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Chemoselectivity of 6-Bromo-2-methyl-3,1-benzoxazin-4-one towards Amines, *Schiff* Bases, and Azines

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Summary. 6-Bromo-2-methyl-3,1-benzoxazin-4-one (**1**) undergoes an unusual cleavage at position 4 when it is allowed to react with *o*-phenylenediamine or anthranilic acid in dry benzene to give the corresponding compounds **2**–**5**, respectively. The reaction of **1** with *Schiff* bases and azines results in the formation of the compounds **6a**–**d** and **8a**, **b**, respectively. The reaction involves a cleavage of the *Schiff* base or the azine into its amine and arylidene moieties which are smoothly incorporated into **1** *via* nucleophilic attack of the amine at position 4 and condensation of the aldehyde with a reactive methyl group, at position 2 respectively. No displacement of the arylidene segment was observed.

Keywords. 6-Bromo-2-methyl-3,1-benzoxazin-4-one; *o*-Phenylenediamine; Anthranilic acid; *Schiff* base; Azine.

Zur Chemoselektivität von 6-Brom-2-methyl-3,1-benzoxazin-4-on gegenüber Aminen, *Schiff*schen Basen und Azinen

Zusammenfassung. 6-Brom-2-methyl-3,1-benzoxazin-4-on reagiert mit *o*-Phenylendiamin oder Anthranilsäure in trockenem Benzol unter einer ungewöhnlichen Bindungstrennung zu den Verbindungen **2**–**5**. Die Reaktion von **1** mit *Schiff*schen Basen und Azinen führt zu den Verbindungen **6a**–**d** und **8a**, **b**. Die Reaktion verläuft über eine Spaltung der *Schiff*schen Base oder des Azins in ihre Amin- und Arylidenreste, die über einen nucleophilen Angriff des Amins an Position 4 und Kondensation des Aldehyds mit der reaktiven Methylgruppe in Position 2 glatt in **1** übergeführt werden. Es wurde kein Arylidenaustausch beobachtet.

Introduction

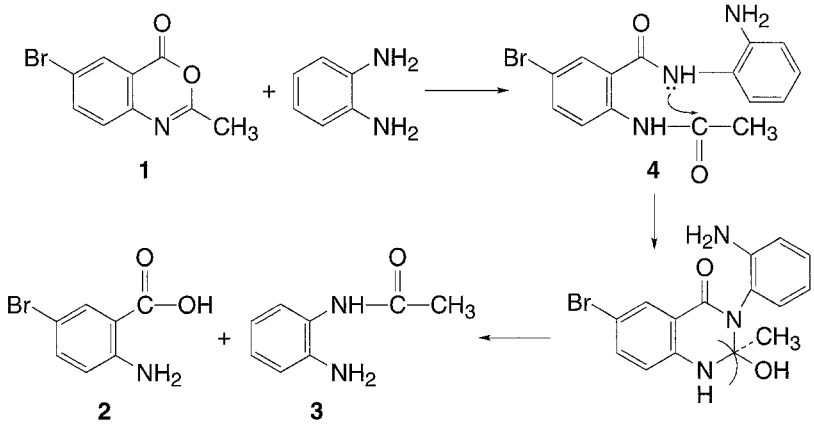
A previous series of publications [1–7] including nucleophilic addition of amines to acetylanthranil derivatives has suggested that the reaction takes place *via* a normal or an abnormal bond cleavage either at position 2 or 4, leading to the formation of different products. That change in reactivity was related to the reaction conditions which have been assumed to be functions of the steric hindrance associated with the substituent at position 2 and on the part of the coreactant amine. *Errede et al.* [1–5] have reported that simple amines, aniline, and long chain amines having a polar group in the ω-position such as OH or COOH undergo attack at position 2.

The above postulation was disputed by *Ismail et al.* [6, 7] who have observed that the reaction of 6,8-dibromo-2-methyl-3,1-benzoxazin-4-one with *o*-phenylenediamine and anthranilic acid follows the other alternative pathway, resulting in the formation of the corresponding *o*-acetamidobenzamide or their cyclodehydrated products.

Results and Discussion

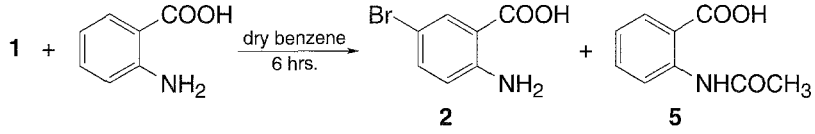
In the light of the above facts, it was tempting to render further support for one of the alternative views. Thus, it seemed interesting to study the reaction of 6-bromo-2-methyl-3,1-benzoxazin-4-one (**1**) with *o*-phenylenediamine and anthranilic acid. The title compound **1** did not receive much attention concerning its behaviour with such *ortho* substituted amines. Thus, when *o*-phenylenediamine was allowed to react with **1** in refluxing benzene, a mixture of 5-bromoanthranilic acid (**2**), 2-aminoacetanilide (**3**), and the corresponding *o*-acetamidobenzamide (**4**) were formed.

The structure of compound **4** was deduced from its microanalytical data and its infrared spectrum which showed a broad absorption frequency at 3100 cm^{-1}, attributable to the NH group, and two strong absorption frequencies at 1650 cm^{-1} and 1668 cm^{-1}, corresponding to two amide carbonyl groups. Moreover, its ^1H NMR spectrum in *DMSO*-d_6 exhibits two singlets at 12.96 and 10.68 ppm, characteristic of the anilide NH proton existing in the tautomeric form $-\overset{H}{\underset{|}{N}}-\overset{O}{\overset{\|}{C}}-CH_3 \rightleftharpoons -N=\overset{OH}{\underset{|}{C}}-CH_3$ (*cf.* Experimental). These exchangeable acidic proton absorptions are removed using deuterium oxide – *DMSO*-d_6, as mixed solvents; instead, a strong singlet appears at 4.3 ppm. The structures of **2** and **3** are substantiated by their infrared absorptions and their ^1H NMR spectra as well. The structure of **2** was unambiguously established by its identity with an authentic sample [8] (*cf.* Experimental).



This methodology presents also a new route for the preparation of compound **3**. The study was extended by replacing *o*-phenylenediamine by anthranilic acid. The beneficial role played by this coreactant amine is that it is a sterically hindered

nucleophile bearing a bulky polar COOH group. Thus, when **1** was treated with anthranilic acid in dry benzene and the reaction mixture was left under reflux for 6 h, a mixture of 5-bromoanthranilic acid (**2**) and acetylanthranilic (**5**) was obtained in good yields. The structures of both products were proven not only from analytical data and their IR and ^{1}H NMR absorption spectra, but also by their identity with authentic samples [8] (*cf.* Experimental).



Bearing in mind these experimental results obtained from the reaction of **1** with both *o*-phenylenediamine and anthranilic acid and those from the previously investigated reactions [1–7], in addition to the failure to isolate any acetamidine intermediates or the cyclodehydrated derivatives, it could clearly be concluded that acetanthranil derivatives show high electrophilicity at position 4, leading to an abnormal cleavage at that site despite the steric hindrance imparted by the *ortho* polar groups in the coreactant aromatic amine.

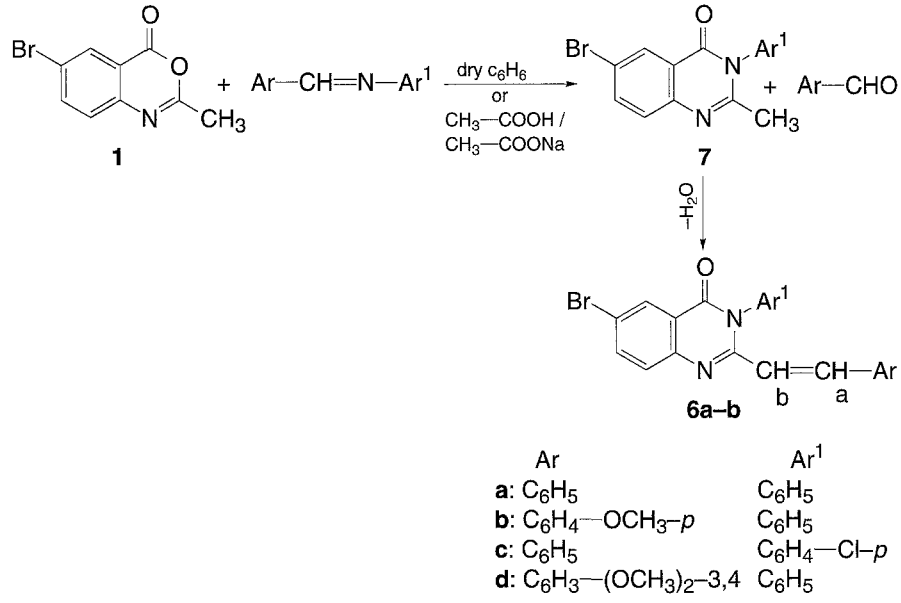
In the search for an attractive synthetic strategy using compound **1**, it was more relevant to apply a modified approach by the treatment with some *Schiff* bases and azines taking into consideration that few publications have been reported concerning this type of reactions. It was obvious that the benefit of these compounds is that they contain both the aldehyde and the amine moieties which are expected to be involved in the reaction upon cleavage under the reaction conditions. Thus, when **1** was allowed to react with equivalent moles of *Schiff* bases, (benzylidene aniline, *p*-methyoxybenzylidene aniline, benzylidene-*p*-chloroaniline, and 3,4-dimethoxybenzylidene aniline) in dry benzene or in glacial acetic acid containing fused sodium acetate as two different media for the reaction conditions, the reaction proceeded smoothly to give quantitative yields of the corresponding 3-aryl-2-styrylquinazolin-4-one derivatives (**6a–d**). Evidently, the reaction involved cleavage of the *Schiff* base into its two reactive segments. The aromatic amine undergoes nucleophilic attack at position 4, and the aldehyde moiety condenses with the reactive methyl group at position 2, leading to the formation of compounds **6a–d**.

Ismail et al. [9] have reported that the reaction of 6,8-dibromo-2-methyl-3,1-benzoxazin-4-one proceeded differently with *Schiff* bases under the same reaction conditions; the reaction resulted in the elimination of the arylidene moiety which did not interact in a condensation reaction with the methyl group at position 2. There was no evidence for the elimination of an arylidene segment.

The structure of compounds **6a–d** was substantiated by their infrared spectra which exhibited strong carbonyl stretching frequencies in the range of 1685–1660 cm^{-1}, whereas they lack absorptions in the 3300 cm^{-1} region, confirming the absence of NH groups. Moreover, the ^{1}H NMR spectra of **6a–c** ($CDCl_3$) and **6d** (*DMSO*-d_6) showed a doublet in the range of 8.41–8.20 ppm for proton *a*, while proton *b* exhibited a doublet in the range of 6.39–6.18 ppm with an integration of

two protons for both H_a and H_b. Compound **6b** showed a singlet at 3.79 ppm, whereas **6d** showed two singlets at 3.85 and 3.78 ppm, corresponding to one and two $-OCH_3$ groups, respectively. The peak appearing as a singlet in the range of 7.96–7.78 ppm is characteristic of proton *c* of the monobromophenyl group. The ^{13}C NMR spectrum of **6a** showed peaks of 161.08 (s, C=O group) and 152.20 ppm (s, C=N group), in addition to two doublets at 130.07 and 119.43 ppm, characteristic of the vinylic –CH=CH– group attached to phenyl group and the heterocyclic system, respectively.

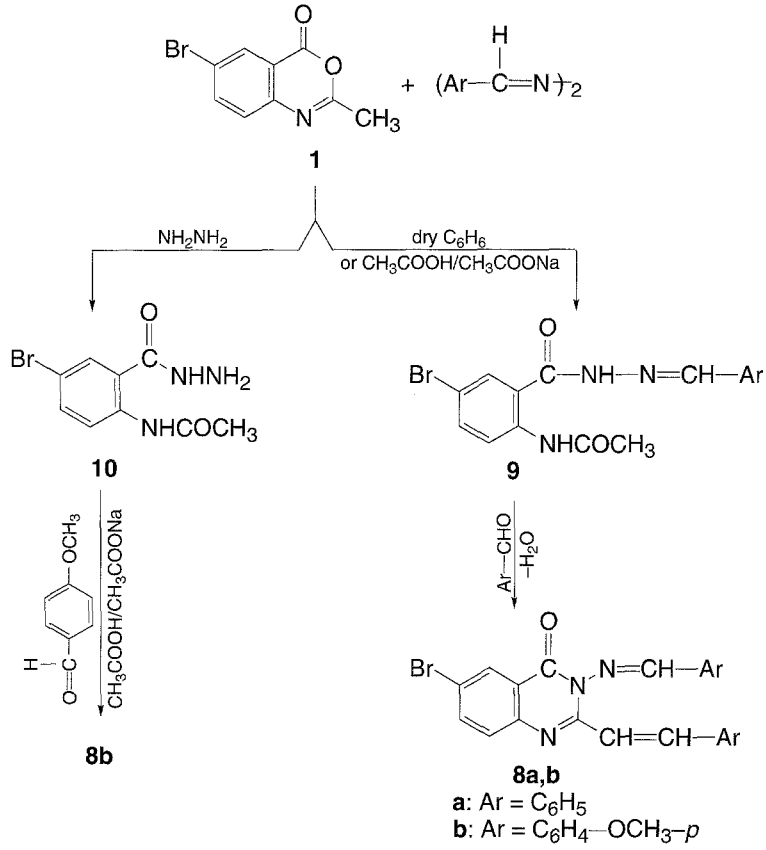
The reaction pathway can be simplified as follows:



	Ar	Ar^1
a:	C_6H_5	C_6H_5
b:	C_6H_4—OCH_3–*p*	C_6H_5
c:	C_6H_5	C_6H_4—Cl–*p*
d:	C_6H_3—$(OCH_3)_2$–3,4	C_6H_5

Compounds **6a** and **b** have been previously prepared [10] from 6-bromo-2-methyl-3,1-benzoxazin-4-one (**1**) *via* a series of reactions involving its treatment with aniline in boiling ethanol. The product was condensed with benzaldehyde or *p*-methoxybenzaldehyde in the presence of anhydrous zinc chloride or an acetic acid – acetic anhydride mixture. The disadvantage of this method is the resulting product mixture and the low yield as compared to our method.

In connection with this study, the *Schiff* base was replaced by azines (benzalazine and *p*-methoxybenzalazine), and the reaction was carried out under similar conditions. However, the reaction needed a longer time for completion. Again, it was believed that the reaction may involve the removal of one or both [9, 11] arylidene moieties. However, this suggestion was discarded by examining the reaction products which were found to be 3-arylideneamino-6-bromo-2-styrylquinazolin-4-one derivatives (**8a** and **b**), respectively. The failure to detect the displacement of arylidene groups from the azine in the reaction media clearly reflected the higher nucleophilicity of the methyl group at position 2 towards the aromatic aldehyde under the given reaction conditions. The reaction route can be represented as follows:



The suggested mechanism for the above reactions with *Schiff* bases and azines seems to be similar to the previously reported reactions of 6,8-dibromo-2-methyl- and 2-phenyl-3,1-benzoxazin-4-ones [9, 11].

The structures of **8a** and **b** were proven by microanalytical data and by their infrared spectra which showed strong carbonyl stretching frequencies at 1692 cm^{-1} and 1682 cm^{-1}, in addition to the absorptions in the region of 1645 cm^{-1}–1625 cm^{-1} characteristic of C=N groups (**8a** and **b**). Both compounds exhibited no bands in the region 3300 cm^{-1}, indicating the absence of NH bands and confirming the cyclic structure of the products. Moreover, the structural assignment was established from the ^1H NMR spectrum of **8b** ($CDCl_3$) which exhibited a singlet at 8.58 ppm and two doublets at 8.38 and 5.85 ppm with integration values of 3 hydrogens, corresponding to protons **a**, **b**, and **c**, respectively. In addition, signals at 3.79 and 3.76 ppm (singlets, 6H) are characteristic of two methoxy groups (*cf.* Experimental).

The structure of **8b** has received further support by its identity with that independently obtained by condensation of 2-acetylamino-5-bromobenzhydrazide [10] (**10**) with *p*-methoxybenzaldehyde in glacial acetic acid containing a catalytic amount of fused sodium acetate.

Experimental

All melting points are uncorrected. Elemental analyses were performed by M.H.W. Laboratories, Phoenix, Az 85018, and the Microanalytical Unit, Ain Shams University. IR spectra (KBr discs) were

obtained using a PYE Unicam SP 1200 spectrophotometer. NMR spectra were recorded on a Bruker AC 200 as solutions in *DMSO*-d_6 or $CDCl_3$ and using *TMS* as the internal standard.

Reaction of 6-bromo-2-methyl-3,1-benzoxazin-4-one (**1**) *with o-phenylenediamine*

The solution of 6-bromo-2-methyl-3,1-benzoxazin-4-one (**1**, 4.79 g, 0.02 mole) in dry benzene (40 ml) was treated with *o*-phenylenediamine (0.02 mole); the reaction mixture was heated under reflux for 6 h, and left to cool. The solid formed was filtered off, treated with an aqueous sodium carbonate solution, and filtered again. The alkaline filtrate was acidified by conc. hydrochloric acid to give a colorless solid which was crystallized from dil. ethanol to give colorless crystals of 5-bromoanthranilic acid (**2**); m.p.: 218–219 °C, yield: 32%. The product showed no depression of m.p. and m.m.p. when admixed with an authentic sample [8]. Calc. for $C_7H_6NO_2Br$: C, 38.97, H, 2.78, N, 6.49; found: C, 39.21; H, 2.77; N, 6.40. IR $\nu_{OH} = 3325\,cm^{-1}$, $\nu_{NH_2} = 3200–3140\,cm^{-1}$, $\nu_{C=O} = 1720\,cm^{-1}$; ^1H NMR ($CDCl_3$): $\delta = 10.94$ (1H, s, OH), 8.72–8.67 (1H, d, ar), 8.25 (1H, s, ar), 7.73–7.69 (1H, d, ar), 2.92–2.78 (2H, br, s, NH_2) ppm.

The insoluble solid was boiled in benzene and filtered while hot. The solid formed after cooling was filtered off and crystallized from a benzene – light petroleum (b.p. 60–80°) mixture to give 2-aminoacetanilide (**3**); m.p.: 130–132 °C (Lit.: 132°; yield: 28%. Calc. for $C_8H_{10}N_2O$: N, 18.66; found: N, 18.02.

The insoluble benzene solid product was filtered off and crystallized from ethanol to give *o*-acetamidobenzamide (**4**) as colorless crystals; m.p.: 250–252 °C, yield: 36%. IR: $\nu_{max} = 3260$, 3220–3160, 3100, 1700–1685, $1665\,cm^{-1}$; ^1H NMR (*DMSO*-d_6): $\delta = 12.96$ (1H, s, –NH–CO), 10.68 (1H, s, –NHCO), 8.61–8.57 (1H, d, ar), 8.22 (1H, d, ar), 8.17–8.13 (1H, d, ar), 8.06 (1H, d, ar), 7.86 (1H, s, ar), 7.69–7.32 (m, ar H), 3.99 (2H, s, br, NH_2), 2.19 (3H, s, CH_3) ppm; calc. for $C_{15}H_{14}N_3O_2Br$: N, 12.08; found: 11.69.

Reaction of 6-bromo-2-methyl-3,1-benzoxazin-4-one (**1**) *with anthranilic acid*

A mixture of **1** (0.01 mole) and anthranilic acid (0.01 mole) was heated under reflux in boiling dry benzene for 6 h and left overnight at room temperature. The solid product formed was filtered off and, extracted with boiling water while hot. The water soluble solution was left to cool to give a precipitated solid which was filtered off and recrystallized from dilute ethanol to give N-acetyanthranilic acid (**5**) as colorless crystals; m.p.: 182–184 °C, yield: 42%. It showed no depression of m.p. and m.m.p. when admixed with an authentic sample [8].

The water insoluble solid was filtered off and recrystallized from ethanol to give 5-bromonthranilic acid (**2**) as colorless crystals; m.p.: 218–219 °C, yield: 45%. The product showed no depression of m.p. and m.m.p. when admixed with authentic samples [8].

Reaction of **1** *with Schiff bases in dry benzene (general procedure)*

A mixture of 6-bromo-2-methylbenzoxazin-4-one (2.39 g, 0.01 mole) and the *Schiff* base was dissolved in dry benzene (40 ml) and heated under reflux for 6 h. The solid product formed was filtered off and recrystallized from a suitable solvent as described in individual examples to give yellow crystals of **6a–d**, respectively.

Reaction of **1** *with Schiff bases in glacial acetic acid (general procedure)*

6-Bromo-2-methylbenzoxazin-4-one (2.39 g, 0.01 mole) and the *Schiff* base (0.01 mole) were dissolved in a solution of glacial acetic acid (30 ml) and fused sodium acetate (0.2 g), heated under reflux for 6 hs. and left to cool and poured onto cold water. The solid product formed was filtered off and treated as described in the previous procedure to give **6a–d**, respectively. It showed no depression of m.p. and m.m.p. when admixed with the corresponding product obtained from the above experiment in dry benzene.

Reaction of **1** *with azines in dry benzene (general procedure)*

A solution of 6-bromo-2-methylbenzoxazin-4-one (4.78 g, 0.02 mole) and the azine (0.01 mole) in dry benzene was heated under reflux for 4 d and left to cool. The solid product obtained was filtered off and recrystallized from a suitable solvent as described in the individual examples to give yellow crystals of **8a, b**, respectively.

Reaction of **1** *with azines in glacial acetic acid*

To a solution of compound **1** (4.78 g, 0.02 mole) in glacial acetic acid (30 ml) and fused sodium acetate (0.2 g), the azine (0.01 mole) was added and heated under reflux for 4 d. The reaction mixture was left to cool and poured into cold water. The solid product formed was collected and treated as described in the above experiment to give the same products (**8a, b**).

Synthesis of an authentic sample of **8b**

A mixture of 2-acetylamino-5-bromobenzyhydrazide (**10**), *p*-methoxybenzaldehyde (0.02 mole), and fused sodium acetate (0.2 g) in glacial acetic acid (30 ml) was heated under reflux for 6 h. After cooling, the product was filtered off and recrystallized from acetone to give 6-bromo-3-*p*-methoxybenzylidene-amino-2-*p*-methoxystyrylquinazolin-4-one; m.p.: 268–269 °C, yield: 63%. The product showed no depression of m.p. and m.m.p. when admixed with **8b**.

	M.p. (°C)	Solvent	Yield (%)	Molecular formula[z]	I.R (cm^{-1}) $\nu_{C=O}$	$\nu_{C=N}$	^{1}NMR (δ, ppm.)
6a[b]	239–240	EtOH	69	$C_{22}H_{15}NO_2Br$	1670	1625	$CDCl_3$; 8.41 (1H, d, H_a), 7.95 (1H, d, ar), 7.87 (1H, d, ar), 7.83 (1H, d, ar), 7.66 (1H, s, ar), 7.61–7.57 (m, ar), 7.32–7.25 (m, ar), 6.34–6.27 (1H, d, H_b)
6b	255–256	Toluene	73	$C_{23}H_{17}N_2O_2Br$	1660	1625	*DMSO*-d_{6i} 8.20 (1H, d, H_a), 8.03 (1H, d, ar), 7.92 (1H, d, ar), 7.85 (1H, s, ar), 7.73–7.33 (m, ar), 6.18 (1H, d, H_b), 3.79 (3H, s, OCH_3)
6c	296–298	CH_3 COOH	64	$C_{22}H_{14}N_2$ OBrCl	1680	1630	$CDCl_3$; 8.41 (1H, d, H_a), 7.96 (1H, s, ar), 7.88 (1H, d, ar), 7.83 (1H, d, ar), 7.67 (1H, s, ar), 7.63 (m, ar), 7.32–7.25 (m, ar), 6.34 (1H, d, H_b)
6d	212–214	EtOH	75	$C_{24}H_{19}N_2O_3Br$	1685	1633	*DMSO*-d_6; 8.28 (1H, d, H_a), 8.13 (1H, d, ar), 7.98 (1H, d, ar), 7.81 (1H, s, ar), 7.76 (1H, d, ar), 7.71–7.01 (m, ar), 6.24 (1H, d, H_b), 3.85 (3H, s, OCH_3), 3.78 (3H, s, OCH_3)

(*Continued*)

(*Continued*)

	M.p. (°C)	Solvent	Yield (%)	Molecular formula[a]	I.r (cm^{-1}) $\nu_{C=O}$	$\nu_{C=N}$	^{1}NMR (δ, ppm)
8a	252–254	EtOH	59	$C_{22}H_{16}N_3OBr$	1692	1645	
8b	268–269	Acetone	67	$C_{25}H_{20}N_3O_3Br$	1682	1655 1625	$CDCl_3$; 8.58 (1H, s, N = CH), 8.38 (1H, d, H_a), 7.79–7.75 (m, ar), 7.35–7.28 (m, ar), 6.87–6.78 (m, ar), 5.85 (1H, d, H_b), 3.79 (3H, s, OCH_3), 3.76 (3H, s, OCH_3)

[a] All elemental analyses (C, H, N) are in agreement with the calculated values; [b] ^{13}C NMR spectrum ($CDCl_3$) of compound **6a**: 161.08 (s), 152.20(s), 130.07(d), 140.69(d), 137.80(d), 136.70(d), 135.13(d), 122.25(s), 120.03(s), 119.43(d) ppm

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