Highly Efficient Diastereoselective Synthesis of Azabicyclo[2.2.2]octanes

Abdolali Alizadeh,*[a] Vahideh Sadeghi,[a] Fahimeh Bayat,[a] Long-Guan Zhu[b]

[a] Department of Chemistry, Tarbiat Modares University, P.O. Box 14115-175, Tehran, Iran
Fax +98(21)88006544; E-mail: aalizadeh@modares.ac.ir; E-mail: abdol_alizad@yahoo.com

[b] Department of Chemistry, Zhejiang University, Hangzhou 310027, P. R. of China

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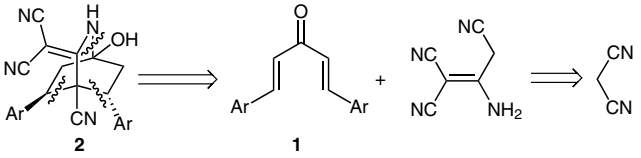
Abstract: A one-pot, diastereoselective synthesis of diverse azabicyclo[2.2.2]octanes from readily available starting materials is reported. The key strategy relies on creation of 2-aminoprop-1-ene-1,1,3-tricarbonitrile through dimerization of malononitrile which undergoes nucleophilic attack on dibenzalacetone at three sites leading to bicyclo[2.2.2]octanes.

Key words: malononitrile, dibenzalacetone, azabicyclo[2.2.2]octanes, one-pot reaction

The interest in the azabicyclo[2.2.2]octane skeleton is connected with the presence of this structure in a great number of natural products characterized by a variety of biological and pharmacological activities.[1] For example, in the family of Cinchona alkaloids, quinine shows analgesic, antimalarial, and anti-inflammatory properties.[2] In addition to natural products synthetic compounds, having the azabicyclo[2.2.2]octane skeleton, such as PHA-543,613 and (+)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)-benzo[*b*]furan-2-carboxamide, act as potent agonists for the α7 neuronal nicotinic acetylcholine receptor.[3]

The large number of potential therapeutic applications of azabicyclo[2.2.2]octane-containing compounds has led chemists to establish effective synthetic methodologies to access them. They are mostly synthesized by Diels–Alder reaction of dihydropyridines with dienophiles. However, the main problem with this approach is low stability of dihydropyridines toward many Lewis acids, so most of these reactions have been carried out under uncatalyzed thermal conditions, resulting in poor *endo–exo* selectivity.[4] Other methods include double conjugate addition of aqueous ammonia onto bifunctional Michael acceptors,[5] radical cyclization of tetrahydropyridines,[6] cyclization of silyl enol ethers onto iminium ions,[7] reaction of 6-acylcyclohex-2-enones with aqueous ammonia,[8] and thermal cyclization of 4-aminocyclohexane carboxaldehyde derivatives.[9]

The development of new one-pot processes for the synthesis of various organic molecules has attracted intense interest in recent years as they minimize the steps of operations and they provide higher yields and less waste generation.[10] In conjunction with our interest in the synthesis of heterocycles as well as one-pot synthesis,[11] we considered the reaction of 2-aminoprop-1-ene-1,1,3-tricarbonitrile, generated from dimerization of malononitrile, with dibenzalacetones **1**. Our plan is outlined in Scheme 1. To the best of our knowledge there are a few reports for the synthesis of azabicyclo[2.2.2]octanes **2** based on one pot reactions.



Scheme 1 Retrosynthetic strategy for azabicyclo[2.2.2]octane

Initially, 2-aminoprop-1-ene-1,1,3-tricarbonitrile generated in situ from dimerization of malononitrile in the presence of NaOH was reacted with dibenzalacetone **1a**. Gratifyingly, we observed a process leading to azabicyclo[2.2.2]octane **2a** in good yield. To the best of our knowledge, no analogous products have been reported in the literature yet. Several polar and nonpolar solvents at different temperatures were explored to optimize reaction conditions, and it was found that the reaction proceeded in good yield at 50 °C in ethanol (Table 1, entry 3) in the presence of piperidine. Performing the reaction at higher temperature generated a complex mixture that was not investigated. In the absence of piperidine no product was obtained.

With optimal conditions established,[12] we then explored the scope of this promising reaction by varying the structures of dibenzalacetone **1** (Table 2). Unfortunately, the reaction did not yield the product when dibenzalacetones having *ortho* substitution (2-Me, 2-Cl, and 2-Br) were used. This is probably due to the steric hindrance. Furthermore, utilizing dibenzalacetones having hydroxyl substitution at the *para* position did not yield the products, presumably due to mesomeric donating effects of the hydroxyl group.

The newly synthesized products **2a**–**f** were fully characterized by their IR, mass, ^{1}H NMR, and ^{13}C NMR spectra and unambiguously confirmed by X-ray crystal-structure analysis of **2a** (Figure 1).

In the IR spectrum of **2a**, absorption bands at 3379 and 3031 cm^{-1} relate to OH and NH stretching frequencies, respectively, and three nitrile absorption bands were observed at 2245, 2186, and 2151 cm^{-1}. The ^{1}H NMR spectrum of **2a** showed hydrogen atoms of two CH_2 groups as one multiplet between δ = 1.56 and 1.61 ppm

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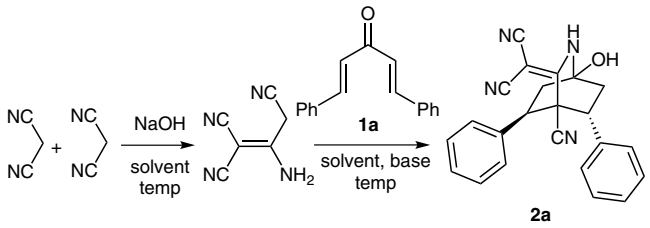
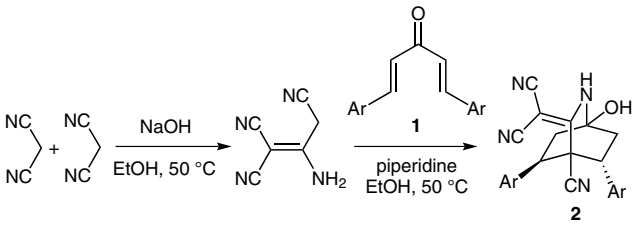
Table 1 Optimization of the Reaction Conditions



Entry	Solvent	Temp (°C)	Base	Yield of **2a** (%)
1	EtOH	r.t.	piperidine	0
2	EtOH	78	piperidine	0
3	EtOH	50	piperidine	89
4	EtOH	50	–	0
5	MeOH	50	piperidine	84
6	acetone	50	piperidine	44
7	DMF	50	piperidine	30
8	$CHCl_3$	50	piperidine	40
9	MeCN	50	piperidine	49
10	toluene	50	piperidine	0
11	H_2O	50	piperidine	0

Table 2 Synthesis Results of Azabicyclo[2.2.2]octanes **2a**–**f** via One-Pot Synthesis



Entry	Ar	Product	Yield (%)
1	Ph	**2a**	89
2	4-ClC_6H_4	**2b**	85
3	3-BrC_6H_4	**2c**	70
4	3-$O_2NC_6H_4$	**2d**	87
5	4-$MeOC_6H_4$	**2e**	76
6	3,4-$(MeO)_2C_6H_3$	**2f**	88

and three double doublets at δ = 1.96, 3.11, and 3.25 ppm. Two CH groups appeared as a double doublet and a multiplet at δ = 1.58 and 3.32 ppm. The ten aromatic hydrogen atoms gave rise to characteristic resonances in the aromatic region of the spectrum. ^{1}H-decoupled ^{13}C NMR spectrum of **2a** was in agreement with the proposed structure.

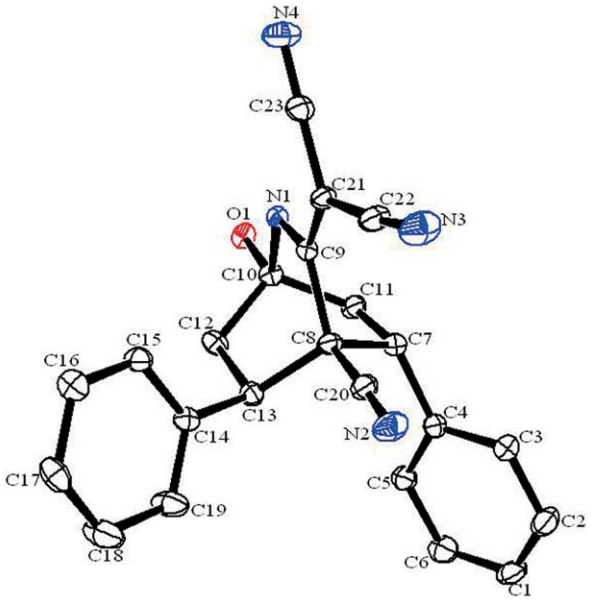
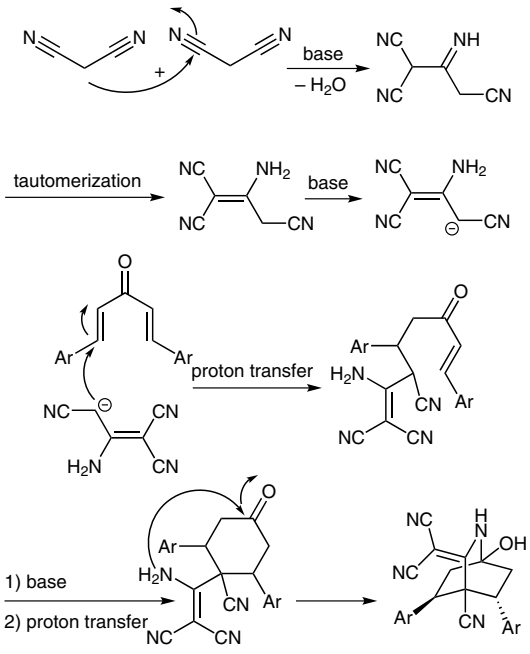


Figure 1 ORTEP diagram of **2a** (asymmetric unit); hydrogens are omitted for more clarity

A possible reaction mechanism is proposed as shown in Scheme 2. Initially, nucleophilic addition of the active methylene of one malononitrile to a nitrile group of another malononitrile in the presence of NaOH generates 2-aminoprop-1-ene-1,1,3-tricarbonitrile. Subsequently, by two base-promoted Michael additions of the CH_2 group of the 2-aminoprop-1-ene-1,1,3-tricarbonitrile onto dibenzalacetone, followed by the NH_2 group attacking the carbonyl group, the desired product **2** is produced.



Scheme 2 Mechanistic rationalization for the formation of **2**

In summary, we have developed an efficient and diastereoselective approach to the synthesis of azabicyclo-[2.2.2]octanes by using malononitrile and dibenzalacetone. The ready accessibility of the starting materials and the generality of this process make the reaction highly valuable in view of the potential interest in these structures in synthetic and medicinal chemistry. The features of this strategy include a convenient one-pot operation, mild conditions, and the absence of byproducts.

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(12) A mixture of malononitrile (1 mmol) and NaOH (2 mmol) was stirred at 50 °C for 30 min, after this time dibenzalacetone (**1**, 1 mmol) and piperidine (one drop) was added and stirred for another 2 h. Upon completion, as monitored by TLC, the mixture was filtered, and the precipitate was washed with EtOH (4 mL) to afford the pure product **2a**–**f**.

2-{4-Cyano-1-hydroxy-5,8-diphenyl-2-azabicyclo[2.2.2]oct-3-yliden}malononitrile (2a)

White powder; yield 0.33 g (89%); mp 195 °C. IR (KBr): 3379 (NH), 3031 (OH), 2245, 2186 and 2151 (CN), 1542 and 1447 (Ar) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ = 1.56–1.61 (m, 1 H, CH_2), 1.85 (dd, $^2J_{HH}$ = 12.6 Hz, $^3J_{HH}$ = 6.3 Hz, 1 H, CH), 1.96 (dd, $^2J_{HH}$ = 12.6 Hz, $^3J_{HH}$ = 6.3 Hz, 1 H, CH_2), 3.11 (dd, $^2J_{HH}$ = 11.6 Hz, $^3J_{HH}$ = 6.1 Hz, 1 H, CH_2), 3.25 (dd, $^2J_{HH}$ = 10.3 Hz, $^3J_{HH}$ = 5.9 Hz, 1 H, CH_2), 3.30–3.35 (m, 1 H, CH), 4.33 (s, 1 H, OH), 5.64 (s, 1 H, NH), 7.03 (d, $^3J_{HH}$ = 6.4 Hz, 2 H, 2 × CH_{ortho} of Ph), 7.17–7.25 (m, 3 H, 3 × CH of Ph), 7.31–7.48 (m, 5 H, 5 × CH of Ph). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 35.78 and 41.46 (2 × CH_2), 42.38 [$C(CN)_2$], 45.09 (2 × CH), 46.42 (C^4), 84.87 (C^1), 118.03 (CN), 123.6 (2 × CN), 126.9 (CH_{para} of Ph), 127.52 (CH_{para} of Ph), 128.04 (2 CH_{ortho} of Ph), 128.10 (2 × CH_{ortho} of Ph), 128.65 (2 × CH_{meta} of Ph), 130.10 (2 × CH_{meta} of Ph), 138.07 (C_{ipso}), 142.15 (C_{ipso}), 159.95 (C^3). MS (EI, 70 eV): *m/z* = 307, 220, 185, 147, 128, 104, 91, 77, 51. Anal. Calcd for $C_{23}H_{18}N_4O$: C, 75.39; H, 4.95; N, 15.29. Found: C, 75.36; H, 4.97; N, 15.30.

Crystal Data for 2a

$C_{46}H_{38}N_8O_5Na_2$ (CCDC 1016275): M_W = 828.82, *a* = 15.9057(10) Å, *b* = 15.8824(11) Å, *c* = 16.6277(11) Å, α = 90.00° β = 90.00°, γ = 90.00°, *V* = 4200.5(5) Å^3, *Z* = 4, D_c = 1.311mg m^{-3}, *F*(000) = 1728, radiation, Mo Kα (λ = 0.71073 Å), 2.84 ≤ 2θ ≤ 25.04, intensity data were collected at 295(2) K with a Bruker APEX area-detector diffractometer, and employing ω/2θ scanning technique, in the range of $-17 \le h \le 18$, $-17 \le k \le 18$, $-16 \le l \le 19$; the structure was solved by a direct method, all nonhydrogen atoms were positioned and anisotropic thermal parameters refined from 3225 observed reflections with *R* (into) = 0.0811 by a full-matrix least-squares technique converged to *R* = 0.0706 and *wR*2 = 0.1985 [$I > 2\sigma(I)$].

2-{5,8-Bis-(4-chlorophenyl)-4-cyano-1-hydroxy-2-azabicyclo[2.2.2]oct-3-yliden}malononitrile (2b)

White powder; yield 0.37 g (85%); mp 255 °C. IR (KBr): 3422 (NH), 3046 (OH), 2193 and 2152 (CN), 1533 and 1491 (Ar) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ = 1.56–1.58 (m, 1 H, CH_2), 1.89–1.91 (m, 2 H, CH and CH_2), 3.18–3.21 (m, 3 H, CH and CH_2), 3.36 (s, 1 H, OH), 5.74 (s, 1 H, NH), 6.69–7.12 (m, 2 H, 2 × CH of Ar), 7.17–7.33 (m, 2 H, 2 × CH of Ar), 7.37–7.96 (m, 4 H, 4 × CH of Ar). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 35.93 and 38.31 (2 × CH_2), 40.88 [$C(CN)_2$], 45.60 (2 × CH), 45.84 (C^4), 84.80 (C^1), 117.96 (CN), 123.4 (2 × CN), 128.10 (4 × CH of Ar), 130.63 (2 ×

CH of Ar), 132.05 (2 × CH of Ar), 131.78 and 132.31 (2 × C_{ipso}Cl), 137.14 and 140.88 (2 × C_{ipso}), 159.39 (C^3). MS (EI, 70 eV): *m/z* = 304, 267, 239, 204, 179, 165, 137, 125, 101. Anal. Calcd for $C_{23}H_{16}Cl_2N_4O$: C, 63.46; H, 3.70; N, 12.87. Found: C, 63.44; H, 3.71; N, 12.89.

2-{5,8-Di-(3-bromophenyl)-4-cyano-1-hydroxy-2-azabicyclo[2.2.2]oct-3-yliden}malononitrile (2c)

White powder; yield 0.37 g (70%); mp 181 °C. IR (KBr): 3414 (NH), 3023 (OH), 2187 and 2152 (CN), 1523 and 1454 (Ar) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ = 1.58–1.60 (m, 1 H, CH_2), 1.82–1.91 (m, 1 H, CH_2), 1.91 (dd, $^3J_{HH}$ = 6.6 Hz, 1 H, CH_2), 2.42 (s, 1 H, OH), 3.00–3.05 (m, 1 H, CH_2), 3.18–3.20 (m, 1 H, CH_2), 3.34 (s, 1 H, CH), 5.64 (s, 1 H, NH), 6.89 (t, $^3J_{HH}$ = 6.6 Hz, 1 H, CH of Ar), 6.91 (s, 1 H, CH of Ar), 7.03 (d, $^3J_{HH}$ = 6.6 Hz, 2 H, 2 × CH of Ar), 7.19 (t, $^3J_{HH}$ = 6.9 Hz, 1 H, CH of Ar), 7.21 (s, 1 H, CH of Ar), 7.32 (d, $^3J_{HH}$ = 6.6 Hz, 2 H, 2 × CH of Ar). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 35.69 and 41.08 (2 × CH_2), 42.5 [$C(CN)_2$], 46.00 (2 × CH), 46.12 (C^4), 84.86 (C^1), 118.18 (CN), 123.70 (2 × CN), 128.57 (2 × CHof Ar), 128.65 (4 × CH of Ar), 129.98 (2 × CH of Ar), 135.14 (C_{ipso}Br), 135.82 (C_{ipso}Br), 136.57 (C_{ipso}), 139.30 (C_{ipso}), 159.84 (C^3). MS (EI, 70 eV): *m/z* = 262, 247, 233, 219, 204, 170, 145, 115. Anal. Calcd for $C_{23}H_{16}Br_2N_4O$: C, 52.70; H, 3.08; N, 10.69. Found: C, 52.71; H, 3.11; N, 10.70.

2-{4-Cyano-1-hydroxy-5,8-di-(3-nitrophenyl)-2-azabicyclo[2.2.2]oct-3-yliden}malononitrile (2d)

White powder; yield 0.40 g (87%); mp 230 °C. IR (KBr): 3471 (NH), 3375 (OH), 2184 and 2152 (CN), 1533 and 1460 (Ar), 1533 and 1352 (NO_2) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ = 1.68–1.70 (m, 1 H, CH_2), 1.97–1.99 (m, 2 H, CH and CH_2), 3.34–3.35 (m, 3 H, CH and CH_2), 5.87 (s, 1 H, OH), 7.46 (d, $^3J_{HH}$ = 11.9 Hz, 1 H, CH of Ar), 7.66–8.26 (m, 7 H, 7 × CH of Ar), 8.62 (s, 1 H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 21.9 and 36.19 (2 × CH_2), 43.2 [$C(CN)_2$], 45.54 (2 × CHAr), 46.12 (C^4), 84.71 (C^1), 118.30 (CN), 121.50 (2 × CN), 122.96 (2 × CH of Ar), 123 (CH of Ar), 125.26 (CH of Ar), 129.63 (2 × CH of Ar), 135.73 (CH of Ar), 136.50 (CH of Ar), 140.12 (C_{ipso}), 143.69 (C_{ipso}), 147.52 (2 × $CH_{ipso}NO_2$), 158.90 (C^3). MS (EI, 70 eV): *m/z* = 176, 146, 128, 115, 102, 89. Anal. Calcd for $C_{23}H_{16}N_6O_5$: C, 60.53; H, 3.53; N, 18.41. Found: C, 60.56; H, 3.54; N, 18.40.

2-{4-Cyano-1-hydroxy-5,8-di-(4-methoxyphenyl)-2-azabicyclo[2.2.2]oct-3-yliden}malononitrile (2e)

White powder; yield 0.32 g (76%); mp 230 °C. IR (KBr): 3487 (OH and NH), 2189 and 2152 (CN), 1542 and 1455 (Ar) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ = 1.53–1.55 (m, 1 H, CH_2), 1.78–1.80 (m, 1 H, CH), 1.87–1.92 (m, 1 H, CH_2), 2.41 (t, $^3J_{HH}$ = 11.6 Hz, 1 H, CH), 3.04 (dd, $^3J_{HH}$ = 6.4 Hz, 1 H, CH_2), 3.15 (dd, $^3J_{HH}$ = 5.8 Hz, 1 H, CH_2), 3.71 (s, 3 H, OMe), 3.77 (s, 3 H, OMe), 5.60 (s, 1 H, OH), 6.78 (d, $^3J_{HH}$ = 8.6 Hz, 2 H, 2 × CH of Ar), 6.93 (d, $^3J_{HH}$ = 8.4 Hz, 2 H, 2 × CH of Ar), 6.95 (d, $^3J_{HH}$ = 8.3 Hz, 2 H, 2 × CH of Ar), 7.35 (d, $^3J_{HH}$ = 8.5 Hz, 2 H, 2 × CH of Ar), 8.30 (s, 1 H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 35.67 (2 × CH_2), 42.7 [$C(CN)_2$], 45.51 (2 × CH), 46.45 (C^4), 55.01 (2 × OMe), 79.16 (C^1), 113.39 (4 × CH of Ar), 118.33 (CN), 123.72 (2 × CN), 129.70 (2 × CH of Ar), 130.05 (C_{ipso}), 131.15 (2 × CH of Ar), 134.31 (C_{ipso}), 158.08 (C_{ipso}OMe), 158.51 (C_{ipso}OMe), 159.74 (C^3). MS (EI, 70 eV): *m/z* = 294, 186, 161, 145, 134, 121, 89. Anal. Calcd for $C_{25}H_{22}N_4O_3$: C, 70.41; H, 5.20; N, 13.14. Found: C, 70.41; H, 5.21; N, 13.13.

2-{4-Cyano-5,8-di-(3,4-dimethoxyphenyl)-1-hydroxy-2-azabicyclo[2.2.2]oct-3-yliden}malononitrile (2f)

White powder; yield 0.43 g (88%); mp 230 °C. IR (KBr): 3421 (NH), 3250 (OH), 2189 and 2155 (CN), 1521 and 1446 (Ar) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ = 1.54–1.56 (m, 1 H, CH_2), 1.78–1.80 (m, 1 H, CH), 1.87–1.91 (m, 1 H, CH_2), 2.40 (t, $^3J_{HH}$ = 11.0 Hz, 1 H, CH), 3.04–3.06 (m, 1 H, CH_2), 3.18–3.20 (m, 1 H, CH_2), 3.31 (s, 1 H, OH), 3.69 (s, 3 H, OMe), 3.73 (s, 3 H, OMe), 3.78 (s, 6 H, 2 × OMe), 5.63 (s, 1 H, NH), 6.47 (d, $^3J_{HH}$ = 7.6 Hz, 1 H, CH of Ar), 6.73 (d, $^3J_{HH}$ = 7.6 Hz, 1 H, CH of Ar), 6.75 (s, 1 H, CH of Ar), 6.97 (d, $^3J_{HH}$ = 7.6 Hz, 2 H, 2 × CH of Ar), 6.99 (s, 1 H, CH of Ar). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 35.85 and 41.25 (2 × CH_2), 42.71 [$C(CN)_2$], 45.87 (C^4), 46.34 (2 × CH),55.06 (OMe), 55.24 (OMe), 55.38 (OMe), 55.56 (OMe), 84.83 (C^1), 110.68, 111.24, 111.47 and 114.78 (4 × CH of Ar), 118.39 (CN), 121.24 and 121.54 (2 × CH of Ar), 123.74 (2 × CN), 130.46 (C_{ipso}), 134.81 (C_{ipso}), 147.73, 147.94, 148.10 and 148.44 (4 × C_{ipso}OMe), 159.91 (C^3). MS (EI, 70 eV): *m/z* = 358, 239, 191, 165, 151, 123, 107, 91. Anal. Calcd for $C_{27}H_{26}N_4O_5$: C, 66.66; H, 5.39; N, 11.52. Found: C, 66.64; H, 5.41; N, 11.53.

