HETEROCYCELS, Vol.55, No.3, pp.439 - 446, Received, 27th September, 2000

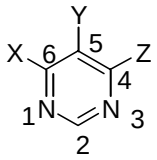
UNSYMMETRICAL 4,6-DIAMINO-2-METHYL-5-NITROPYRIMIDINE SYNTHESIS VIA 4,6-BIS(TOSYLATES)

Gary A. Cain* and James P. Beck

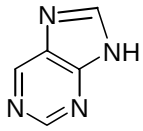
Chemical and Physical Sciences Department, DuPont Pharmaceuticals Company, Experimental Station E336/109, P.O. Box 80336, Wilmington, DE 19880-0336 USA
Email: gary.a.cain@dupontpharma.com

Abstract -Chlorides have traditionally been used as leaving groups for the introduction of 4- and 6-heteroatomic substituents onto pyrimidines. Use of 4,6-dichloro-2-methyl-5-nitropyrimidine allows the sequential introduction of different 4- and 6-heteroatomic substituents onto this core; however, this reagent is highly hazardous to handle. We have found that the analogous 4,6-bis(tosylate) offers a less hazardous substance which undergoes the same nucleophilic aromatic substitution chemistry as the dichloride, including sequential introduction of different nucleophiles.

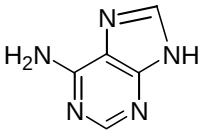
4,6-Diaminopyrimidines are widely found in natural products and synthetic biologically active substances, notably the purines. A large number of these compounds contain 4,5,6-tri-heteroatomic substituents, as shown below, including adenine and caffeine.



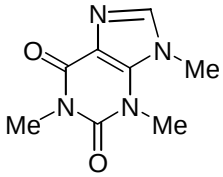
pyrimidine core



purine



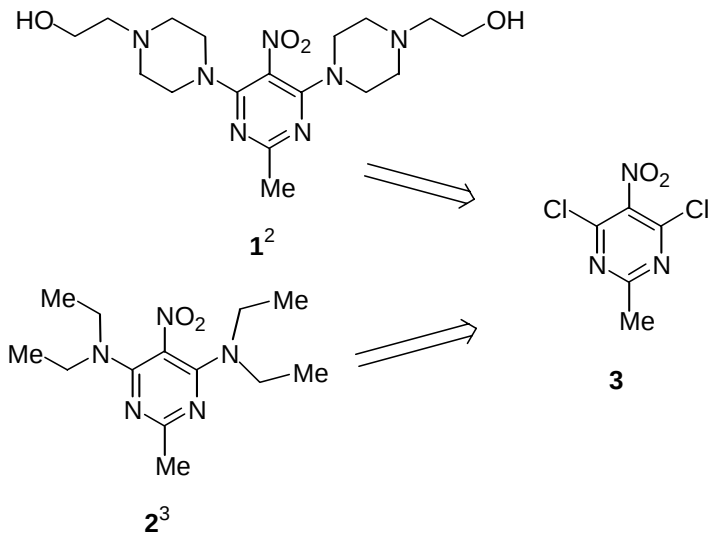
adenine



caffeine

A subset of compounds of this type known in the literature possess a 4,6-diamino-2-methyl-5-nitropyrimidine core,[1-3] such as **1** and **2**, which have been reported to have cardiotonic,[2] diuretic,[2] and

hypolipidemic[3] activities. These compounds were invariably synthesized by standard amine addition/elimination reactions on the 4,6-dichloro intermediate (**3**).



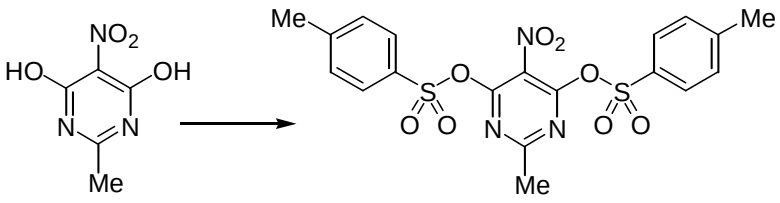
Our interest centered on 4,6-diamino-2-methyl-5-nitropyrimidines as chemical intermediates for the synthesis of arylamino-fused pyrimidines as corticotropin releasing factor antagonists.[4] We were particularly interested in the ability to prepare unsymmetrical 4,6-diamines, wherein the different amines would be incorporated independently. Clark[1] and Yanagibashi[3] have reported that nonsymmetrical 4,6-adducts could be obtained in good to excellent yields by treating dichloride (**3**) with 1.2 – 1.7 equivalents of the first amine under mild conditions. The resulting monoamine/monochloride, when treated with the second amine under more vigorous conditions, such as higher temperature, displaced the second chloride.

With this background we began to use dichloride (**3**) in our own work. We quickly discovered, however, that **3** is physically a very unpleasant substance to work with. Although **3** is a solid (mp 42-44 ^{o}C),[3] it is quite volatile. Even using well ventilated hoods, handling of dichloride (**3**) would quickly fill the lab with an extremely unpleasant odor. Dichloropyrimidines, being generally corrosive and lacrymatory, coupled with the volatility of **3**, led us to consider its use as a serious exposure hazard to laboratory personnel. We were, therefore, led to seek an alternate reagent which would undergo similar reactions with nucleophiles, yet be non-volatile enough not to present exposure hazards.

The use of –Cl as a leaving group for the introduction of other heteroatoms at the ring carbon next to the heterocyclic nitrogen is nearly ubiquitous. As a first guess as to how we might replace the chloride we considered that the volatility problem might be reduced by increasing the molecular weight of the reagent. That, coupled with the requirement of possessing good leaving group ability, led us to consider 4,6-bis(sulfonates). A literature search revealed only two examples of pyrimidine-4,6-bis(sulfonates). The first[5]

reported isolation of 5-benzyl-2,4,6-tris(methanesulfonyloxy)pyrimidine as a 4% by-product from the reaction of triethylammonium 5-benzylbarbiturate with 1.1 equivalent of methanesulfonyl chloride in DMF at room temperature. No subsequent use of this compound was described. The second[6] reported the synthesis and use of 2-methylthio-4,6-bis(trifluoromethanesulfonyl)pyrimidine in Stille couplings to introduce 4,6-carbon substituents.

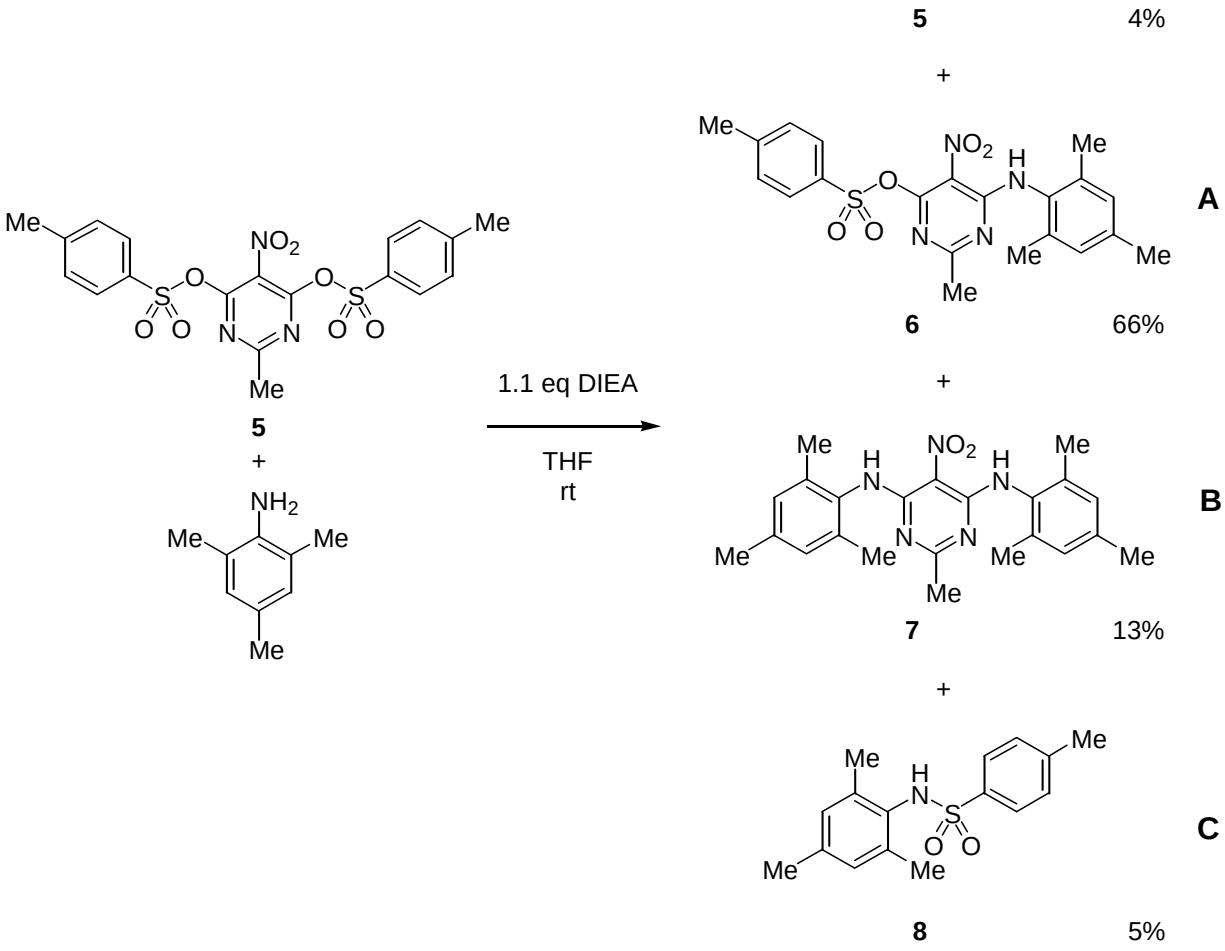
Being concerned that –OMs and –OTf analogs of dichloride (**3**) might still be volatile, and knowing that tosylates tend to be crystalline solids, we chose to pursue the previously unknown 4,6-bis(tosylate). In the first experiment to convert diol (**4**)[3] into target 2-methyl-5-nitropyrimidine-4,6-bis(*p*-toluenesulfonate) (**5**) we modified the earlier mentioned[6] 4,6-bis(triflate) preparation conditions (2 eq Et_3N, 2 eq sulfonic anhydride, CH_2Cl_2, room temperature) using diisopropylethylamine (DIEA) and *p*-toluenesulfonic anhydride. After flash chromatography using the same CH_2Cl_2 eluent we were gratified to isolate our desired 4,6-bis(tosylate) (**5**) as a colorless, crystalline solid,[7] although in only 13% yield. Subsequently the preparation was improved by using 2,4,6-collidine in MeCN to raise the yield of **5** to 90%. This solid was high melting (mp 180-2 ^oC) and possessed a faint odor, similar to TsCl, only noticeable when weighing the material outside of the hood. The greatly improved physical characteristics of the reagent had been achieved.



With **5** in hand, we needed to determine whether it would undergo the same sequential amine addition/elimination chemistry as dichloride (**3**). At this time we were not at all certain how **5** would react with nucleophiles. The 4,6-carbons would be highly electron deficient, being influenced by both the electron withdrawing ring nitrogens and the neighboring nitro group, and so were expected to be reactive with heteroatomic nucleophiles. However, the tosyl sulfur would itself be electron deficient, with the connecting oxygen atom being strongly effected by the nitropyrimidine ring. In this manner, reagent (**5**) could react simply as a fancy tosylating reagent. To preliminarily gauge its stability/reactivity, **5** was subjected to both aqueous acidic (1 M HCl) and basic (1 M NaOH) extractions with ethyl acetate to ensure it would survive a typical reaction workup. Under both sets of extraction conditions the bis(tosylate) was recovered unchanged by ^1H NMR.

The initial test of the reactivity of **5** with amine nucleophiles was its treatment with one equivalent of 2,4,6-trimethylaniline and 1.1 eq DIEA in THF at room temperature (Table 1, Ex. 1). After stirring overnight TLC analysis revealed that aniline consumption was complete and three components were present. Workup and

separation by flash chromatography yielded recovered bis(tosylate) (**5**) (4%), as well as monoaniline/monotosylate (**6**) (66%) and bis(aniline) adduct (**7**) (13%). Although it coeluted with monoadduct (**6**) and was not isolated, an additional product that was visible by ^{1}H NMR and HPLC was assigned as aniline sulfonamide (**8**). The identity of **8** was confirmed by independent synthesis from reaction of 2,4,6-trimethylaniline with *p*-TsCl and Et_3N in THF. By using the data from this authentic sulfonamide, the yield
of **8** in the crude mixture was established to be 5% from the starting aniline.

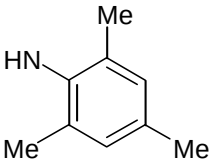
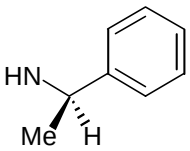
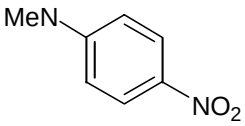
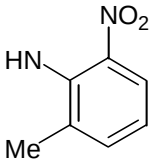
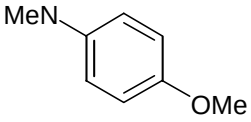
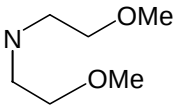
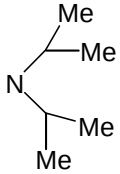


Thus the first amine experiment revealed that bis(tosylate) (**5**) would undergo the desired mono displacement in good yield, that both tosylates could be displaced by amine, and that **5** could undergo the alternate reaction mode and act as a tosylating agent.

With the amine/tosylate displacement chemistry established we then examined the scope of **5** reaction with amines of varying electron density and steric bulk, as shown in Table 1. These experiments were conducted under the same reaction conditions as just described above in Ex. 1, except as noted. Some of the reactions

were sluggish and required heating to achieve reasonable rates. The highest reaction temperature ultimately required to achieve complete reaction and the time at that temperature are given. The reactions were monitored by TLC and/or ^{1}H NMR, and once judged to be complete were worked up and purified, usually by flash chromatography on Kieselgel 60, eluting with EtOAc/hexane solvent systems. The results given in the table show the yields of the most significant components in the crude product mixture as estimated by ^{1}H NMR integrations and/or HPLC. The actual isolated yields are given in parentheses. To assist in the crude product structure assignments, authentic amine sulfonamides were prepared as above for comparison.

Table 1[a]**.** Products from reaction of **5** with 1 eq HNRR'.

Ex.	-NRR'	time h[b]	temp °C[b]	% **5**	% A	% B	% C
1		24	rt	8 (4)[c]	66 (68)[d]	23 (13)	3
2		7	rt	5 (3)	71 (61)	15 (14)	9 (7)
3		16	reflux	15 (7)	18	26	41 (24)
4		16	reflux	no identifiable products			
5		4	rt	0	92 (92)	0	8 (8)
6		72[e]	rt	0	97 (97)	0	3
7		48[f]	60	trace	95 (49)[g]	0	0

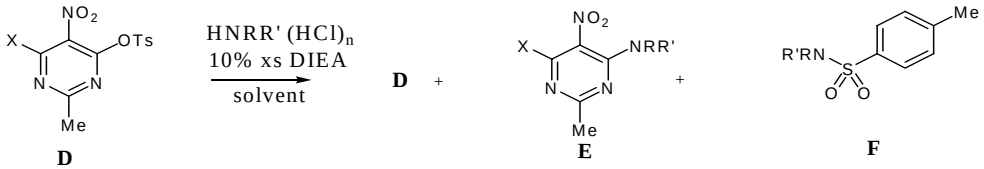
a) Conditions as Example 1 except as indicated. A = monoamine/monotosylate. B = bis(amine). C = sulfonamide. b) Yields in parentheses are isolated yields. c) Reactions were begun at </=rt. Times at highest temperatures given. d) Includes inseparable sulfonamide. e) Over weekend; not checked earlier. f) After 72 h at rt reaction was 70% complete. g) After recrystallization.

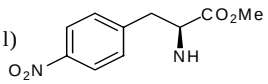
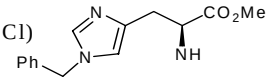
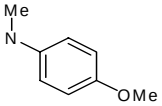
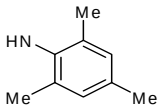
A few reactivity trends are readily apparent from the data in Table 1. First, the aliphatic amines and electron rich anilines nearly all reacted at room temperature, with only the highly hindered diisopropylamine (Ex. 7) requiring some heating to push to completion. The electron rich amines displaced the first tosylate much faster than the second, with bis(amine) addition ranging from 0% (Ex. 5-7) to a maximum of 23% (Ex. 1). This selectivity could be rationalized by the additional electron density being delocalized into the ring system once the first amine bond had formed; the carbon bearing the second tosylate was thereby rendered less electrophilic and less reactive. In this regard, the bis(tosylate) directly mimics the reactivity of the original dichloride. Electron rich amines also reacted preferentially on the pyrimidine ring versus attact on the electrophilic tosylate sulfur atom. Less than 10% sulfonamide was formed in Ex. 1, 2, 5-7.

Conversely, the electron deficient anilines of Ex. 3 and 4 were not good substrates for reaction with the already electron poor bis(tosylate). Reflux temperatures were required to initiate the reactions and the yields and selectivities were much poorer, with the sulfonamide formed as the major product in Ex. 3. In Ex. 4, with additional steric hindrance present around the amine, complete decomposition was observed under the forcing conditions required to initiate reaction.

We next explored the ability of representative monotosylate/monoamine adducts to undergo a second tosylate displacement with different amines, as shown in Table 2. Because of the poor results seen for the electron poor amines above, we examined only electron rich amines here.

Table 2. Products from reaction of select monotosylates with 1 eq HNRR'.



Ex.	X	-NRR'	time	temp	solvent	% **D**	% **E**	% **F**
8	$N(CH_2CH_2OMe)_2$	(HCl) 	7 d	rt	THF	10	(90)	0
9	$N(CH_2CH_2OMe)_2$	2 (HCl) 	4 d	rt	CH_3CN[a]	0	(85)	3
10	$N(CH_2CH_2OMe)_2$		3 d	rt	THF	0	(72)	0
11	$(Me)NC_6H_4$-*p*-OMe		6 d	reflux	CH_3CN[a]	0	66[b]	14[b]

a) Excessively slow rxn in THF. b) Inseparable by flash chromatography.

As expected from the Table 1 results, the second tosylates were not as easily displaced as the first. Each of the Table 2 examples required longer times; some needed higher temperatures and/or more effective solvents as well. Examples 8 and 10 did proceed at room temperature, but 7 and 3 days were needed to reach completion, respectively. Examples 9 and 11 barely proceeded at all in THF, even after days at reflux. By switching to a more polar solvent, acetonitrile, Ex. 9 did then react at room temperature, although 4 days was still required for completion. Example 11, with its greater steric demands, required 6 days in acetonitrile at reflux to complete.

The unsymmetrical diamine adducts were thus successfully formed in good to excellent yields. Similar results were observed here regarding the monotosylates exhibiting the alternate reaction mode of *p*-oluenesulfonamide formation. Little to no amine attack on the electrophilic tosylate sulfur atom was found; only Examples 9 and 11 formed *p*-toluenesulfonamide by-products in 3% and 14% yields, respectively.
In summary, the first pyrimidine 4,6-bis(tosylate) has been prepared, and it was found to undergo similar addition/elimination reactions with amine nucleophiles as the analogous pyrimidine 4,6-dichloride. The tosylates could be selectively displaced one at a time, allowing efficient preparation of unsymmetrical 4,6-diamines from a symmetrical precursor. Both the mono- and bis(tosylates) exhibited a minor alternate reaction mode in which the amine attacked the electrophilic tosylate sulfur atom, leading to a *p*-toluenesulfonamide by-product.

REFERENCES AND NOTES

1. J. Clark and T. Ramsden, *J. Chem. Soc. C*, **1971**, 679.
2. J. Kosary, E. Diesler, P. Matyus, and E. Kasztreiner, *Acta Pharm. Hung.*, **1989**, *59*, 241.
3. K. Yanagibashi, K. Mizuguchi, S. Onishi, and K. Murakami, US Patent 5397781, 1985 (*Chem. Abstr.*, **1995**, *121*, 9416).
4. R. Bakthavatchalam, A. Arvanitis, J. Beck, G. Cain, R. Chorvat, P. Gilligan, and R. Olson, WO Patent 9735539, 1997 (*Chem. Abstr.*, **1997**, *127*, 331497).
5. I. Candiani, W. Cabri, A. Bedeschi, T. Martinengo, and S. Penco, *Heterocycles*, **1992**, *34*, 875.
6. K. Sandosham, and K. Undheim, *Heterocycles*, **1994**, *37*, 501.
7. Bis(tosylate) (**5**) procedure: *p*-Toluenesulfonic acid (25 g, 74 mmol) was added all at once to a suspension of finely powdered 4,6-dihydroxy-2-methyl-5-nitropyrimidine (5.6 g, 33 mmol) and 2,4,6-collidine (9.8 mL, 74 mmol) in MeCN (400 mL) with stirring at rt under nitrogen. After 2.5 h, the solvent was evaporated *in vacuo*, keeping the bath temperature below 32 ^{o}C. The resulting solid was dissolved in minimal CH_2Cl_2 and loaded onto a Kieselgel 60 silica gel column (1 kg, packed in CH_2Cl_2). After eluting with CH_2Cl_2 and concentrating, **5** was isolated as a pale pink crystalline solid (14.3 g, 90%), mp 180-182 ^{o}C. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.98 (d, 4H, J = 8 Hz), 7.49 (d, 4H, J = 8 Hz), 2.62 (s, 3H), 2.48 (s, 6H). ^{13}C NMR (75.44 MHz, $CDCl_3$, δ): 169.01, 156.37, 147.07, 132.39, 129.93, 129.44, 25.73, 21.85 (C-NO_2 too weak to identify). IR (ν, cm^{-1}, KBr): 1680, 1590, 1574, 1392, 1196, 1072. HRMS (NH_3-

CI/DEP): calcd ($M+H^+$) 480.0535, found 480.0521. Anal.: Calcd for $C_{19}H_{17}N_3O_8S_2$; C, 47.59; H, 3.57; N, 8.76; S, 13.38. Found: C, 47.29; H, 3.51; N, 8.64; S, 13.43.

8. Typical procedure, Table 1, Example 5: N-Methyl-4-methoxyaniline (0.58 g, 4.2 mmol) was added to a 0 ^oC solution/suspension of bis(tosylate) (**5**) (2.0 g, 4.2 mmol), and N,N'-diisopropylethylamine (0.80 mL, 4.6 mmol) in dry THF (10 mL) with stirring under nitrogen. The reaction was allowed to warm to rt over 2 hours, then maintained at rt for 2h. The mixture was then diluted with EtOAc (200 mL) and extracted consecutively with 1 M HCl (20 mL), H_2O (20 mL), sat. aq. $NaHCO_3$ (20 mL), and brine (20 mL). After drying (Na_2SO_4) and filtration, the sample was concentrated *in vacuo*. The crude product mixture was flash chromatographed on E. Merck Silica Gel 60 (100 g), slurry packed with hexane. The sample was loaded in minimal CH_2Cl_2, then eluted with a gradient from hexane to 4:1 hexane/EtOAc. Similar fractions, as judged by TLC (E. Merck Silica Gel 60 F_{254} plates, 7:3 hexane/EtOAc elution, UV detection) were combined and concentrated *in vacuo*. The first eluted product (TLC R_f = 0.41), sulfonamide (**5C)**was obtained as a viscous oil (0.10 g, 8 %). ^1H NMR (300 MHz, $CDCl_3$, δ): 7.45 (d, 2H, J = 8 Hz), 7.25 (d, 2H, J = 8 Hz), 7.00-6.96 (m, 2H), 6.83-6.78 (m, 2H), 3.80 (s, 3H), 3.13 (s, 3H), 2.43 (s, 3H). ^{13}C NMR (75.44 MHz, $CDCl_3$, δ): 158.69, 143.43, 134.32, 133.67, 129.32, 128.12, 127.98, 114.03, 55.43, 38.45, 21.54. IR (ν, cm^{-1}, KBr): 1608, 1598, 1585, 1509, 1346, 1247, 1171, 1155. HRMS (Electrospray ionization): calcd ($M+H^+$) 292.1007, found 292.0988. Anal.: Calcd for $C_{15}H_{17}NO_3S$; C, 61.83; H, 5.88; N, 4.82. Found: C, 62.12; H, 5.91; N, 4.77. The second eluted product (TLC R_f = 0.33), monoadduct (**5A)** was obtained as a yellow crystalline solid (1.7 g, 92%), mp 125-127 ^oC. ^1H NMR (300 MHz, $CDCl_3$, δ): 7.94 (d, 2H, J = 8 Hz), 7.34 (d, 2H, J = 8 Hz), 7.03 (d, 2H, J = 9 Hz), 6.82 (d, 2H, J = 9 Hz), 3.79 (s, 3H), 3.49 (s, 3H), 2.52 (s, 3H), 2.45 (s, 3H). ^{13}C NMR (75.44 MHz, $CDCl_3$, δ): 167.02, 159.04, 156.16, 155.03, 145.99, 135.55, 133.47, 129.59, 129.15, 127.26, 120.19, 114.82, 55.43, 41.66, 25.87, 21.74. IR (ν, cm^{-1}, KBr): 1651, 1587, 1555, 1545, 1511. HRMS (Electrospray ionization): calcd ($M+H^+$) 445.1182, found 445.1176. Anal.: Calcd for $C_{20}H_{20}N_4O_6S$; C, 54.05; H, 4.55; N, 12.61; S, 7.21. Found: C, 53.90; H, 4.49; N, 12.42; S, 7.25.