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LITHIUM BROMIDE CATALYZED EHRLICH-SACHS REACTIONS USING SOLVENT-FREE CONDITIONS

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ABSTRACT

Lithium bromide proves to be an efficient catalyst for Ehrlich-Sachs reaction of nitroso arenes with active methylene compounds under microwave irradiation through simple solvent-free reaction conditions.

The Ehrlich-Sachs and Kröhnke reactions, though first reported in the 19th century, are the important methods for the synthesis of imines and imine oxides[1,2] from arylnitroso compounds. The reaction[3–5] has been reported catalyzed by a variety of bases[3–5] (NaOH, piperidine, alkoxides, potassium cyanide, trisodium phosphate, etc.) and occurs with various active methylene components, including arenemethyl cyanides, malonic esters, β-keto esters, β-diketones, fluorenes, cyclopentadienes, and nuclear-activated arenemethyl derivatives[6–8] (e.g., 2,4-dinitrotoluene). In general, the reaction leads to a mixture and there is limited success in predicting a predominance of dehydration or oxidation products. Azomethine formation

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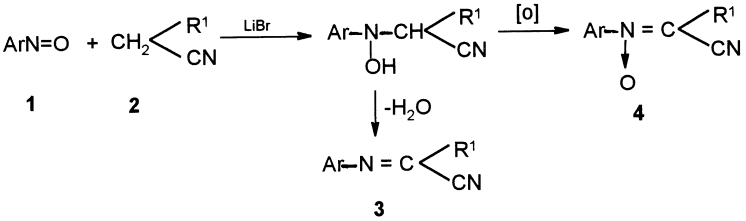
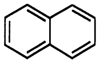


Scheme 1.

tends to be favored over nitrone formation when strong basic catalysts are used to effect condensation.[9] The Ehrlich-Sachs reaction is also limited in its synthetic utility, owing to the relative inaccessibility of the nitrosoarene starting material and the low yields due to competing nitrone formation. In continuation of our studies on imines[10–12] we report Ehrlich-Sachs reactions for the synthesis of unconventional imines in near neutral solvent-free conditions using lithium bromide under microwave activation. To our knowledge, this is the first report that discloses lithium bromide as a new catalyst in the said reaction under neutral conditions. The application of microwave energy to accelerate organic reactions is a matter of increasing interest and offers several advantages.[13–18] It has been used for a variety of organic reactions and here the reaction proceeds efficiently in excellent yield at ambient pressure within seconds in the absence of a solvent.

Typically, N,N-dimethyl-4-nitrosoaniline, benzylcyanide, and lithium bromide were mixed together without solvent in an Erlenmeyer flask and irradiated for 2 min in a commercial microwave oven (operating at 2450 Mhz frequency and 70 Watts). The reaction mixture was allowed to reach room temperature, washed with water, and extracted with dichloromethane. Removal of solvent and purification of the residue by column chromatography using petroleum ether:chloroform (4:1) as eluent gave the corresponding imines **3** (entry 1) in 90% yield, m.p. 90°C (lit.[19,20] m.p. 91°C) without the formation of any imine oxide **4**. According to Barrow[19, 20] this reaction gives a mixture of imine and imine oxides when carried out with 30% KOH. Similarly, other substrates were used and the corresponding imines **3** were isolated in 80–90% yields. As shown in Table 1, several structurally varied nitrosoarenes underwent clean and remarkably fast Ehrlich-Sachs reactions with a variety of active methylene compounds using this procedure. Many reactions are complete within a period of 30–130 s. Interestingly, it was also observed that the presence of solvent slowed the reaction and gave mixture of imine **3** and nitrone **4** when carried out in ethanol; the reasons for the efficiency of the process in the solid phase are not yet clear. Except in the case of (2-cyanomethyl)naphthalene, where

***Table* 1.** Ehrlich-Sachs Reaction Catalyzed by LiBr Under Microwave Irradiation

Product	Ar	R^1	Time M.W. (s)	Yield[a] (%)
3a	$-C_6H_4NMe_2$–p	$-C_6H_5$	120	90
3b	$-C_6H_4NHCH_3$–p	$-C_6H_5$	125	85
3c	$-C_6H_5$	$-C_6H_5$	115	85
3d	$-C_6H_4NMe_2$–p	–CN	30	89
3e	$-C_6H_4NMe_2$–p	$-CO_2Et$	122	85
3f	$-C_6H_4NMe_2$–p	–COPh	126	85
3g	$-C_6H_4Nme_2$–p	$-CONH_2$	125	85
3h	$-C_6H_4NMe_2$–p	–CONHPh	123	85
3i	$-C_6H_4NMe_2$–p	$-C_6H_4Me$–p	125	80
3j	$-C_6H_4NMe_2$–p		130	60
3k	$-C_6H_5$	–COOMe	120	80

[a]All the yields refer to isolated chromatographically pure compounds. All the assigned structure have been confirmed by spectroscopic data.

the yield is low presumably due to the formation of a polymeric material, the yields in general are very high. Also when 2,4-dinitrotoluene was treated with 4-nitrosotoluene in the presence of lithium bromide under microwave irradiation, the imine **3** was isolated as the sole product, but literature[21,22] reports suggest exclusive formation of nitrone **4** when carried out in the presence of KOH. To check the reaction rate improvements, the thermal reaction was also carried out without microwave energy in the solid state. The reaction proceeds similarly, but the completion time is 25–30 min longer and the yield is not satisfactory (see Experimental). Further, increased, reaction time gave no significant improvement in yields; rather, decomposition of products occurred. Without lithium bromide, the reaction did not proceed at all.

In conclusion, a new catalyst for Ehrlich-Sachs reaction under neutral condition without solvent has been developed. It offers significant improvement over the existing procedures and gives various adducts in a shorter reaction time with good yield.

EXPERIMENTAL

M.p.s were taken in open capillary tubes on a Büchi melting point apparatus and were uncorrected. IR spectra were recorded as KBr discs on a Perkin-Elmer 237B IR spectrometer. Microanalyses were performed on a

Perkin-Elmer 240C analyser. The ^1H NMR spectra were recorded at Varian T-60 machine using tetramethylsilane (TMS) as the internal standard. The chemical shifts are recorded as δ values. All the chemicals were purified by distillation or crystallization prior to use.

Lithium Bromide Catalyzed Condensation Between Active Methylene Group and Aromatic Nitroso Compounds Under Thermolytic Condition

N,N-Dimethyl-4-nitrosoaniline (**1a**, Ar = $C_6H_4NMe_2$-p, 1.50 g, 0.01 mol) was finely mixed with benzyl cyanide (**2a**, 1.17 g 0.01 mol) and placed in a 100- mL round-bottomed flask fitted with a condenser. LiBr was added (0.43 g 5 mmol). The reaction mixture was heated to 80°–90°C in an oil bath for 30 min. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was cooled to room temperature and washed with water. The organic layer was extracted with CH_2Cl_2 (2 × 30 mL), dried over anhydrous Na_2SO_4, and the solvent was distilled off to obtain crude product. Chromatography (pet. Ether/$CHCl_3$ 4:1) gives the imine **3a** in 55% yield. Other nitrosoarenes reacted similarly and the corresponding imines **3b–k** were obtained in 45–56% yields. All the compounds obtained were characterized by spectroscopic data and finally by comparison with authentic samples prepared by following literature procedure.

Lithium Bromide Catalyzed Condensation Between Active Methylene Group and Aromatic Nitroso Compounds Under Microwave Irradiation in a Solvent-Free Condition

N,N-Dimethyl-4-nitrosoaniline (**1a**, Ar = $C_6H_4NMe_2$-p, 1.50 g 0.01 mol), benzyl cyanide (**2a**, 1.17 g, 0:01 mol), and LiBr (0.43 g, 5 mmol) were mixed in an Erlenmeyer flask and placed in a commercial microwave oven (operating at 2450 MHz frequency and 70 Watt). The reaction mixture was irradiated for 2 min, allowed to cool to room temperature, washed with water, and extracted with CH_2Cl_2 (2×34 mL). Removal of solvent and purification by column chromatography of the residue using pet.ether/$CHCl_3$ (4:1) as eluent, afforded exclusively the imine **3a** in 90% yield (entry 1) without the formation of any N-oxide **4**. Crystallization from EtOH gave the pure imine, red crystals m.p. 90°C (lit.[19,20] m.p. 91°C in 90%). Similar treatment of other nitrosoarenes under identical conditions gave the corresponding imines in 80–90% yields, as summarized in Table 1. All the imines obtained were characterized by comparison with authentic samples and by spectroscopic data, which are recorded here, 3a, m.p. 90.4°C lit.[7] m.p. 91 °C, ^{1}H NMR 2.20 (s, 6H, NMe_2), 7.02–7.32 (m, 9H, ArH). IR (KBr); 2130 cm^{-1}. MS m/e 249 (M^+) Anal. calc. (found) for $C_{16}H_{15}N_3$ C, 77.11(77.16); H, 6.02(6.12); N, 16.86(16.94). **3b**, m.p.127°C, lit.[19,20] m.p. 128°C, ^{1}H NMR 2.10 (s, 3H, CH_3), 7.6–7.36 (m, 10H, ArH & NH). IR (KBr): 2130 cm^{-1}. MS m/e 235 (M^+). Anal. calc. (found) for $C_{15}H_{13}N_3$; C, 76.59(76.64); H, 5.53(5.61); N, 17.87(17.78). **3c**, m.p. 170°C, lit.[19,20] m.p. 170°C, ^{1}H NMR 7.10–7.42 (m, 10H, ArH). IR (KBr): 2135 cm^{-1}. MS m/e 206 (M^+), Anal. calc. (found) for $C_{14}H_{10}N_2$: C, 81.55(81.46); H, 4.85(4.96); N, 13.59(13.64). **3d**, m.p. 162°C, lit.[23] m.p.. 160°–167°C, ^{1}H NMR 2.12 (s, 6H, NMe_2) 7.04–7.32 (m, 4H, ArH). IR (KBr): 2125 cm^{-1}. MS *m/e* 198 (M^+). Anal. calc. (found) for $C_{11}H_{10}N_4$; C, 66.66(66.74); H, 5.05(5.13); N, 28.28(28.19). **3e** m.p. 91°C, lit.[24] m.p. 91°C, ^{1}H NMR 2.20 (s, 6H, NMe_2), 1.10 (t, 3H, CH_2CH_3), 4.12 (q, 2H, CH_2CH_3,) 6.98–7.26 (m, 4H, ArH). IR (KBr): 2130 cm^{-1} MS m/e 245 (M^+). Anal. calc. (found) for $C_{13}H_{15}N_3O_2$; C, 63.67(63.76); H, 6.12(6.24); N, 17.14(17.22). **3f** m.p. 126°C, lit.[25] m.p. 126°–27°C, ^{1}H NMR 2.12 (s, 6H, NMe_2), 7.02–7.36 (m, 9H, ArH). IR (KBr): 2135 cm^{-1}. MS m/e 277 (M^+). Anal. calc. (found) for $C_{17}H_{15}N_3O$; C, 76.64(76.55); H, 5.41(5.46); N, 15.16(15.26). **3g**, m.p. 223°C, lit.[23] m.p. 223°C, ^{1}H NMR 2.16 (s, 6H, NMe_2), 7.10–7.42 (m, 4H, ArH). IR (KBr): 2130 cm^{-1}. MS m/e 216 (M^+). Anal. calc. (found) for $C_{11}H_{12}N_4O$; C, 61.11(61.22); H, 5.55(5.63); N, 25.92(25.99). **3h**, m.p. 160°C, lit.[23] m.p. 160°C, ^{1}H NMR 2.12 (s, 6H, NMe_2), 7.04–7.42 (m, 10H, ArH & NH), IR (KBr): 2135 cm^{-1}. MS M/e 292 (M^+). Anal. calc. (found) for $C_{17}H_{16}N_4O$; C, 69.86(69.91); H, 5.48(5.59); N, 19.17(19.19). **3i**, m.p. 148°C ^{1}H NMR 1.62 (s, 3H, CH_3), 2.16 (s, 6H, NMe_2) 7.12–7 45 (m, 8H, ArH). IR (KBr): 2130 cm^{-1}. MS m/e 263 (M^+). Anal. calc. (found) for $C_{17}H_{17}N_3$; C, 77.56(77.48); H, 6.46(6.56); N, 15.97(16.05).3j m.p. 77°C, lit.[27] m.p. 76°–79°C. ^{1}H NMR. 2.86 (s, 3H, CH_3), 7 12–7.38 (m, 5H, ArH). IR (KBr): 2135 cm^{-1}. MS m/e 299 (M^+). Anal. calc. (found) for $C_{20}H_{17}N_3$; C, 80.26(80.35); H, 5.68(5.73); N, 14.04(14.18). **3k**, m.p. 159°C, lit.[24] m.p. 159°C, ^{1}H NMR 2.18 (s, 6H, NMe_2), 7.02–7.48 (m, 12H, ArH). IR (KBr): 2130 cm^{-1}. MS m/e 188 (M^+). Anal. calc. (found) for $C_{10}H_8N_2O_2$; C, 63.82(63.76); H, 4.25(4.35); N, 14.88(14.94).

REFERENCES

1. Ehrlich, P.; Sachs, F. Ber. **1899**, *32*, 1179.
2. Kröhnke, F.; Kröhnke, G. Chem. Ber. **1958**, *91*, 1474.
3. Colonna, M. Gazz. Chim. Ital. **1960**, *90*, 117.

4. Horner, L.; Hoffmann, H.; Wippel, H.G.; Klahre, G. Chem. Ber. **1959**, *92*, 2499.
5. Kröhnke, F.; Kröhnke, G.; Chem. Ber. **1958**, *91*, 1474.
6. Layer, R.W. Chem. Rev. **1963**, *63*, 489.
7. Smith, P.A. In *Open Chain Nitrogen Compounds*; Benjamin: New York, **1965**; vol. 1, 327–336.
8. Dayagi, S.; Degani, *Y. The Chemisry of the Carbon-Nitrogen Double Bond*; Patai, S., Ed.; Interscience: New York, **1970**; 61–147.
9. Assam, R.C. Proc. Egypt Acad. Sci. **1953**, *9*, 89–95; Chem Abstr., **1956**, *50*, 16685.
10. Sain, B.; Sandhu, J.S. Heterocycl. **1987**, *777*.
11. Prajapati, D.; Mahajan, A.R.; Sandhu, J.S. J. Chem. Soc. Perkins Trans 1 **1992**, 1821.
12. Baruah, B.; Prajapati, D.; Sandhu, J.S. Tetrahedron Lett. **1995**, *36*, 6747.
13. Cruz, P.; Hoz, A.; Langa, F.; Illescas, B.; Martin, N. Tetrahedron **1997**, *53*, 2599.
14. Majdoub, M.; Loupy, A.; Peter, A.; Roudesli, M.S. Tetrahedron **1996**, *52*, 617.
15. Caddick, S. Tetrahedron **1995**, *51*, 10403.
16. Mingos, D.M.; Baghurst, D.R. Chem. Soc. Rev. **1991**, *20*, 1–47.
17. Giguere, R.J. Organic Synthesis: Theory and Application; JAI Press: **1989**, Vol. 1, 103.
18. Bose, A.K.; Manhas, M.S.; Ghosh, M.; Shah, M.; Raju, V.S.; Bari, S.S.; Newaz, S.N.; Banik, B.K.; Choudhury, A.G.; Borakat, K.J. J. Org. Chem. **1991**, *56*, 6968.
19. Barrow, F.; Thorneyeroft, F.J. J. Chem. Soc. **1939**, 769–773.
20. Chardonnens, L.; Heinrich, P. Helv. Chim. Acta. **1939**, *22*, 1471.
21. Tananescu, J.; Nabu, J. Ber. **1942**, *75*, 650.
22. Tananescu, J.; Nabu, J. Ber. **1942**, *75*, 1287.
23. Kröhnke, F. Chem. Ber. **1950**, *83*, 50–59.
24. Kröhnke,, F.; Stevernagel, H.H. Ber. **1963**, *96*, 486–493.

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