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Combined Alkylating Agents as a Resolution for Highly Selective N-Alkylation of 2-Hydroxybenzaldehyde Acylhydrazones

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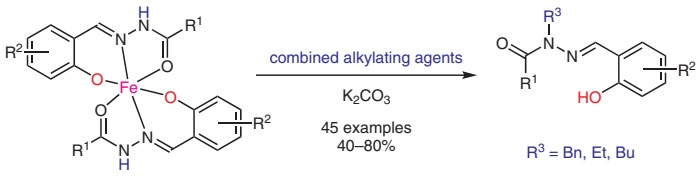

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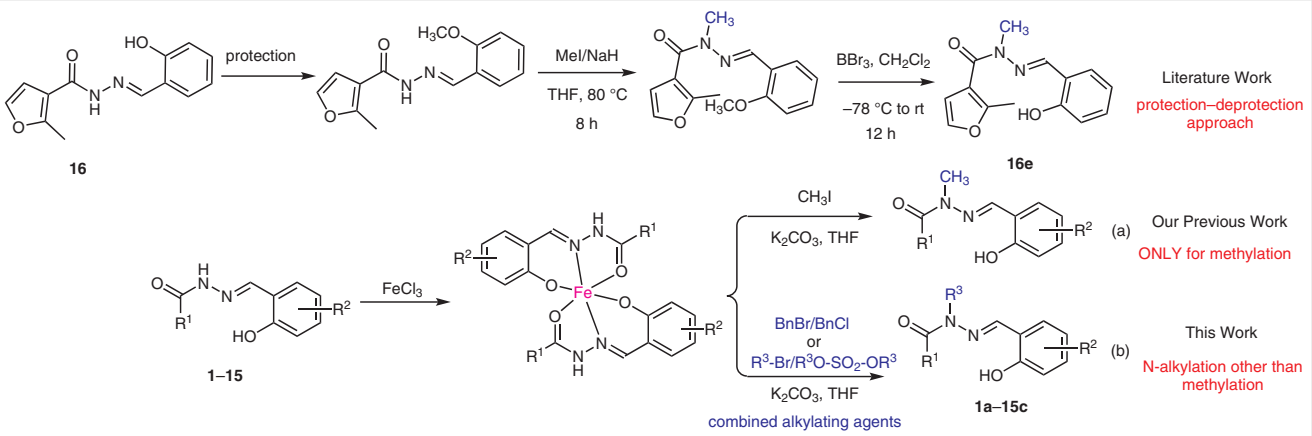
Abstract Although 2-hydroxybenzaldehyde acylhydrazones, such as salicylaldehyde acylhydrazones, are intriguing bioactive molecules, few of their N-alkylated derivatives are known, and only methyl analogues have been reported previously. We achieved selective N-alkylation of 2-hydroxybenzaldehyde acylhydrazones, as their Fe(III) complexes, by using combinations of alkylating agents (for example, an alkyl bromide and a dialkyl sulfate). Fifteen substrates were examined, and 45 new 2-hydroxybenzaldehyde acyl(alkyl)hydrazones were synthesized in moderate to good yields. In all cases, the target products were obtained exclusively, and no O-alkylation byproducts were produced. The method provides an efficient way of preparing 2-hydroxybenzaldehyde acyl(alkyl)hydrazones.

Key words alkylation, regioselectivity, medicinal chemistry, salicylaldehyde acylalkylhydrazones, hydrazones

The acylhydrazone moiety, which structurally resembles an amide group, is often considered a privileged building block in medicinal chemistry. Not surprisingly, compounds containing such moieties have demonstrated intriguing bioactivities.[1–4] For example, salicylaldehyde acylhydrazones and their analogues have been suggested as potential inhibitors against human glutathione transferase[5] and β-glucuronidase.[6] Moreover, metal complexes of the acylhydrazones of salicylaldehyde or substituted salicylaldehydes have been showed to have antioxidant and antiproliferative potency.[7] As such, these complexes might be potentially useful for the treatment of cancer,[8,9] Alzheimer's disease,[10] inflammation,[11] or diseases caused by Gram-positive bacteria.[12] Previous studies have shown that the introduction of a methyl group onto the acylated nitrogen atom of acylhydrazones can lead to distinct biological responses.[3,13–15] Although N-alkylation is of great interest, only limited range of N-alkyl derivatives of acylhydrazones are



Scheme 1 N-Alkylation of 2-hydroxybenzaldehyde acylhydrazones

known. We believe that selective N-alkylation might alter this situation and provide a range of new molecules for biological study.

In drug discovery, N-alkylation is a common strategy for enlarging the range of nitrogen-containing compounds. Recently, efficient methods have been developed for the N-alkylation of common amines by using inexpensive alkylating agents such as methanol[16,17] or quaternary ammonium salts.[18] Nevertheless, there are few reports of examples of the selective N-alkylation of acylhydrazones, especially 2-hydroxybenzaldehyde acylhydrazones, and only their N-methylation with methyl iodide has been reported.[19,20] The challenge in selective N-alkylation of these substrates lies in the regioselectivity between alkylation of the nitrogen atom of the hydrazone and the oxygen atom of the hydroxy group. A protection–deprotection method in which a strong Lewis acid (BBr_3) was employed to remove the O-protecting group has previously been used (Scheme 1; literature work).[3] This method involves a number of steps and is environmentally unfriendly. We previously found that coordinating a 2-hydroxybenzaldehyde acylhydrazone with Fe(III) and then using the complexes as substrates dramatically improved the selectivity of N-methylation (Scheme 1; previous work).[20] Unfortunately, the scope of this method is limited; when alkylating agents other than methylating agents were used, the desired substitution was not achieved. For example, no alkylated products were detected upon treating the substrates with ethyl bromide, ethyl iodide, or diethyl sulfate, whereas reaction with benzyl bromide resulted in undesired N,O-dibenzylation.

Here we report a new method in which a combination of alkylating agents is used to achieve selective N-alkylation of 2-hydroxybenzaldehyde acylhydrazones (Scheme 1; this work). As previously mentioned, we noticed that benzyl bromide overreacted with these substrates. This observation led us to test benzyl chloride, an agent with a relatively lower reactivity. Although the reaction turned out to be unsuccessful, a serendipitous addition of benzyl bromide to the reaction system dramatically improved both the reactivity and the selectivity. Further modification of this reaction showed that a combination of 0.8 equivalents of benzyl chloride and 0.2 equivalents of benzyl bromide in THF worked best. We then synthesized a series of 2-hydroxybenzaldehyde acylhydrazones[20] to explore the scope of the method. To our delight, the strategy worked well in all the cases, and the yields of products **1a–15a** (R = Bn) were in the range 60–80% (Figure 1).[21] However, increasing the amount of the more reactive benzyl bromide usually resulted in formation of the O,N-dibenzylated products, and the yields of the N-benzylated products were reduced correspondingly.

Our success with the use of benzyl chloride and benzyl bromide as combined alkylating agents inspired us to explore a similar, but more general, method for selective N-al-

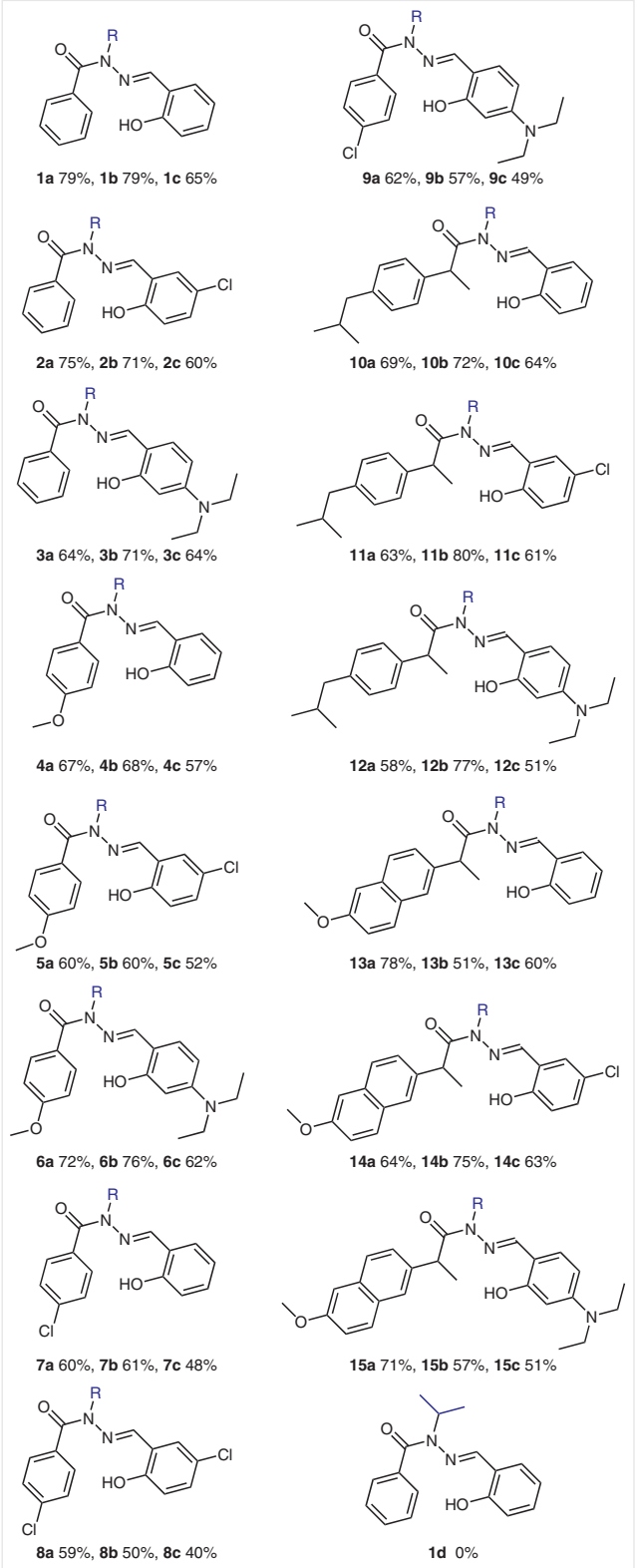


Figure 1 Yields and structures of N-alkylated products **1a–15c** (**a**, R = Bn; **b**, R = Et; **c**, R = Bu; **d**, R = *i*-Pr). The synperiplanar (*E*)-configuration was suggested by the crystal structure of **11b**.

kylation, for example, N-ethylation or N-butylation, which could not be achieved by using a corresponding alkylating agent alone. We finally established that a combination of an alkyl bromide and the corresponding dialkyl sulfate improved both the efficiency and the selectivity of the reaction. Employing any of these agents independently, even in an excess amount, barely gave any of the N-alkylated product. An investigation of the reaction conditions showed that the optimal molar ratio of the alkyl bromide to the dialkyl sulfate was 5:1. Under the optimized conditions, the site-specific N-alkylation products **1b–15b** (R = Et) and **1c–15c** (R = Bu) were obtained in yields of 40–80% (Figure 1; R = Et, Bu).[21] Notably, this reaction appeared to be sensitive to steric hindrance. Ethylation usually gave a higher yield than butylation, whereas combined agents containing secondary halides did not react with the substrates at all.

All the compounds were characterized, and the N-alkylated feature was unambiguously identified by using IR, NMR, and elemental analyses. To confirm the proposed structures, a single-crystal structural analysis of **11b** was also performed (Figure 2). Again, this established that the products that we obtained were the expected alkyl(acyl)hydrazones.

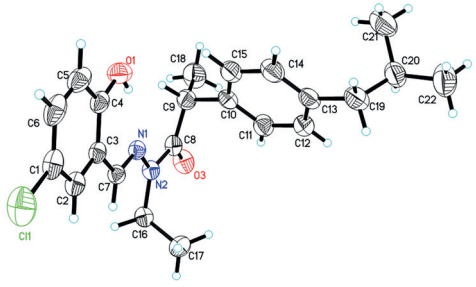
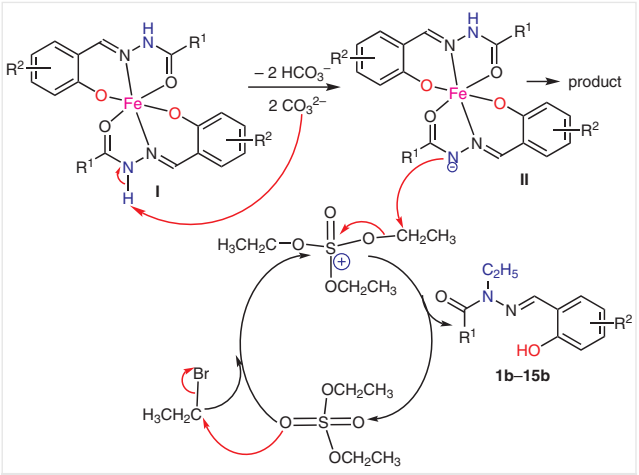


Figure 2 Single crystal structure of **11b**.

The fact that the combination of an alkyl bromide and a dialkyl sulfate worked better than the individual alkylating agents indicated that the two types of agent might react with one another to form a more reactive species, because it had been proved these agents alone are insufficiently reactive to bring about the expected alkylation. We therefore propose that alkyl bromide and the dialkyl sulfate might react to form a transient trialkyl sulfate intermediate, an active species that operates as the real alkylating agent (Scheme 2). Although it could not be detected by NMR in our hands, such a species has been generated by methylating dimethyl sulfate with cationic $MeOSO^+$ and subsequently characterized.[22] Another interesting aspect of the reaction was that the free products rather their Fe(III) complexes were obtained on completion of the reaction. This is because the Fe(III) complexes of the N-alkylated products decompose under the reaction conditions whereas the Fe(III) complexes of the substrates do not do so.

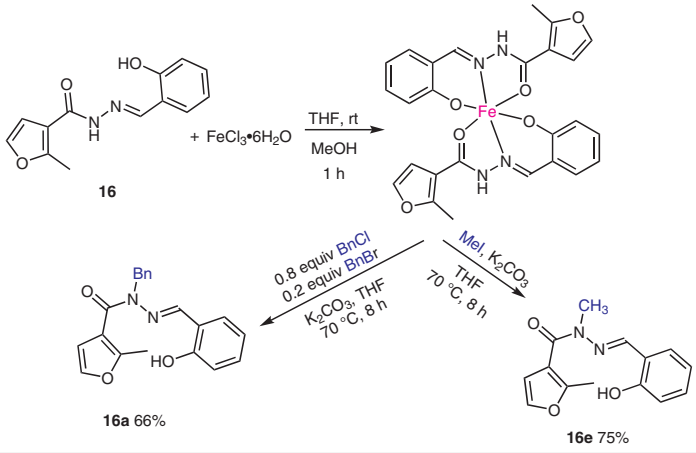


Scheme 2 Plausible reaction mechanism for N-alkylation using ethyl bromide and diethyl sulfate as combined alkylating agents

To gain insight into the mechanism of benzylation, we carried out several further experiments. Whereas benzylation proceeded in the presence of BnBr, no reaction occurred when BnBr was replaced with a bromide source such as tetrabutylammonium bromide. These observations indicated that BnBr is the active species. With catalytic amount of reactive benzyl bromide in the reaction system, it is reasonable that the agent attacks the more spatially available and nucleophilic nitrogen rather than the Fe(III)-coordinated oxygen. BnBr, once consumed, might be regenerated from BnCl. When BnBr was added slowly by using a syringe pump, the N-benzylated product was initially formed, but as the addition proceeded the reaction time was extended and the N,O-dibenzylated byproduct was also formed. Therefore, the role of BnCl was not only to regenerate BnBr, but also, somehow, to regulate the reactivity of BnBr.

The previous[20] and current methods developed for selective N-alkylation have great potential in the preparation of bioactive acylhydrazone derivatives. For example, we applied our methods to the synthesis of *N*′-[(2-hydroxyphenyl)methylene]-2-methyl-3-furohydrazide (**16e**),[3] a methyl derivative of **16**, which is a potent inhibitors of *Schistosoma mansoni* NAD^+ catabolizing enzyme (Scheme 3). Under the conditions that we previously reported,[20] the desired product was obtained in 75% yield with excellent selectivity. As a comparison, the method reported in the literature[3] involved both a protection–deprotection procedure and harmful reagents. When methyl iodide was replaced with combined benzyl bromide and benzyl chloride, the unreported derivative **16a** was produced smoothly in 66% yield. Biological studies on molecules of this type are ongoing.

In summary, we successfully developed a combined-alkylating-agent protocol for the synthesis of 2-hydroxybenzaldehyde acyl(alkyl)hydrazones through site-specific N-alkylation of the corresponding Fe(III) complexes. A variety of 2-hydroxybenzaldehyde acyl(alkyl)hydrazones were ob-



Scheme 3 Application of selective N-alkylation to the synthesis of **16a** and **16e**

tained with excellent regioselectivities in moderate to good yields. We have not been able to find any other strategy for performing this selective and widely applicable transformation reported in the literature.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1611823.

References and Notes

(1) dos Santos, J. M. Filho.; Pinheiro, S. M. *Green Chem.* **2017**, *19*, 2212.
(2) Lima, P. C.; Lima, L. M.; da Silva, K. C. M.; Léda, P. H. O.; de Miranda, A. L. P.; Fraga, C. A. M.; Barreiro, E. J. *Eur. J. Med. Chem.* **2000**, *35*, 187.
(3) Jacques, S. A.; Kuhn, I.; Koniev, O.; Schuber, F.; Lund, F. E.; Wagner, A.; Muller-Steffner, H.; Kellenberger, E. *J. Med. Chem.* **2015**, *58*, 3582.
(4) Palanimuthu, D.; Wu, Z.; Jansson, P. J.; Braidy, N.; Bernhardt, P. V.; Richardson, D. R.; Kalinowski, D. S. *Dalton Trans.* **2018**, *47*, 7190.
(5) Georgakis, N. D.; Karagiannopoulos, D. A.; Thireou, T. N.; Eliopoulos, E. E.; Labrou, N. E.; Tsoungas, P. G.; Koutsilieris, M. N.; Clonis, Y. D. *Chem. Biol. Drug Des.* **2017**, *90*, 900.
(6) Taha, M.; Arbin, M.; Ahmat, N.; Imran, S.; Rahim, F. *Bioorg. Chem.* **2018**, *77*, 47.
(7) Hrušková, K.; Potůčková, E.; Opálka, L.; Hergeselová, T.; Hašková, P.; Kovaříková, P.; Šimůnek, T.; Vávrova, K. *Chem. Res. Toxicol.* **2018**, *31*, 435.
(8) Gou, Y.; Zhang, Y.; Zhang, Z.; Wang, J.; Zhou, Z.; Liang, H.; Yang, F. *Mol. Pharmaceutics* **2017**, *14*, 1861.
(9) Cindrić, M.; Bjelopetrović, A.; Pavlović, G.; Damjanović, V.; Lovrić, J.; Matković-Calogović, D.; Vrdoljak, V. *New J. Chem.* **2017**, *41*, 2425.
(10) D'Acunto, C. W.; Kaplánek, R.; Gbelcová, H.; Kejík, Z.; Bríza, T.; Vasina, L.; Havlík, M.; Ruml, T.; Král, V. *Eur. J. Med. Chem.* **2018**, *150*, 140.
(11) Chimmalagi, G. H.; Kendur, U.; Patil, S. M.; Gudasi, K. B.; Frampton, C. S.; Budri, M. B.; Mangannavar, C. V.; Muchchandi, I. S. *Appl. Organomet. Chem.* **2018**, *32*, e4337.
(12) Fekri, R.; Salehi, M.; Asadi, A.; Kubicki, M. *Appl. Organomet. Chem.* **2018**, *32*, e4019.
(13) Pereira, S. L.; Kummerle, A. E.; Fraga, C. A. M.; Barreiro, E. J.; Sudo, R. T.; Zapata-Sudo, G. *Fundam. Clin. Pharmacol.* **2014**, *28*, 29.
(14) Silva, A. G.; Zapata-Sudo, G.; Kummerle, A. E.; Fraga, C. A. M.; Barreiro, E. J.; Sudo, R. T. *Bioorg. Med. Chem.* **2005**, *13*, 3431.
(15) Kümmerle, A. E.; Raimundo, J. M.; Leal, C. M.; da Silva, G. S.; Balliano, T. L.; Pereira, M. A.; de Simone, C. A.; Sudo, R. T.; Zapata-Sudo, G.; Fraga, C. A. M.; Barreiro, E. J. *Eur. J. Med. Chem.* **2009**, *44*, 4004.
(16) Wang, L.-M.; Jenkinson, K.; Wheatley, A. E. H.; Kuwata, K.; Saito, S.; Naka, H. *ACS Sustainable Chem. Eng.* **2018**, *6*, 15419.
(17) Polidano, K.; Allen, B. D. W.; Williams, J. M. J.; Morrill, L. C. *ACS Catal.* **2018**, *8*, 6440.
(18) Ray, P. C.; Pawar, Y. D.; Singare, D. T.; Deshpande, T. N.; Singh, G. P. *Org. Process Res. Dev.* **2018**, *22*, 520.
(19) Kümmerle, A. E.; Schmitt, M.; Cardozo, S. V. S.; Lugnier, C.; Villa, P.; Lopes, A. B.; Romeiro, N. C.; Justiniano, H.; Martins, M. A.; Fraga, C. A. M.; Bourguignon, J.-J.; Barreiro, E. J. *J. Med. Chem.* **2012**, *55*, 7525.
(20) Li, Z.; Wu, L.; Zhang, T.; Huang, Z.; Qiu, G.; Zhou, Z.; Jin, L. *Dalton Trans.* **2014**, *43*, 7554.

(21) **2-Hydroxybenzaldehyde Acyl(benzyl)hydrazones (1a–15a); General Procedure**

K_2CO_3 (0.55 g, 4.0 mmol), BnCl (0.36 mL, 3.2 mmol), and BnBr (0.05 mL, 0.8 mmol) were added to a solution of the Fe(III) complex of the appropriate hydroxybenzaldehyde acylhydrazone (prepared from 4.0 mmol of the hydrazone) in THF (10 mL). The black mixture was refluxed for 8–16 h before removal of the solid by hot filtration. The mother solution was concentrated, and the product was harvested by crystallization from MeOH.

***N*-Benzyl-*N*′-[(2-hydroxyphenyl)methylene]benzohydrazide (1a)**

White solid; yield: 1.04 g (79%); mp 132–133 °C. IR (KBr): 3448 (m), 3058 (vs), 1666 (vs), 1616 (s), 1600 (s) cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 9.76 (s, 1 H), 8.12 (s, 1 H), 7.67 (d, *J* = 7.2 Hz, 2 H), 7.57–7.50 (m, 3 H), 7.41–7.37 (m, 4 H), 7.30–7.25 (m, 2 H), 7.17 (t, *J* = 8.0 Hz, 1 H), 6.75 (t, *J* = 8.0 Hz, 2 H), 5.45 (s, 2 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 170.9, 156.7, 141.1, 135.8, 135.5, 131.5, 130.6, 129.3, 128.7, 128.7, 128.4, 127.7, 127.0, 119.8, 119.6, 116.6, 44.4. Anal. Calcd for $C_{21}H_{18}N_2O_2$: C, 76.34; H, 5.49; N, 8.48. Found: C, 76.33; H, 5.63; N, 8.36.

***N*-Ethyl-*N*′-[(2-hydroxyphenyl)methylene]benzohydrazide (1b)**

Prepared by following the general procedure, but using EtBr and Et_2SO_4 in a 5:1 ratio, to give a white solid; yield: 850 mg (79%); mp 108–110 °C. IR (KBr): 3425 (m), 2982 (vs), 1654 (vs), 1518 (s), 1604 (s) cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 9.87 (s, 1 H), 8.26 (s, 1 H), 7.62–7.34 (m, 6 H), 7.20 (m, 1 H), 6.83 (t, *J* = 8.0 Hz, 1 H), 6.78 (d, *J* = 8.0 Hz, 1 H), 4.18 (q, *J* = 7.2 Hz, 2 H), 1.21 (t, *J* = 7.2 Hz, 3 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 170.1, 156.8, 141.4, 136.1, 131.4, 130.4, 129.7, 128.4, 119.8, 119.6, 116.6, 35.7, 11.2. Anal. Calcd for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.44. Found: C, 71.43; H, 6.00; N, 10.39.

***N*-Butyl-*N*′-[(2-hydroxyphenyl)methylene]benzohydrazide (1c)**

Prepared by following the general procedure, but using BuBr and Bu_2SO_4 in a 5:1 ratio, to give a white solid; yield: 770 mg (65%); mp 99–100 °C. IR (KBr): 3174 (m), 2954 (vs), 1658 (vs), 1626 (s), 1601 (s). ^1H NMR (400 MHz, DMSO-d_6): δ = 9.83 (s, 1 H), 8.24 (s, 1 H), 7.52–7.40 (m, 6 H), 7.20 (t, *J* = 7.6 Hz, 1 H), 6.83 (t, *J* = 7.6 Hz, 1 H), 6.78 (d, *J* = 8.4 Hz, 1 H), 4.15 (t, *J* = 7.2 Hz, 2 H), 1.62 (m, 2 H), 1.40 (m, 2 H), 0.96 (t, *J* = 7.2 Hz, 3 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 170.5, 156.8, 141.3, 136.2, 131.4, 130.3, 129.7, 128.4, 128.2, 119.7, 119.6, 116.6, 27.6, 20.0, 14.1. Anal. Calcd for $C_{18}H_{20}N_2O_2$: C, 72.95; H, 6.80; N, 9.45. Found: C, 73.07; H, 6.99; N, 9.02.

(22) Christie, J. J.; Lewis, E. S.; Casserly, E. F. *J. Org. Chem.* **1983**, *48*, 2531.