, R^2 = H), and *N,N*-dimethyl babituric acid (1mmol) in EtOH (4 ml) in the presence of Et_3N (1mmol) at reflux temperature. After 1 h, hydrazonoyl chloride **2a** (1mmol, X = H) was added to the above mixture and the reaction was stirred at room temperature for 7 h to afford spiropyrazole **3a** in high yield.

In order to extend the scope of this reaction, different aromatic aldehydes and some hydrazonoyl chlorides were applied in the same reaction condition. As shown in Table, all products were obtained in high yields.

TableSynthesis of spiropyrazole derivatives **3a-g**

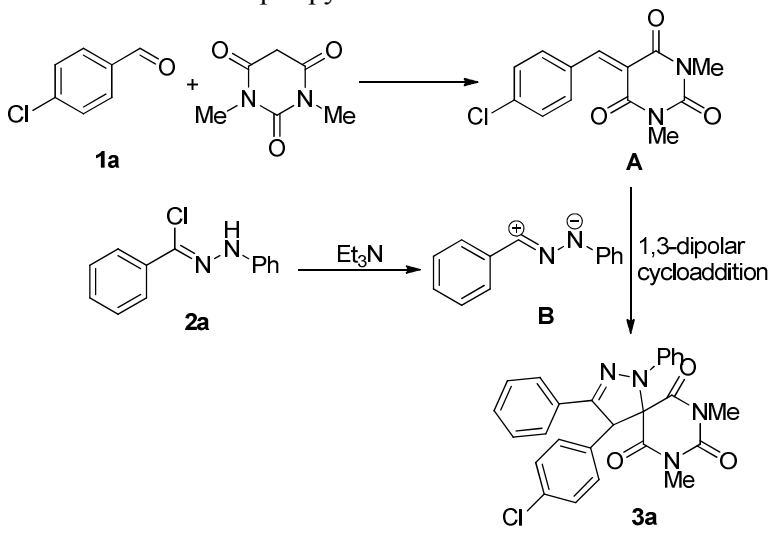


Entry	R^1	R^2	X	Time (h)	Yield of **3**(%)
a	Cl	H	H	6	85
b	Cl	H	Cl	6	87
c	H	Br	H	8	75
d	H	Br	Cl	7	80
e	OMe	H	H	6	86
f	OMe	H	Cl	6	88
g	H	OMe	H	7	78

The structures of compounds **3a-g** were characterized by spectroscopic analysis. The mass spectrum of **3a** displayed a molecular ion peak at *m/z* 472. The ^{1}H NMR spectrum exhibited three singlets at δ = 2.62, 3.30 and 5.98 ppm arising from two methyl and one methine groups

respectively. The aromatic H-atoms gave rise to characteristic chemical shift and coupling constant in the aromatic region of the spectrum. Appearance of 20 distinct signals in the ^{1}H-decoupled ^{13}CNMR spectrum of **3a** confirmed the proposed structure.

A plausible mechanism for this reaction is indicated in Scheme 2. Initially, *N,N*-dimethyl babituric acid condenses with aromatic aldehyde **1a** to give adduct intermediate **A**. 1,3-Dipolar cycloaddition of nitrile imine **B** (which generated *in situ* from hydrazonoyl chloride **2a**) on **A**, leads to the formation of spiropyrazole **3a**.



Scheme 2 Mechanism for this reaction

Conclusion

In conclusion, a convenient and simple method for the synthesis of spiropyrazole using 1,3-dipolar cycloaddition is described. The present method has some advantages like mild reaction condition, using available starting material, high yield of products and operational simplicity.

Experimental Section

General

Elemental analyses for C, H and N were performed using a *Heraeus CHN–O–Rapid* analyzer. Mass spectra were recorded on a *FINNIGAN-MATT 8430* mass spectrometer operating at an ionization potential of 70 eV. ^{1}HNMR (400 MHz) and ^{13}CNMR (100 MHz) spectra in DMSO-d_6 were obtained using *Bruker DRX-400 AVANCE* spectrometers. IR spectra were recorded as KBr pellets on a *NICOLET FT-IR 100* spectrometer; absorbencies are reported in cm^{-1}.

General procedure for the synthesis of 3a-g

A mixture of benzaldehyde (**1**; 1 mmol) and *N,N*-dimethyl babituric acid (1 mmol) in the presence of Et_3N (1 mmol) in EtOH (4 ml) was stirred at reflux temperature for 1 h. Then hydrazonoyl chloride (**2**, 1mmol) was added to the above mixture and the reaction was stirred at room temperature for appropriate time. After completion of the reaction (TLC), the mixture was filtered and washed with EtOH to afford the pure products**3a-g** in high yields.

4-(4-Chlorophenyl)-7,9-dimethyl-1,3-diphenyl-1,2,7,9-tetraazaspiro[4.5]dec-2-ene-6,8,10-trione (3a):

White powder; yield: 0.4 g, (85%); mp 228-230 °C. IR (KBr): 1692 (NCO), 1594, 1490 (Ar) cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.62 (s, 3H, CH_3), 3.30 (s, 3H, CH_3), 5.98 (s, 1H,

CH), 6.85 (t, $^3J_{HH}$ = 7.2 Hz, 2H, 2×CH_{para} of 2Ph), 7.01 (d, $^3J_{HH}$ = 8.0 Hz, 2H, 2×CH_{ortho} of Ph), 7.22 (t,$^3J_{HH}$ = 7.6 Hz, 4H, 2×CH of Ar + 2×CH_{ortho} of Ph), 7.33 (d,$^3J_{HH}$ = 7.6 Hz, 4H, 4×CH_{meta} of 2Ph), 7.53 (d, $^3J_{HH}$ = 8.0 Hz, 2H, 2×CH of Ar). ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 28.4 (CH_3), 29.4 (CH_3), 62.8 (CH), 77.3 (C_{spiro}), 113.7 (2×CH_{ortho} of Ph), 119.8 (CH_{para} of Ph), 126.2 (2×CH_{ortho} of Ph), 128.6 (2×CH_{meta} of Ph), 128.7 (2×CH_{meta} of Ph), 128.9 (2×CH of Ar), 129.0 (CH_{para} of Ph), 130.1 (C_{ipso}), 131.2 (2CH of Ar), 132.3 (C_{ipso}), 133.5 (C_{ipso}-Cl), 141.8 (C_{ipso}-N), 145.2 (C=N), 150.0 (N_2C=O), 163.5 (NC=O), 165.8 (NC=O). MS (EI, 70 eV) *m/z* (%) : 472 [M^+], 367, 309, 91, 77, 51.Anal. Calcd. for$C_{26}H_{21}ClN_4O_3$ (472.93): C, 66.03; H, 4.48; N, 11.85. Found: C, 66.07; H, 4.40; N, 11.91.

Bis(4-chlorophenyl)-7,9-dimethyl-1-phenyl-1,2,7,9-tetraazaspiro[4.5]dec-2-ene-6,8,10-trione (3b):

Cream powder; yield: 0.44 g (78%); mp 142-144 °C. IR (KBr): 1691 (NCO), 1596, 1493 (Ar) cm^{-1}. ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 2.62 (s, 3H, CH_3), 3.30 (s, 3H, CH_3), 6.00 (s, 1H, CH), 6.86 (t, $^3J_{HH}$ = 6.4 Hz, 1H, CH_{para} of Ph), 7.01 (d, $^3J_{HH}$ = 7.2 Hz, 2H, 2×CH_{ortho} of Ph), 7.21 (t, $^3J_{HH}$ = 6.4 Hz, 2H, 2×CH_{meta} of Ph), 7.42 (d, $^3J_{HH}$ = 7.6 Hz, 4H, 4×CH of 2Ar), 7.52 (d, $^3J_{HH}$ = 7.6 Hz, 4H, 4 ×CH of 2Ar). ^{3}C NMR (DMSO-d_6, 100 MHz): δ = 28.4 (CH_3), 29.4 (CH_3), 62.6 (CH), 77.3 (C_{spiro}), 113.7 (2×CH_{ortho} of Ph), 120.0 (CH_{para} of Ph), 127.8 (2×CH of Ar), 128.6 (2×CH of Ar), 128.8 (2×CH_{meta} of Ph), 128.9 (2×CH of Ar), 129.0 (C_{ipso}), 131.2 (2×CH of Ar), 132.0 (C_{ipso}), 133.5 (C_{ipso}-Cl), 133.6 (C_{ipso}-Cl), 141.6 (C_{ipso}-N), 144.1 (C=N), 149.9 (N_2C=O), 163.4 (NC=O), 165.7 (NC=O). MS (EI, 70 eV) *m/z* (%):508 [M^++2], 506 [M^+], 401, 343, 91, 77**.** Anal. Calcd. for$C_{26}H_{20}Cl_2N_4O_3$ (507.37): C, 61.55; H, 3.97; N, 11.04. Found: C, 61.62; H, 3.90; N, 11.09.

4-(3-Bromophenyl)-7,9-dimethyl-1,3-diphenyl-1,2,7,9-tetraazaspiro[4.5]dec-2-ene-6,8,10-trione (3c):

White powder; yield: 0.38 g (75%); mp 108-109 °C. IR (KBr): 1693 (NCO), 1594, 1495 (Ar) cm^{-1}. ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 2.63 (s, 3H, CH_3), 3.30 (s, 3H, CH_3), 5.98 (s, 1H, CH), 6.85 (t, $^3J_{HH}$ = 7.6 Hz, 1H, CH_{para} of Ph), 7.01 (d, $^3J_{HH}$ = 8.0 Hz, 2H, 2×CH_{ortho} of Ph), 7.22 (t, $^3J_{HH}$ = 8.4 Hz, 2H, 2×CH_{meta} of Ph), 7.31-7.37 (m, 3H, 2×CH of Ph + CH of Ar), 7.52-7.58 (m, 3H, 2×CH of Ph + CH of Ar), 7.60-7.64 (m, 2H, 2×CH of Ar). ^{3}C NMR (DMSO-d_6, 100 MHz): δ = 28.4 (CH_3), 29.4 (CH_3), 62.8 (CH), 77.3 (C_{spiro}), 113.7 (2×CH_{ortho} of Ph), 119.8 ($CH_{para}$of Ph), 121.5 (C_{ipso}-Br), 126.2 (2×CH of Ph), 128.6 (CH of Ar), 128.7 (2×CH of Ph), 128.9 (2×CH of Ph), 130.7 (C_{ipso}), 131.4 (CH_{para} of Ph), 131.5 (CH of Ar), 132.0 (C_{ipso}), 132.1 (CH of Ar), 135.8 (CH of Ar), 141.8 (C_{ipso}-N), 144.9 (C=N), 149.9 (N_2C=O), 163.4 (NC=O), 165.7 (NC=O). MS (EI, 70 eV) *m/z* (%): 518 [M^+], 411, 277, 165, 91, 77. Anal. Calcd. for$C_{26}H_{21}BrN_4O_3$ (517.38): C, 60.36; H, 4.09; N, 10.83. Found: C, 60.31; H, 4.02; N, 10.80.

4-(3-Bromophenyl)-3-(4-chlorophenyl)-7,9-dimethyl-1-phenyl-1,2,7,9-tetraazaspiro[4.5]dec-2-ene-6,8,10-trione (3d):

White powder; yield: 0.44 g (80%); mp 180-183 °C. IR (KBr): 1695 (NCO), 1595, 1493 (Ar) cm^{-1}. ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 2.62 (s, 3H, CH_3), 3.30 (s, 3H, CH_3), 5.99 (s, 1H, CH), 6.87 (t, $^3J_{HH}$ = 7.2 Hz, 1H, CH_{para} of Ph), 7.01 (d, $^3J_{HH}$ = 7.6 Hz, 2H, 2×CH_{ortho} of Ph), 7.22 (t, $^3J_{HH}$ = 7.6 Hz, 2H, 2×CH_{meta} of Ph), 7.42-7.45 (m, 4H, 4×CH of Ar), 7.53-7.55 (m, 4H, 4×CH of Ar). ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 28.4 (CH_3), 29.5 (CH_3), 62.6 (CH), 77.4 (C_{spiro}), 113.8 (2×CH_{ortho} of Ph), 120.1 ($CH_{para}$of Ph), 121.6 (C_{ipso}-Br), 127.8 (2×CH of Ar), 128.5 (CH of Ar), 128.8 (2×CH of Ar), 128.9 (2×CH_{meta} of Ph), 130.7 (C_{ipso}), 131.7 (CH of Ar), 131.8 (CH of Ar), 132.0 (C_{ipso}), 133.6 (C_{ipso}-Cl), 135.6 (CH of Ar), 141.6 (C_{ipso}-N), 143.8 (C=N), 149.9 (N_2C=O), 163.3 (NC=O), 165.6 (NC=O);MS (EI, 70 eV) *m/z* (%) : 552 [M^+], 447, 368, 236, 165, 77. Anal. Calcd. for$C_{26}H_{20}BrClN_4O_3$ (551.82): C, 56.59; H, 3.65; N, 10.15. Found: C, 56.67; H, 3.69; N, 10.11.

4-(4-Methoxyphenyl)-7,9-dimethyl-1,3-diphenyl-1,2,7,9-tetraazaspiro[4.5]dec-2-ene-6,8,10-trione (3e):

White powder; yield: 0.40 g (86%); mp 280 °C dec. IR (KBr): 1688 (NCO), 1597, 1498 (Ar) cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz): δ = 2.59 (s, 3H, CH_3), 3.30 (s, 3H, CH_3), 3.70 (s, 3H, OCH_3), 5.87 (s, 1H, CH), 6.84 (t, $^3J_{HH}$ = 7.2 Hz, 1H, CH_{para} of Ph), 6.99 (d, $^3J_{HH}$ = 8.0 Hz, 2H, 2×CH of Ar), 7.21-7.23 (m, 5H, 5×CH of Ph), 7.28-7.31 (m,4H, 2×CH of Ar + 2×CH of Ph), 7.53 (d, $^3J_{HH}$ = 8.0 Hz, 2H, 2×CH_{ortho} of Ph). ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 28.4 (CH_3), 29.4 (CH_3), 55.1 (OCH_3), 63.6 (CH), 77.4 (C_{spiro}), 113.6 (2×CH_{ortho} of Ph), 113.8 (2×CH of Ar), 119.7 ($CH_{para}$of Ph), 124.9 (C_{ipso}), 126.3 (2×CH of Ph), 128.5 (2×CH of Ph), 128.8 (CH_{para} of Ph), 128.9 (2×CH of Ph), 130.4 (C_{ipso}), 130.7 (2×CH of Ar), 141.9 (C_{ipso}-N), 145.6 (C=N), 150.1 (N_2C=O), 159.3 (C_{ipso}-OMe), 163.7 (NC=O), 166.2 (NC=O);MS (EI, 70 eV) *m/z* (%): 468 [M^+], 362, 208, 194, 91, 77. Anal. Calcd. for$C_{27}H_{24}N_4O_4$ (468.51): C, 69.22; H, 5.16; N, 11.96. Found: C, 69.17; H, 5.22; N, 12.02.

3-(4-Chlorophenyl)-4-(4-methoxyphenyl)-7,9-dimethyl-1-phenyl-1,2,7,9-tetraazaspiro[4.5]dec-2-ene-6,8,10-trione (3f):

White powder; yield: 0.44 g (78%); mp 275-277 °C, IR (KBr): 1694 (NCO), 1597, 1498 (Ar)cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz): δ = 2.57 (s, 3H, CH_3), 3.30 (s, 3H, CH_3), 3.70 (s, 3H, OCH_3), 5.88 (s, 1H, CH), 6.68 (t, $^3J_{HH}$ = 7.2 Hz, 1H, CH_{para} of Ph), 6.83 (d, $^3J_{HH}$ = 6.8 Hz, 2H, 2×CH of Ar), 7.00 (d, $^3J_{HH}$ = 7.2 Hz, 2H, 2×CH_{ortho} of Ph), 7.20-7.23 (m, 4H, 2×CH_{meta} of Ph + 2×CH of Ar), 7.40 (d, $^3J_{HH}$ = 7.2 Hz, 2H, 2×CH of Ar), 7.52 (d, $^3J_{HH}$ = 7.2 Hz, 2H, 2 ×CH of Ar).^3C NMR (DMSO-d_6, 100 MHz): δ = 28.4 (CH_3), 29.4 (CH_3), 55.1 (OCH_3), 63.4 (CH), 77.5 (C_{spiro}), 113.6 (2×CH_{ortho} of Ph), 113.9 (2×CH of Ar), 119.7 ($CH_{para}$of Ph), 124.6 (C_{ipso}), 127.9 (2×CH of Ar), 128.6 (2×CH_{meta} of Ph), 128.9 (2×CH of Ar), 129.3 (C_{ipso}), 130.7 (2×CH of Ar), 133.3 (C_{ipso}-Cl), 141.8 (C_{ipso}-N), 144.5 (C=N), 150.1 (N_2C=O), 159.4 (C_{ipso}-OMe), 163.6 (NC=O), 166.1 (NC=O);MS (EI, 70 eV) *m/z* (%):504 [M^++2], 502 [M^+], 396, 368, 236, 91, 77. Anal. Calcd. for$C_{27}H_{23}ClN_4O_4$ (502.95): C, 64.48; H, 4.61; N, 11.14. Found: C, 64.42; H, 4.58; N, 11.23.

4-(3-Methoxyphenyl)-7,9-dimethyl-1,3-diphenyl-1,2,7,9-tetraazaspiro[4.5]dec-2-ene-6,8,10-trione (3g):

White powder; yield: 0.36 g (78%); mp 188-189 °C, IR (KBr): 1691 (NCO), 1594, 1489 (Ar)cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz): δ = 2.56 (s, 3H, CH_3), 3.31 (s, 3H, CH_3), 3.41 (s, 3H, OCH_3), 5.88 (s, 1H, CH), 6.82-6.89 (m, 3H, 2×CH of Ar + CH_{para} of Ph), 6.99 (d, $^3J_{HH}$ = 7.6 Hz, 2H, 2×CH_{ortho} of Ph), 7.21 (t, $^3J_{HH}$ = 8.4 Hz, 2H, 2×CH_{meta} of Ph), 7.29-7.34 (m, 5H, 2×CH_{meta} of Ph + 2×CH of Ar + CH_{para} of Ph), 7.54 (d, $^3J_{HH}$ = 7.2 Hz, 2H, 2×CH_{ortho} of Ph).^3C NMR (DMSO-d_6, 100 MHz): δ = 28.4 (CH_3), 29.4 (CH_3), 55.0 (OCH_3), 63.9 (CH), 77.5 (C_{spiro}), 113.6 (2×CH_{ortho} of Ph), 113.8 (CH of Ar), 113.9 (CH of Ar), 119.6 ($CH_{para}$of Ph), 121.7 (C_{ipso}), 126.3 (2×CH_{ortho} of Ph), 128.6 (2×CH_{meta} of Ph), 128.8 (CH_{para} of Ph), 128.9 (2×CH_{meta} of Ph), 129.6 (CH of Ar), 130.4 (C_{ipso}), 134.7 (CH of Ar), 141.9 (C_{ipso}-N), 145.2 (C=N), 150.1 (N_2C=O), 159.0 (C_{ipso}-OMe), 163.5 (NC=O), 166.1 (NC=O);MS (EI, 70 eV) *m/z* (%):468 [M^+], 363, 305, 277, 91, 77. Anal. Calcd. for$C_{27}H_{24}N_4O_4$ (468.51): C, 69.22; H, 5.16; N, 11.96. Found: C, 69.18; H, 5.21; N, 11.88.

Acknowledgements

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