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Synthesis and characterization of *N*-alkyl 1,3-diamino-4,6-diamidobenzenes

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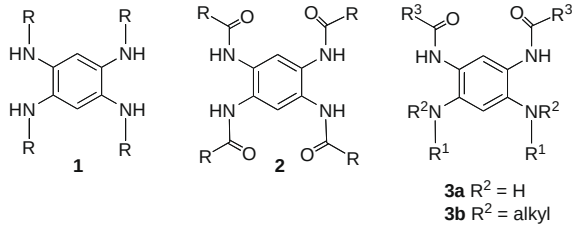
ABSTRACT

A new preparation of N-substituted 1,3-diamino-4,6-diamidobenzenes has been achieved. This synthesis affords the first *N*-alkylamino derivatives for which a fine-tuning of the NR^1R^2 substituents should modify the reactivity of the amine functions.

Introduction of substituent(s) on the benzene ring[1,2] has been the object of extensive studies leading to hundreds of compounds with tunable changes of the properties depending on the nature of the substituent(s).[3] Among them, N-functionalized benzenes substituted in positions 1, 2, 4, and 5 have attracted a major interest in organic, supramolecular, and coordination chemistry owing to the ability of the substituents to act as nucleophiles,[4–12] donor or acceptor sites[12], and coordinating moieties,[13,14] respectively. N-substituted 1,2,4,5-tetraaminobenzenes **1** (R = aryl or alkyl) could be recently isolated[15,16] but their use appeared limited owing to the high ability of these electron-rich arenes to oxidize under air. In contrast, the 1,2,4,5-tetraamidobenzene analogues of type **2** are much more air-stable due to the presence of the four amido functions. Such systems could then be used as bis-chelating[13] or non-innocent[14] ligands in coordination chemistry but also in supramolecular chemistry.[12] Therefore, it is surprising that the aromatic system **3a**, which combines the structural elements of **1** and **2**, has been poorly explored whereas the substitution pattern of its amino and amido groups should allow their use as ligand for complexation of metal centers or as building block for non-covalent interactions by analogy with the 1,3-arylamides.[17–20] To the best of our knowledge, only very few molecules of type **3a** have been reported in the literature and all of them are NR^1-substituted by an aryl group.[21,22]



Their syntheses involved condensation reactions of aromatic compounds which strongly limit the nature of the N-substituents (R^1 = aryl group, R^2 = H).[21,22] Therefore, an alternative route that would give access to new 1,3-diamino-4,6-diamidobenzenes of type **3a** could be useful to enlarge the scope of this class of molecules. For instance, the preparation of N–R^1 alkyl analogues, hitherto unknown, should strongly modify the reactivity of the amino groups in **3a** (i.e., their basicity and/or nucleophilic character) owing to the presence of more electron-donating substituents. As an extension of this study, further substituted analogues of type **3b**, previously unknown, appear very attractive in the development of new and tunable 1,2,4,5-tetranitrogenated benzenes.

Herein, we wish to report a new and versatile synthesis of 1,3-diamino-4,6-diamidobenzenes which allowed the preparation of the first N-alkyl-substituted compounds of type **3a** (R^1 = *n*-Bu), and N,N′-disubstituted analogues of type **3b**.

The commercially available precursor **4** was first reacted with *n*-butylamine in refluxing EtOH to afford **5** in almost quantitative yield (99%) (Scheme 1).[23] To the best of our knowledge, although reported in the literature,[24,25] compound **5** has not been fully characterized

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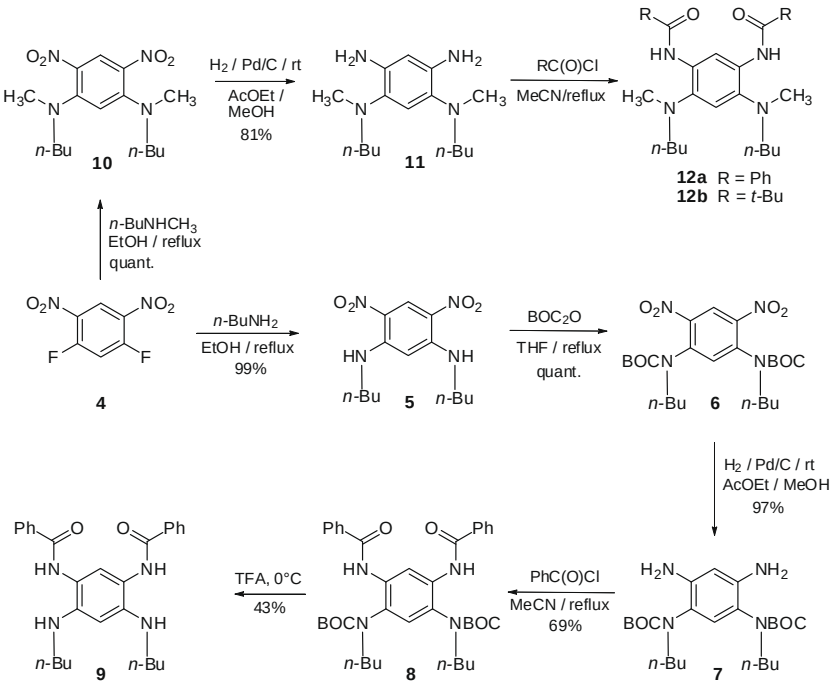
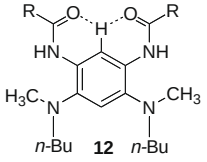


Scheme 1. Synthesis of N-alkyl diamino-diamidobenzenes.

(i.e., including by NMR). The direct reduction of **5** led to the formation of a large number of unidentified compounds due to the air oxidation of the corresponding diamino derivative and further possible side reactions such as hydrolysis and co-condensation.[26] Introduction of protective groups was then envisaged in order to prevent the oxidation of the reduced species. Compound **5** was thus treated with BOC_2O (4 equiv) in refluxing THF in the presence of a catalytic amount of 4-DMAP to yield quantitatively **6**.[23] The reduction of the nitro groups could not be performed with $SnCl_2$ owing to the BOC deprotection in acidic medium. Compound **6** was then reduced by catalytic hydrogenation to afford **7** (97% yield),[23] which was further acylated with PhC(O)Cl in refluxing MeCN to allow the isolation of **8** (69% yield).[23] Finally, deprotection of **8** in TFA gave access to **9** as a yellow solid (43% yield).[23] Its ^{1}H NMR shows two broad singlets at 4.75 and 9.49 ppm corresponding to the amino and amido NH protons, respectively. As expected, molecule **9** is air stable due to the presence of the two amido groups.

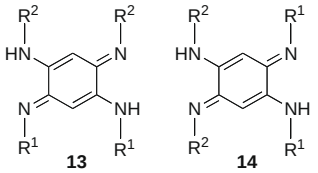
Interestingly, the ^{1}H NMR spectrum of **7** shows the presence of a larger number of signals than expected for a symmetry analogue to that of **6**. Two signals ($I = 1$) instead of one appear at $\delta = 6.45$ and 6.50 ppm for the aromatic proton located between the 'NBOC' substituents. In addition, the NH_2 groups appear as two broad singlets at 4.21 and 4.24 ppm, and the NCH_2 methylenic protons as two broad multiplets at 3.16 and 3.69 ppm. These observations would suggest the presence of two conformations in equilibrium in solution resulted from H-bonded interactions involving the BOC groups and the newly formed NH_2 sites. Intermolecular aggregation could be excluded upon the dilution conditions of the NMR experiments.

The use of secondary amines was also investigated in order to extend this procedure to a broader applicability. Similarly to the preparation of **5**, molecule **4** was reacted with N-methyl-*n*-butylamine to yield quantitatively **10** as an orange solid (Scheme 1).[23] Its reduction could be achieved by catalytic hydrogenation to afford **11** as a brown oil (81% yield). Acylation reaction of **11** with different acyl groups (R = aryl or alkyl) gave access to **12a** or **12b** as yellow oils in 79 and 89% yield, respectively. In contrast to **7**, the ^{1}H NMR spectrum of **11** shows a symmetrical geometry in agreement with the presence of one compound in solution and the key role of the BOC substituents in the formation of two different conformers for **7**. It is noteworthy that the aromatic protons adjacent to the amide functions in **12a** and **12b** are strongly downfield ($\delta = 9.73$ and 9.35 ppm, respectively) by comparison with **9** ($\delta = 6.93$ ppm).[23] These observations suggest for molecules of type **12** H-bonding interactions between the carbonyl groups of the amide functions in 4,6-positions and the C–H aromatic hydrogen [C–H···O=C].[27]



This phenomenon can be explained in **12a** and **12b** by steric hindrance of the methyl groups which prevent the rotation of the (O)C–N bonds. In the case of **9**, the amino groups in 1,3-positions do not affect the amido functions in 4,6-positions allowing the free rotation of the (O)C–N bonds (no hydrogen bonding interactions in solution).

In the course of the preparation of unsymmetrical 12π electron quinones such as **13**, molecule **9** appeared to be a precursor of choice by analogy with the recent synthesis of the closely related analogue **14**.[26] However, similarly to **5**, the reduction of **9** led to a large mixture of compounds and despite successive purification steps, compound **13** could be only identified by ^{1}H NMR among several by-products.



In summary, we have disclosed a new synthesis of N-substituted 1,3-diamino-4,6-amidobenzenes. The first member of N-alkylamino

derivatives (**9**) has been prepared in five steps with an overall yield of 28%. N,N′-substituted analogues have been also synthetized with aryl (**12a**) or alkyl (**12b**) acyl group (overall yield up to 72%). The fine-tuning of the different substituents should enlarge the scope of this family of molecules by analogy with other N4 donors.[28]

Acknowledgments

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23. *Synthesis of* **5**: To a solution of *n*-BuNH$_2$ (v = 490 μL, 4.90 mmol, 2 equiv) in EtOH were added **4** (m = 500 mg, 2.45 mmol, 1 equiv) and NEt(*i*-Pr)$_2$ (850 μL, 4.90 mmol, 2 equiv). The mixture was then stirred at room temperature for 1/2 h and under reflux for 1 h. The obtained precipitate was then isolated by filtration affording **5** as a yellow solid (99% yield). ^{1}H NMR (250 MHz, acetone-d_6) δ 0.99 (t, $^3J_{HH}$ = 7.2 Hz, 6H, CH$_3$), 1.49 (qt, $^3J_{HH}$ = 7.2 Hz, 4H, CH$_3$–C*H*$_2$), 1.77 (qt, $^3J_{HH}$ = 7.2 Hz, 4H, CH$_3$–CH$_2$–C*H*$_2$), 3.45 (td, $^3J_{HH}$ = 7.2 Hz, $^3J_{HH}$ = 5.2 Hz, 4H, HN–C*H*$_2$), 5.94 (s, 1H, HN–C=C*H*–C–NH), 8.40 (br s, 2H, NH), 9.07 (s, 1H, O$_2$N–C=CH–C–NO$_2$). ^{13}C NMR (62 MHz, acetone-d_6) δ 14.0 (CH$_3$), 20.9, 31.1, 43.5 (CH$_2$), 91.4, 124.6, 129.5, 149.4 (aromatic C). MS (ESI)$^+$: m/z = 311 [M+H]$^+$. Anal. Calcd for $C_{14}H_{22}N_4O_4$: C, 54.18; H, 7.15; N, 18.05. Found: C, 54.14; H, 7.23; N 18.04.
Synthesis of **6**: To a solution of **5** (1.00 g, 3.22 mmol, 1 equiv) in dry THF were added BOC$_2$O (m = 2.84 g, 13.01 mmol, 4 equiv) and 4-DMAP (0.08 g, 0.65 mmol, 0.2 equiv) under Ar. The mixture was then stirred under reflux for 1 h. After evaporation of the THF, the residue was purified by SiO$_2$ chromatography affording quantitatively **6** as a yellow solid. ^{1}H NMR (250 MHz, acetone-d_6) δ 0.91 (t, $^3J_{HH}$ = 7.25 Hz, 6H, C*H*$_3$–CH$_2$), 1.50 (m, 26H, C(CH$_3$)$_3$ and CH$_3$–C*H*$_2$–CH$_2$), 3.84 (br s, 4H, N–CH$_2$), 7.78 (s, 1H, N–C=CH–C–N), 8.60 (s, 1H, O$_2$N–C=CH–C–NO$_2$). ^{13}C NMR (62 MHz, acetone-d_6) δ 14.0 (CH$_3$), 20.7 (CH$_2$), 27.9 (C(*C*H$_3$)$_3$), 31.2 (CH$_2$), 50.7 (N–CH$_2$), 82.6 (*C*(CH$_3$)$_3$), 123.6, 128.2, 141.7, 143.5 (aromatic C), 152.4 (C=O). MS (ESI)$^+$: m/z = 533 [M+Na]$^+$. Anal. Calcd for $C_{24}H_{38}N_4O_8$: C, 56.46; H, 7.50; N, 10.97. Found: C, 56.90; H, 7.50; N 10.80.
Synthesis of **7**: To a solution of **6** (1.14 g, 2.23 mmol, 1 equiv) in a dry mixture of AcOEt/MeOH (v/v: 1/1) was added Pd/C (5%). The mixture was then stirred at rt under H$_2$ pressure (P = 20 bars) for 2 h and filtered on Celite. After concentration of the solvents, **7** was isolated as a brown solid (97% yield). ^{1}H NMR (250 MHz, acetone-d_6) δ 0.80 (br t, $^3J_{HH}$ = 7.2 Hz, 12H, C*H*$_3$–CH$_2$), 1.30–1.40 (br m with br s, 44H, CH$_3$–C*H*$_2$ and C(CH$_3$)$_3$), 1.48 (br m, 8H, CH$_3$–CH$_2$–C*H*$_2$), 3.16 (br m, 4H, N–CH$_2$), 3.69 (br m, 4H, N–CH$_2$), 4.21 (br s, 4H, NH$_2$), 4.24 (br s, 4H, NH$_2$), 6.17 (br s, 2H, H$_2$N–C=C*H*–C–NH$_2$), 6.45 (br s, 1H, N–C=CH–C–N), 6.50 (br s, 1H, N–C=CH–C–N). MS (ESI)$^+$: m/z = 451 [M+H].$^+$ Anal. Calcd for $C_{24}H_{42}N_4O_4$: C, 63.97; H, 9.39; N, 12.43. Found: C, 63.97; H, 9.60; N 12.36.
Synthesis of **8**: To a solution of **7** (0.42 g, 0.94 mmol, 1 equiv) in dry MeCN in the presence of NEt$_3$ (4 equiv) was dropwise added PhC(O)Cl (330 μL, 2.84 mmol, 3 equiv) under Ar. After stirring under reflux for 12 h, the solvent was evaporated and the residue was taken up in AcOEt and washed with H$_2$O. The organic layers were then concentrated and purified by SiO$_2$ chromatography affording **8** a yellow oil (69% yield). ^{1}H NMR (250 MHz, acetone-d_6) δ 0.70 (t, $^3J_{HH}$ = 7.2 Hz, 6H, C*H*$_3$–CH$_2$), 1.16 (m, 4H, CH$_3$–C*H*$_2$), 1.30 (br s, 18H, C(CH$_3$)$_3$), 1.38 (m, 4H, CH$_2$), 3.54 (t, $^3J_{HH}$ = 8.0 Hz, 4H, N–CH$_2$), 7.45 (m, 6H, aromatic H), 7.81 (m, 4H, aromatic H), 7.92 (m, 2H, aromatic H), 8.65 (br s, 1H, NH), 8.80 (br s, 1H, NH). ^{13}C NMR (62 MHz, acetone-d_6) δ 14.0 (CH$_3$), 20.6 (CH$_2$), 28.4 (C(*C*H$_3$)$_3$), 31.3 (CH$_2$), 50.5 (N–CH$_2$), 81.2 (*C*(CH$_3$)$_3$), 128.0, 129.3, 129.6, 130.4, 132.7, 133.7, 134.9, 135.8 (aromatic C), 155.4 (O–C=O), 165.5 (HN–C=O). MS (ESI)$^+$: m/z = 681 [M+Na]$^+$.
Synthesis of **9**: A solution of **8** (0.26 g, 0.40 mmol) in TFA was stirred at 0 °C for 2 h under Ar. The end of the reaction was monitored by TLC, and TFA was then evaporated under reduced pressure. The residue was taken up in a saturated solution of NaHCO$_3$ and extracted with CH$_2$Cl$_2$. The organic layers were then concentrated before adding acetone. The insoluble suspension was isolated by filtration affording **9** as a yellow solid (43% yield). ^{1}H NMR (250 MHz, DMSO-d_6) δ 0.92 (t, $^3J_{HH}$ = 7.2 Hz, 6H, C*H*$_3$–CH$_2$), 1.39 (sext, $^3J_{HH}$ = 7.2 Hz, 4H, CH$_3$–C*H*$_2$), 1.57 (qt, $^3J_{HH}$ = 7.2 Hz, 4H, CH$_2$), 3.09 (br q, 4H, N–CH$_2$), 4.75 (t, 2H, H$_2$C–N*H*), 5.97 (s, 1H, HN–C=C*H*–C–NH), 6.93 (s, 1H, (O)CN–C=CH–C–NC(O)), 7.51 (m, 6H, aromatic H), 7.98 (m, 4H, aromatic H), 9.49 (s, 2H, (O)CNH). ^{13}C NMR (62 MHz, DMSO-d_6) δ 13.9 (CH$_3$), 19.9 (CH$_2$), 31.1 (CH$_2$), 42.8 (N–CH$_2$), 93.7, 111.9, 126.5, 127.7, 128.3, 131.2, 134.8, 143.3 (aromatic C), 165.8 (C=O). MS (ESI)$^+$: m/z = 459 [M+H].$^+$ Anal. Calcd for $C_{28}H_{34}N_4O_2{\cdot}1/3(CH_3)_2C(O)$: C, 72.88; H, 7.59; N, 11.72. Found: C, 72.44; H, 7.60; N, 11.91.
Synthesis of **10**: *n*-BuMeNH (v = 577 μL, 4.90 mmol, 2 equiv); **4** (m = 500 mg, 2.45 mmol, 1 equiv); NEt(*i*-Pr)$_2$ (854 μL, 4.90 mmol, 2 equiv). EtOH was concentrated under reduced pressure, and the residue was taken up in ethyl acetate and washed with H$_2$O. The organic layer was then concentrated affording **10** as an orange solid (quantitative). ^{1}H NMR (250 MHz, acetone-d_6) δ 0.92 (t, $^3J_{HH}$ = 7.2 Hz, 6H, CH$_3$), 1.36 (qt, $^3J_{HH}$ = 7.2 Hz, 4H, CH$_3$–C*H*$_2$), 1.68 (qt, $^3J_{HH}$ = 7.2 Hz, 4H, CH$_3$–CH$_2$–C*H*$_2$), 2.91 (s, 6H, N–CH$_3$), 3.31 (t, $^3J_{HH}$ = 7.2 Hz, 4H, N–CH$_2$), 6.43 (s, 1H, N–C=CH–C-N), 8.43 (s, 1H, O$_2$N–C=CH–C–NO$_2$). ^{13}C NMR (62 MHz, acetone-d_6) δ 14.0 (CH$_3$), 20.6, 29.7, 40.2 (CH$_2$), 54.3 (CH$_3$), 105.0, 130.20, 130.24, 150.2 (aromatic C). MS (ESI)$^+$: m/z = 339 [M+H]$^+$. Anal. Calcd for $C_{16}H_{26}N_4O_4$: C, 56.79; H, 7.74; N, 16.56. Found: C, 56.52; H, 7.97; N, 16.33.
Synthesis of **11**: To a solution of **10** (247 mg, 0.73 mmol, 1 equiv) in a dry mixture of AcOEt/MeOH (v/v: 1/1) was added 5% Pd/C. The mixture was then stirred at rt under H$_2$ pressure (P = 20 bars) overnight and filtered on Celite. After concentration of the solvents, **11** was isolated as a brown oil (81% yield). ^{1}H NMR (250 MHz, acetone-d_6) δ 0.87 (t, $^3J_{HH}$ = 7.2 Hz, 6H, C*H*$_3$–CH$_2$), 1.37 (m, 8H, CH$_3$–C*H*$_2$–C*H*$_2$), 2.50 (s, 6H, N–CH$_3$), 2.75 (t, $^3J_{HH}$ = 7.0 Hz, 4H, N–CH$_2$), 4.21 (br s, 4H, NH$_2$), 6.11 (s, 1H, H$_2$N–C=C*H*–C–NH$_2$), 6.77 (s, 1H, N–C=CH–C–N). ^{13}C NMR (62 MHz, acetone-d_6) δ 14.4 (CH$_3$), 21.1, 30.9, 43.3 (CH$_2$), 57.0 (CH$_3$), 102.0, 114.4, 130.4, 141.6 (aromatic C). MS (ESI)$^+$: m/z = 279 [M+H]$^+$.
Synthesis of **12**: To a solution of **11** (1 equiv) in dry MeCN in the presence of triethylamine (4 equiv) was dropwise added acyl chloride (3 equiv) under argon. After stirring under reflux overnight, the solvent was evaporated and the residue was taken up in ethyl acetate and washed with H$_2$O. The organic layers were then concentrated and purified by SiO$_2$ chromatography affording **12a** or **12b**.
Compound **12a**: **11** (143.4 mg, 0.52 mmol, 1 equiv), NEt$_3$ (v = 290 μL, 2.06 mmol, 4 equiv), PhC(O)Cl (v = 180 μL, 1.55 mmol, 3 equiv). The crude product was purified by flash SiO$_2$ chromatography (eluent: cyclohexane/ethyl acetate 10/0, 9/1, 8/2, 7/3) affording **12a** as a yellow oil (79%). ^{1}H NMR (250 MHz, acetone-d_6) δ 0.83 (t, $^3J_{HH}$ = 7.0 Hz, 6H, C*H*$_3$–CH$_2$), 1.32 (m, 4H, CH$_3$–C*H*$_2$), 1.48 (m, 4H, CH$_3$–CH$_2$–C*H*$_2$), 2.70 (s, 6H, N–CH$_3$), 2.95 (t, $^3J_{HH}$ = 7.0 Hz, 4H, N–CH$_2$), 7.39 (s, 1H, N–C=CH–C–N), 7.58 (m, 6H, aromatic H), 8.02 (m, 4H, aromatic H), 9.67 (br s, 2H, NH), 9.73 (s, 1H, HN–C=C*H*–C–NH). ^{13}C NMR (62 MHz, acetone-d_6) δ 14.2 (CH$_3$), 21.0, 30.8 (CH$_2$), 43.7 (N–CH$_3$), 57.3 (N–CH$_2$), 111.4, 116.0, 127.7, 129.6, 132.4, 132.95, 136.4, 138.9 (aromatic C), 164.6 (C=O). MS (ESI)$^+$: m/z = 487 [M+H].$^+$ Anal. Calcd for $C_{30}H_{38}N_4O_2{\cdot}3/4AcOEt{\cdot}3/4C_6H_{12}$: C, 73.14; H, 8.67; N, 9.10. Found: C, 73.12; H, 8.08; N, 8.69.
Compound **12b**: **11** (139.4 mg, 0.50 mmol, 1 equiv), NEt$_3$ (v = 280 μL, 2.00 mmol, 4 equiv), *t*-BuC(O)Cl (v = 185 μL, 1.50 mmol, 3 equiv). The crude product was purified by flash SiO$_2$ chromatography (eluent: cyclohexane/ethyl acetate 8/2, 7/3) affording **12b** as a yellow oil (89% yield). ^{1}H NMR (250 MHz, acetone-d_6) δ 0.74 (t, $^3J_{HH}$ = 7.0 Hz, 6H, C*H*$_3$–CH$_2$), 1.35–1.15 (m, 26H, CH$_3$–C*H*$_2$–C*H*$_2$ and C(*C*H$_3$)$_3$), 2.50 (s, 6H, N–CH$_3$), 2.78 (t, $^3J_{HH}$ = 7.0 Hz, 4H, N–CH$_2$), 7.12 (s, 1H, N–C=CH–C–N), 8.92 (br s, 2H, NH), 9.35 (s, 1H, HN–C=C*H*–C–NH). ^{13}C NMR (62 MHz, acetone-d_6) δ 14.2 (CH$_3$), 21.0 (CH$_2$), 27.8 (C–CH$_3$), 30.7 (CH$_2$), 40.4 (C), 44.1 (N–CH$_3$), 56.7 (N–CH$_2$), 110.5, 115.5, 133.3, 137.4 (aromatic C), 175.7 (C=O). MS (ESI)$^+$: m/z = 447 [M+H]$^+$. Anal. Calcd for $C_{26}H_{46}N_4O_2{\cdot}1/3$AcOEt: C, 68.96; H, 10.30; N 11.77. Found: C, 69.46; H, 10.71; N, 11.36.
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