Asian Journal of Chemistry; Vol. 24, No. 10 (2012), 4675-4678

ASIAN JOURNAL OF CHEMISTRY

www.asianjournalofchemistry.co.in

Molten Ammonium Salt As a Solvent for Menschutkin Quaternization Reaction (Synthesis of Ionic Liquids) and Other Heterocyclic Compounds

GAURAV R. GUPTA[1], GANESH R. CHAUDHARI[1], PREETI A. TOMAR[2], GOVINDA P. WAGHULADE[3] and KESHAR SINGH J. PATIL[4,*]

[1]Department of Chemistry, M.J. College, Jalgaon-425 001, India
[2]JSPM's Rajashri Shahu College of Engineering, Pune-411 027, India
[3]D.D. Bhole College, Bhusawal-425 201, India
[4]School of Chemical Sciences, North Maharashtra University, Jalgaon-425 001, India

*Corresponding author: E-mail: patilkesharsingh@hotmail.com

(*Received*: 24 August 2011; *Accepted*: 11 May 2012) AJC-11466

An efficient one pot synthesis of ionic liquids (ILs) employing molten salt as a solvent is described. The imidazolium salts and pyridinium bromide and other heterocyclic compounds were synthesized using tetrabutylammonium halides as ionized solvents when melt. The yields were good and compounds were confirmed by their mass and spectral data. The utility of the method as a green one is suggested by comparing yield and kinetic time requirements with other known well established methods.

Key Words: Ionic liquids, Ionized solvents, Menschutkin quternization reaction, 2,4,5-Triarylimidazole, *bis*(indolyl)methanes.

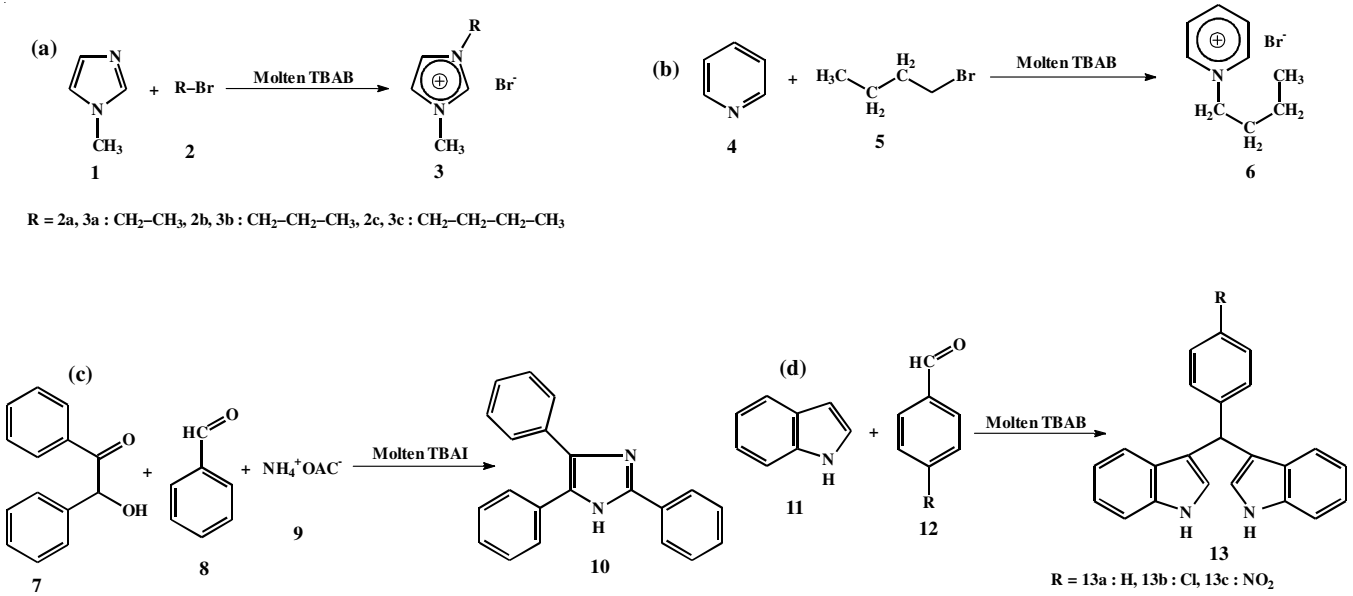
INTRODUCTION

Menschutkin[1] recognized the importance of solvents to chemical reactivity before the turn of the century and the reaction which bears his name has provided much information on how the solvents can affect the rates of reaction[2]. Menschutkin reaction is a process of central importance in biochemistry and a widely used strategy in organic synthesis; it is the reaction generally used to prepare ionic liquids[3]. Ionic liquids are the liquid electrolytes composed entirely of ions[4]. During the past decade, ionic liquids have attracted increasing attention as a neoteric solvent[5] an older material finding new applications as a solvent in chemistry. Chemists first discovered the earliest generation of ionic liquids then termed molten salt. Currently it may seem that the difference between ionic liquids and molten salts is just a matter of degree (literally)[6] .

Systematic exploration of the role of fused salts in organic chemistry is of recent date to the late development of the fundamentals of fused-salt chemistry itself. The bulk of our knowledge of inorganic melts has evolved since about 1950. Organic applications are limited by the high freezing point and low solvent power for organic nonelectrolytes displayed by liquid inorganic salts. Molten salts have long been known in the family of quaternary ammonium salts.

MacFarlane and co-workers[7] cited the pioneering work by Gordon and Subba Rao, which manifest that the total number of carbons as well as the symmetry of the quaternary ammonium cation effectively elucidate the melting point of a molten salt of the quaternary ammonium cation. In their comprehensive book Charlot and Tremillon, reported that some of the quaternary ammonium salts which in the melt state behaves like an ionized solvent[8]. Successful utilization of these ionized solvent (molten tetrabutylammonium bromide) in the synthesis of palladium nanoparticles was reported by Bras and co-workers[9] and also the significant role of molten tetrabutylammonium bromide in thioacetalization of acetals was pointed out by Ranu *et al.*[10] .

Notwithstanding the numerous advantages of ionic liquids as a reaction media for catalytic processes widespread industrial applications have not yet been forthcoming. The reason for this probably is related to their relatively high prices. In this article, we report an efficient, one pot synthetic methodology which has been designed and adopted for Menschutkin quaternization reaction. In other words a strategy for the synthesis of 1-ethyl-3-methylimidazolium bromide [(emim)(br)], 1-methyl-3-propylimidazolium bromide [(prmim)(br)], 1-butyl-3-methylimidazolium bromide [(bmim)(br)], N-butylpyridinium bromide [(bpy)(br)], 2,4,5-triarylimidazole and *bis*(indolyl)methanes compounds, (the synthesis of ionic liquids) employing molten salt as a solvent is described. As a preliminary our search was aimed to find if molten quaternary ammonium salt (ionized solvent) acts as an effective solvent for Menschutkin quaternization reaction (**Scheme-I**) of 1-methylimidazole and pyridine with alkyl halides in the



Scheme-I: (a) synthesis of 1,3-dialkylimidazolium bromide. (b) synthesis of N-butylpyridinium bromide. (c) synthesis of 2,4,5 triarylimidazole. (d) synthesis of *bis*(indolyl)methanes

synthesis of [emim][br], [prmim][br], [bmim][br] and [bpy][br], further utilizing the technique, the synthesis of 2,4,5-triaryl-imidazole and *bis*(indolyl) methanes derivatives was also accomplished. During the course of the reaction, temperature required to melt tetrabutylammonium bromide (*i.e.*, 110 115 ºC) is higher than the boiling temperature of the reactants (particularly alkyl halides). Thus, to avoid the loss in reaction mass gradual addition of the reactants through the water condenser has been adopted. The synthesis of heterocycles proceeded *via* direct addition of the reactants to the molten tetrabutyl-ammonium halide. In addition to that work on other derivatives of indole using the same methodology is underway.

EXPERIMENTAL

All commercially available reagents were used without further purification Chemical shifts of ^{1}H (300 MHz) spectra were recorded in ppm (δ), using a Varian Mercury YH300 instrument. Mass spectra were recorded using and GC-MS/MS set ups having triple quadruple detection system.

General procedure for Menschutkin quaternization of 1-methylimidazole and pyridine adopted involves the followings: (a) A stirred solution of 1-methylimidazole (30 mmol) and alkyl halide (30 mmol) was gradually added to molten tetrabutylammonium bromide. [Caution:alkyl halide is volatile in nature; to avoid explosion, make additions in portions through water condenser]. After addition, the reaction mixture was cooled to room temperature and ethyl methyl ketone was added. The resulting mixture separated in two layers, which were then separated; after washing with excess ethyl methyl ketone, the products were collected and transferred to vaccume oven for drying. Here the ethyl methyl ketone plays a significant role to separate the ionic liquid from the reaction mixture because all the reactants including catalyst were soluble in ethyl methyl ketone but the product is immiscible in ethylmethylketone. Solvents like acetonitrile. Chloroform, ethanol, methanol, THF give a homogeneous solution (no separation was achieved).

The product obtained were identified ^{1}H NMR spectra by comparison with the data reported in literature or with those of authentic samples[11]. LC-MS/MS* study was done to confirm molecular weights of the products. The interpretations of LC-MS/MS results for the synthesised compounds are consistent with the observations made by Bortoloini *et al.*[12] for the characterization of 1-ethyl-3-methylimidazolium bromide and 1-butyl-3-methylimidazolium bromide.

1-Ethyl-3-methylimidazolium bromide: FTIR (NaCl plates, cm^{-1}): 3439, 2978-2831, 1643-1462 (C=N), 1087 (C-N), 752. ^{1}H NMR (300 MHz, D_2O): δ =1.54 (t, 3H, -CH_3), 3.91 (s, 3H, -N-CH_3), 4.26 (q, 2H, -N-CH_2), 7.44-7.50 (d, 2H, -N-CH-CH-N-), 8.73 (s, 1H, -N-CH-N-). LC-MS/MS (methanol): 242.7 Da → 100.2 Da.

*The m/z data obtained through LC-MS/MS and GC-MS/MS, were found to be in agreement with that visualised on the basis of structures of 2,4,5-triarylimidazole and [bpy][br] compounds (molecular weights are 296.3 and 136.1, respectively). The m/z ratios for [bmim][br] found here also in agreement with structural data, involving initially the loss of bromide ion and subsequently the side chain carbon skeleton. However, the situation is more complex in the case of [emim][br] and [prmim][br]. We observed from the spectra that the m/z ratio peaks occurred at 142.2 and 100.2, respectively. The studies of these compounds were performed in methanol. Therefore, we propose that during ionisation, there is a rearrangement of the electronic charge around the nitrogen centre, making it quaternary rather than tertiary due to its interaction with MeOH. The resultant fragmentation pattern of the products indicates the incorporation of the solvent molecule and it exceeds the m/z value by 32 in the case of [emim][br]. However, due to the structural effect, the incorporation of the solvent molecule is observed in [prmim][br] after the subsequent loss of a methyl radical. The detailed mechanism of the fragmentation pattern for the studied ionic liquids will be published separately.

1-Propyl-3-methylimidazolium bromide: FTIR (NaCl plates, cm^{-1}): 3313, 2962-2874, 1614-1427 (C=N), 1089 (C-N), 738. ^1H NMR (300 MHz, D_2O): δ= 0.93 (t, 3H, $-CH_3$), 1.90 (m, 2H, $-CH_2-CH_3$), 3.92 (s, 3H, $-N-CH_3$), 4.19 (t, 2H, $-N-CH_2$), 7.46-7.51 (d, 2H, -N-CH-CH-N-), 8.75 (s, 1H, -N-CH-N-). LC-MS/MS (methanol): 242.3 Da → 142.2 Da.

1-Butyl-3-methylimidazolium bromide: FTIR (NaCl plate, cm^{-1}): 3429, 3074-2935, 1568 C=N), 1087 (C-N), 756. ^1H NMR (300 MHz, D_2O): δ = 0.98 (t, 3H, $-CH_3$), 1.38 (m, 2H, $-CH_2-CH_2-CH_3$), 1.89 (m, 2H, $-CH_2-CH_2-CH_2-$), 3.93 (s, 3H, $-N-CH_3$), 4.24 (t, 2H, $-N-CH_2$), 7.48-7.53 (d, 2H, -N-CH-CH-N-), 8.77 (s, 1H, -N-CH-N-). LC-MS/MS (methanol): 139.2 Da → 42.5 Da.

A stirred solution of pyridine (100 mmol) and N-butyl bromide (100 mmol) was slowly added to molten tetrabutylammonium bromide. [Caution:alkyl halide is volatile in nature; to avoid explosion, make additions in portions through water condenser]. After this addition, the reaction mixture was cooled to room temperature and had the appearance of a white solid. It was washed with an excess of tetrahydrofuran and the oily white solid of N-butylpyridinium bromide was collected and transferred to vaccume oven for drying. In this case the removal of catalyst was successfully performed by using tetrahydrofuran or benzene. The similar problem mentioned earlier was arrised by using the solvents acetonitrile. chloroform, ethanol, methanol. The product was identified ^1H NMR spectra. LC-MS/MS study was done to confirm molecular weight of the product.

N-Butylpyridinium bromide: FTIR (KBr pellete, cm^{-1}): 3500, 3074-2874, 1633-1487 (C=N), 1028 (C-N), 773. ^1H NMR (300 MHz, D_2O): δ = 1.00 (t, 3H, $-CH_3$), 1.45 (m, 2H, $-CH_2-CH_2-CH_3$), 2.07 (m, 2H, $-CH_2-CH_2-CH_2-$), 4.70 (t, 2H, $-N-CH_2$), 8.15 (t, 2H), 8.62 (t, 2H), 8.93 (t, 2H). LC-MS/MS (methanol): 351.3 Da → 136.1 Da.

General procedure for the synthesis of 2,4,5-triarylimidazole: Using two-necked flasks benzoin (5 mmol), benzaldehyde (10 mmol) and ammonium acetate (20 mmol) were gradually added to the molten tetrabutylammonium iodide (7.5 mmol). The progress of the reaction was monitored by TLC. After completion of the reaction the reaction froth was dissolved into ethanol, which yielded a white solid of 2,4,5-triarylimidazole. The similar condensation reaction was carried out by using molten tetrabutylammonium bromide. However, it was noted that the process is slow and also fails to give satisfactory yield.

The product was identified by ^1H NMR spectra by comparison with the data reported in literature[13]. GC-MS/MS study was done to confirm molecular weight of the product.

2,4,5-Triarylimidazole: m.p. 274-276 ºC. FTIR (KBr pellet, cm^{-1}): 3435 (N-H), 2854 (C-H), 1550 (C=N), 1442 (C=C), 1030 (C-N), 767. ^1H NMR (300 MHz, DMSO): δ = 7.22-7.56 (complicated spectra is observed for three benzene rings), 8.07 (s, 1H). GC-MS/MS: 296.20 Da.

General procedure for the synthesis of *bis*(indolyl)-methanes: The reaction involves the addition of indole (10 mmol) and aldehyde (5 mmol) to molten tetrabutylammonium bromide (5 mmol). Further processing the reaction product with acidified methanol and keeping ice-cold conditions causes the solid *bis*(indolyl)methanes separating out. Purification of the derivatives of *bis*(indolyl)methane: in a 100 mL beaker the solids of *bis*(indolyl)methane was dissolved in dichloromethane, which gives a homogeneous solution, wash the solution with water (*ca.* 10 times), then remove the water layer with the help of separating funnel, anhydrous sodium sulfate was use to dry the layer of dichloromethane. Finally dichloromethane was removed off with the help of rotary evaporator. Results the crystals of *bis*(indolyl)methane.

The products were identified on the basis of physical constant and FTIR[14] values, further characterizations by ^1H NMR and mass spectral study are under progress.

Phenyl-3,3'-*bis*(indolyl)methane: m.p. 124-126 ºC. FTIR (KBr pellet, cm^{-1}): 3414 (N-H), 1618-1417 (aromatic C=C), 1091-1030 (C-N), 798-742.

4-Chlorophenyl-3,3'-*bis*(indolyl)methane: m.p. 74-76 ºC FTIR (KBr pellet, cm^{-1}): 3416 (N-H), 1413 (aromatic C=C), 1093-1018 (C-N), 696-802 (C-Cl).

4-Nitrophenyl-3,3'-*bis*(indolyl)methane: m.p. 222-224 ºC FTIR (KBr pellet, cm^{-1}): 3414 (N-H), 1599-1415 (aromatic C=C), 1344 ($-NO_2$), 1095-1024 (C-N), 802-694.

RESULTS AND DISCUSSION

Tetrabutylammonium bromide is the quaternary ammonium salt with 16 carbon atom and higher symmetry in the cation has melting point of 110-115 ºC. Thermal gravimetric analysis of TBAB manifests that the salt is stable up to 170 ºC.

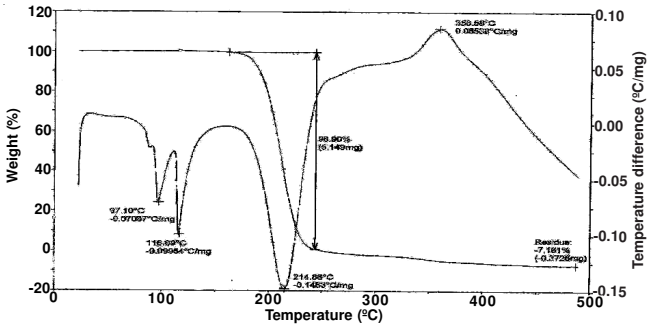


Fig. 1. TGA-DTA analysis of TBAB under nitrogen atmosphere and maintaining heating rate 4 ºC/min

Adopting the **Scheme-I**, we could achieve the synthesis of [emim][br], [prmim][br], [bmim][br] and [bpy][br], 2,4,5-triarylimidazole and *bis*(indolyl)methanes derivatives within very short time (as compared to the methods reported in the literature[15]) *i.e.*, within 0.5 h. The details about the results are summarized in Table-1. Thus, the method is far superior as compared to usual methods used for synthesis of Ils as well as for the synthesis of heterocycles reported in this communication.

It is well known that tetrabutylammonium bromide salts form complexes with urea[16], thus such interaction can cause as interference if the concentration is high. The examination of Table-1 indicates that when the concentration of the catalyst (*i.e.*, is the salt) is far less than the stoichiometric concentration, the product yield is high (in case of 1,3 dialkylimidazolium bromide product **3a**, **3b**, **3c**), which also points out that the catalyst at high concentrations probably interact with the reactants. The situation is similar however, it seems that some critical concentration of the salt in terms of stoichiometry is needed, although less than that of 1:1 stoichiometric concentration to achieve maximum yield of the product for (bpy)(br)

TABLE-1
SCOPE AND LIMITATIONS OF MOLTEN AMMONIUM SALTS AS A SOLVENT FOR SYNTHESIS OF IONIC LIQUID AS WELL AS DERIVATIVES OF HETEROCYCLES

Entry	Substrate			Product	Catalyst (mmol)[a]	t (min)[b]	Yield (%)
1	1	2a	–	3a	20	30	55
–	–	–	–	–	10	30	69
–	–	–	–	–	7.5	30	80
–	–	–	–	–	5	30	70
2	1	2b	–	3b	15	30	59
–	–	–	–	–	10	30	89
–	–	–	–	–	7.5	30	93
–	–	–	–	–	5	30	86
3	1	2c	–	3c	15	30	22
–	–	–	–	–	10	30	37
–	–	–	–	–	7.5	30	52
–	–	–	–	–	5	30	88
4	4	5	–	6	20	30	90
–	–	–	–	–	15	30	65
–	–	–	–	–	10	30	38
5	7	8	9	10	7.5*	50	58
6	11	12a	–	13a	5	30	74
–	–	12b	–	13b	5	30	78
–	–	12c	–	13c	5	30	83

1 = N-Methylimidazole, 2 = alkyl halide, 3a = 1-ethyl-3-methylimidazolium bromide, 3b = 1-methyl-3-propylimidazolium bromide, 3c = 1-butyl-3-methylimidazolium bromide, 4 = pyridine, 5 = *N*-butyl bromide, 6 = N-butylpyridinium bromide, 7 = benzoin, 8 = benzaldehyde, 9 = ammonium acetate, 10 = 2,4,5-triarylimidazole, 11 = indole, 12a = benzaldehyde, 12b = *p*-chlorobenzaldehyde, 12c = *p*-nitrobenzaldehyde.
[a]TBAB, *TBAI, [b]time required for completion of the reaction.
Concentrations of reactants; 1-30 mmol, 2a,2b,2c- 30 mmol, 4,5 – 100 mmol, 7 – 5 mmol, 8-10 mmol, 9-20 mmol, 11-10 mmol, 12-5 mmol.

(product 6). Synthesis of 2,4,5-triarylimidazole and *bis*(indolyl)methanes were carried out at a fix concentration of tetrabutylammonium bromide.

Conclusion

Considering the increasing importance of "green chemistry," one pot synthesis and the reuse of the catalyst and solvents are preferable, we have observed in present work that molten ammonium salts accelerate the reactions to a great extent, indicating the importance and balancing of electrostatic interactions. At this point although we are emphasizing that tetrabutylammonium bromide acts as a catalyst, there exists the possibility of autocatalysis by formation of imidazolium ions. If this is true, we may say that ionic (charge) atmosphere for electrostatic interaction is provided by the molten salt solvent system. However, there is a need to have deeper analysis to establish these catalytic and autocatalytic effects.

The above suggested methodology points out that the synthesis are accomplished by avoiding several hours heating conditions, neither practicing volatile carcenogenous solvents, nor having expensive catalyst. Therefore the method offers a greener, cost effective and convenient strategy for the Menschutkin quaternization of 1-methyliomidazole and pyridine and also for compounds like 2,4,5-triarylimidazole and *bis*(indolyl)-methanes, which we could able to synthesize successfully.

ACKNOWLEDGEMENTS

The authors are thankful to Dr. V.P. Dhande for valuable guidance, as well as Mr. A.G. Rao Principal of M.J. College, Jalgaon and Dr. D.G. Hundiwale from the School of Chemical Sciences, North Maharashtra University, Jalgaon for encouragement and facilities.

REFERENCES

1. M.R.J. Dack, In Solutions and Solubilities, John Wiley & Sons, INC, p. 105 (1976).
2. (a) C. Reichardt, In Solvents and Solvent Effect in Organic Chemistry, Willey-VCH, pp. 167, 230 (2003); (b) E.D. Amis, In Solvent Effects on Reaction Rates and Mechanisms, Academic Press; New York and London, p. 133 (1966).
3. R. Bini, C. Chiappe, C.S. Pamelli and B. Parisi, *J. Org. Chem.*, **74**, 8522 (2009).
4. J. Dupont, R.F. Desouza and A.Z.S. Paulo, *Chem. Rev.*, **102**, 3667 (2002).
5. N.V. Plechkova and K.R. Seddon, In eds.: T. Pietro, P. Alvise and Z. Fulvio, In Methods and Reagents for Green Chemistry, John Willey & Sons, INC., p. 112 (2007).
6. J.S. Wilkes, *Green Chem.*, **4**, 73 (2002).
7. J. Sun, M. Forsyth and D.R. MacFarlane, *J. Phys. Chem. B*, **102**, 8858 (1998).
8. G. Charlot and B. Tremillon, In ed.: P.J.J. Harvey, In Chemical Reactions in Solvents and Melts, Pergamon Press; Oxford, p. 439 (1969).
9. J.L. Bras, D.K. Mukherjee, S. Gonzalez, M. Tristany, B. Ganchegui, M.M. Manas, R. Pleixats, F. Henin and J. Muzar, *New J. Chem.*, **28**, 1550 (2004).
10. B.C. Ranu, A. Das and S. Samanta, *J. Chem. Soc, Perkin Trans. I*, 1520 (2002).
11. E.R. Parnham and R.E. Morris, *Chem. Mater.*, **18**, 4882 (2006).
12. O. Bortolini, M. Bottai, C. Chiappe, V. Conte and D. Pieraccini, *Green Chem.*, **4**, 621 (2002).
13. (a) J.N. Sangshetti, N.D. Kokare, S.A. Kotharkara and D.B. Shinde, *J. Chem. Sci.*, **120**, 463 (2008); (b) M. Kidwai, P. Mothsra, V. Bansal and R. Goyal, *Monatsh. Chem.*, **137**, 1189 (2006).
14. R.G. Vaghei, H. Veisi, H. Keypour and A.A.D. Firouzabadi, *Mol. Divers*, **14**, 87 (2010).
15. (a) A.K. Burrell, R.E. Del Sesto, S.N. Baker, T.M. McCleskeya and G.A. Baker, *Green Chem.*, **9**, 449 (2007); (b) J. Dupont, C.S. Consorti, P.A.Z. Suarez and R.F. deSouza, *Org. Synth.*, **10**, 184 (2004).
16. S. Saito, M. Lee and W. Wen, *J. Am. Chem. Soc.*, **88**, 5107 (1966).