Tetrahedron Vol. 45, No. 3, pp. 629 to 636, 1989
Printed in Great Britain.

0040-4020/89 $3.00+.00

USE OF HEXAMETHYLPHOSPHORAMIDE (HMPA) IN THE ALKYLATION OF AROMATIC AMINES: SYNTHESIS OF AZETIDINES, PYRROLIDINES, PIPERIDINES AND HEXAHYDROAZEPINES

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(*Received in USA* 2 *August* 1988)

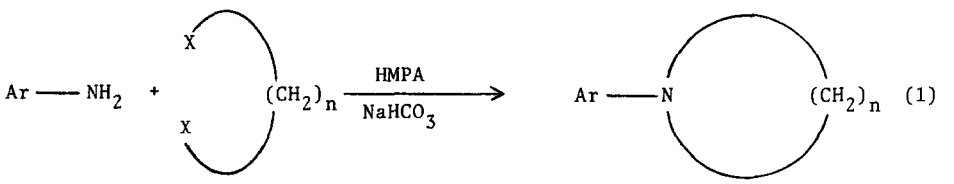
ABSTRACT

The direct alkylation of p-toluidine, as a model of aromatic amines, with 1,3-, 1,4-, 1,5- and 1,6-ditosylates, -dibromides or -dimesylates in HMPA as solvent affords the corresponding cyclic amines. The convenience of this reaction and some observed limitations are discussed.

INTRODUCTION

The speed of cyclic-amine formation from open-chain precursors varies markedly in the ring-size order 5 > 3 > 6 > 7 > 4.[1] The slower rate of four-membered ring formation is attributed to the less favorable enthalpy of activation since the entropy of activation is the same for three- and four-membered amines.[2] Nevertheless the azetidine nucleus has been found to convey interesting pharmacological properties to organic molecules,[3,4] and the development of synthetic routes to the azetidines is therefore a rewarding endeavor.

In this respect, the preparation of N-arylazetidines has proven particularly challenging since methods allowing for the alkylation of open-chain amines are thwarted by the decreased reactivity of aromatic amines toward alkylating agents due to the delocalized nature of the nitrogen lone pair of electrons. However, HMPA has been used recently as solvent in the mono- and dialkylation of anilines,[5,6] and this suggested that N-arylazetidines, -pyrrolidines, -piperidines and -hexahydroazepines could be prepared by the direct dialkylation of aromatic amines (Eq. 1).



(1)

RESULTS AND DISCUSSION

A. N-Arylazetidines. Table I summarizes the results from the reaction of p-toluidine (as a model for aromatic amines) and 2-substituted 1,3-propanediol ditos-

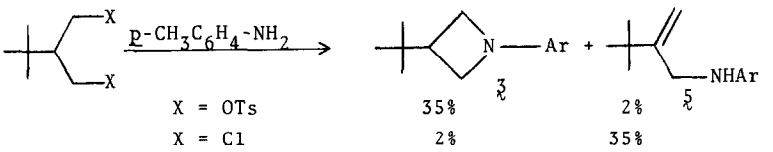
ylates. Although the yields are not uniformly good, they seem to compare favorably with the other methods described in the literature.[7]

Table I. Reaction of p-Toluidine with 2-Substituted 1,3-Propanediol Ditosylates or Dimesylates in HMPA as Solvent.

R	X	T(°C)	Reaction Time (h)	Azetidine	Isolated Yield (%)
Et	OTs	reflux	16	1	99.6[a]
Me	OMs	130	9	2	58.0
t-Bu	OTs	130	10	3	35.0
C_6H_5	OTs	130	6	4	25.0
C_6H_5	OMs	130	6	4	29.1

[a]This experiment was performed by J.D. Reyna, see reference 5c.

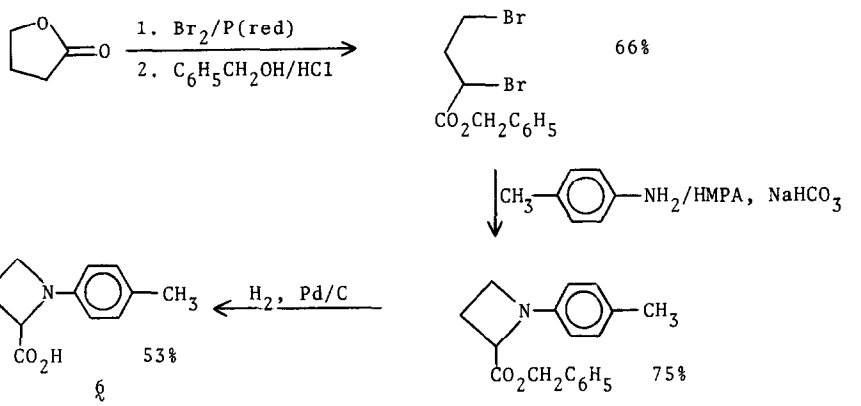
In general, dihalides afforded lower yields of the desired azetidines due mainly to competitive elimination reactions (Eq. 2). However, (±)-1-p-tolyl-2-



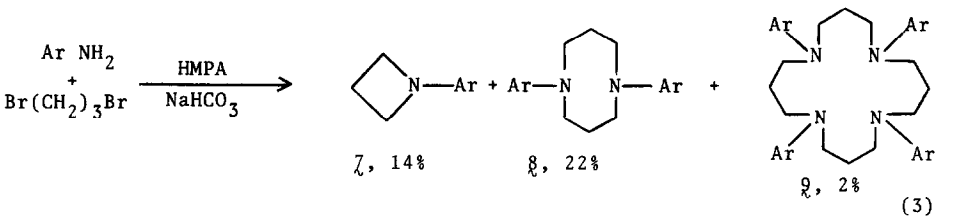
(2)

-azetidinecarboxylic acid could be prepared in good yield according to the sequence shown in Scheme I.[8]

Scheme I.



The reaction of p-toluidine with 1,3-propanediol ditosylate afforded the expected azetidine in a scanty 14% isolated yield. This reaction was complicated by polymerization of the monoalkylated intermediate, as evidenced by the isolation of cyclic diamine and tetramine (Eq. 3).[9]

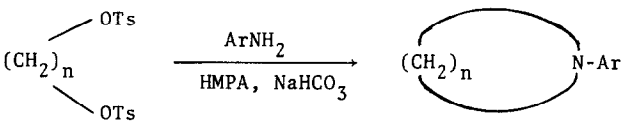


7, 14% 8, 22% 9, 2%

(3)

B. N-Aryl-Pyrrolidines, -Piperidines and -Hexahydroazepines. These five-, six- and seven-membered derivatives were prepared in good isolated yields as indicated in Scheme II.

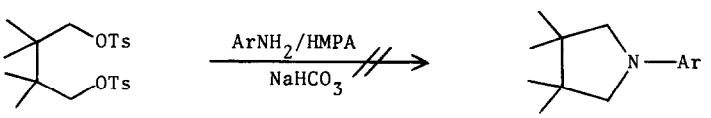
Scheme II[a].



10, n = 4, 77%
11, n = 5, 57%
12, n = 6, 53%[b]

[a] Ar = p-CH_3-C_6H_4. [b] 1,6-Diamine was also isolated in 14% yield.

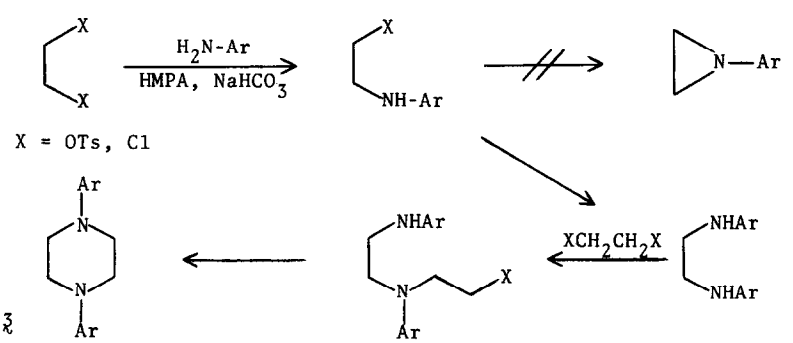
On the other hand, the displacement reaction of the neopentylic tosylates in 2,2,3,3-tetramethyl-1,4-butanediol ditosylate[10] was not successful (Eq. 4).



(4)

C. Attempted Preparation of N-Aryl-aziridines. p-Toluidine was treated with 1,2-ethanediol ditosylate or 1,2-dichloroethane in an attempt to obtain N-(p-tolyl) aziridine; N,N'-bis(p-tolyl)piperazine was formed instead (Scheme III).

Scheme III.



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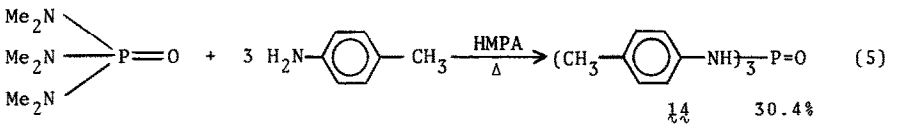
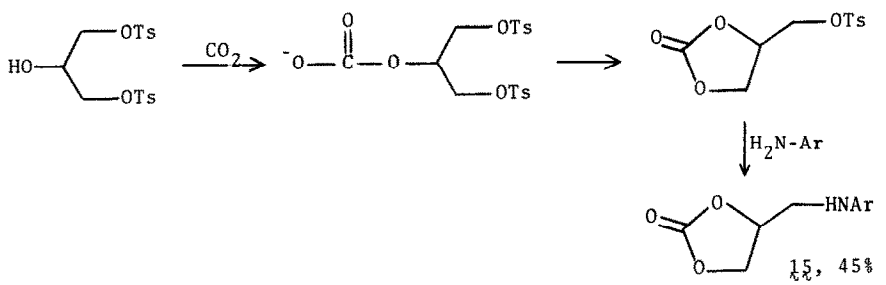
D. Reaction Temperature. In spite of the fact that HMPA is remarkably stable to nucleophiles,[11] attack by the aniline was observed under refluxing conditions. Indeed, complete substitution of the dimethylamino groups was attained from the reaction of HMPA with three equivalents of p-toluidine, at reflux for 10 hours (Equation 5). This undesirable reaction does not appear to take place at 130°C, which was then adopted as the optimal reaction temperature.



(5)

Another side reaction was observed when 2-hydroxy-1,3-propanediol-ditosylate was treated with p-toluidine at the boiling temperature of HMPA, in presence of $NaHCO_3$: a carbonate was isolated in 45% yield, which probably originates from the reaction with CO_2 generated from thermal decomposition of $NaHCO_3$.[12] (Scheme IV).

Scheme IV.



EXPERIMENTAL

General Procedure. The amine (p-toluidine, 1.0 g, 9.34 mmol) was placed in a 100-mL round-bottomed flask and dissolved in 30-50 mL of dry HMPA (Caution: cancer suspect agent, handle with care). A 100% excess of sodium bicarbonate was added, as well as the ditosylate, dimesylate or dihalide (9.34 mmol), and then the reaction mixture was stirred under nitrogen at 130°C. The reaction was monitored by tlc [hexane-ethyl acetate (90:10)] and the product extracted with ether and concentrated. Purification of the product was achieved by flash chromatography, followed by distillation in a Kugelrohr apparatus or recrystallization.

Spectroscopic Properties of the Cyclic Amines.

3-Ethyl-N-(p-tolyl)azetidine (1). Boiling point: 50-53°C/0.2 mm. ^{1}H NMR ($CDCl_3$, 90 MHz) δ: 0.89 (t, J = 7 Hz, 3 H, CH_3CH_2), 1.62 (dq, J = J' = 7 Hz, 2 H, CH_3CH_2), 2.27 (s, 3 H, CH_3Ar), 2.68 (ttt, J ≈ J' ≈ J" ≈ 7 Hz, 1 H, Et-CH), 3.40 (dd, J ≈ J' ≈ 7 Hz, 2 H, $H_{2,4eq}$), 3.93 (dd, J ≈ J' ≈ 7 Hz, 2 H, $H_{2,4ax}$), 6.36 (d, J = 8.7 Hz, 2 H, H_{ortho}), 7.0 (d, J = 8.7 Hz, 2 H, H_{meta}). ^{13}C NMR ($CDCl_3$, 22.49 MHz) δ: 11.39 (CH_3CH_2), 20.43 (CH_3Ar), 27.47 (CH_3CH_2), 32.10 (Et-CH), 57.54 ($C_{2,4}$), 111.31 (C_{ortho}), 125.94 (C_{para}), 129.18 (C_{meta}), 150.05 (C_{ipso}). Mass spectrum, m/e: 175 (M^+), 119 (M^+-56), 91 (M^+-84).

3-Methyl-N-(p-tolyl)azetidine (2). Boiling point: 75-80°C/0.3 mm. ^{1}H NMR ($CDCl_3$, 90 MHz) δ: 1.25 (d, J = 7 Hz, 3 H, CH_3C), 2.27 (s, 3 H, CH_3Ar), 2.85 (m, 1 H, CH_3CH), 3.40 (dd, J = J' = 7 Hz, 2 H, $H_{2,4eq}$), 3.98 (dd, J = J' = 7 Hz, 2 H,

$H_{2,4ax}$), 6.30 (d, J = 9 Hz, 2 H, H_{ortho}), 7.08 (d, J = 9 Hz, 2 H, H_{meta}). ^{13}C NMR ($CDCl_3$, 22.49 MHz) δ: 19.53 ($\underline{C}H_3CH$), 20.36 ($\underline{C}H_3Ar$), 25.30 (C_3), 59.36 ($C_{2,4}$), 111.41 (C_{ortho}), 126.15 (C_{para}), 129.27 (C_{meta}), 150.2 (C_{ipso}). Mass spectrum, m/e: 161 (M^+), 119 (M^+-42), 91 (M^+-70), 65 (M^+-96).

3-t-Butyl-N-(p-tolyl)azetidine (3). Melting point: 77-78°C. ^1H NMR ($CDCl_3$, 90 MHz) δ: 2.24 (s, 3 H, CH_3Ar), 2.57 (m, 1 H, CH), 3.58 (dd, J = J' = 7 Hz, 2 H, $H_{2,4eq}$), 3.80 (dd, J = J' = 7 Hz, $H_{2,4ax}$), 6.39 (d, J = 9 Hz, 2 H, H_{ortho}), 7.05 (d, J = 9 Hz, 2 H, H_{meta}). ^{13}C NMR ($CDCl_3$, 22.49 MHz) δ: 20.41 (CH_3Ar), 26.35 [$(CH_3)_3C$], 30.60 [$(CH_3)_3C$], 41.04 ($CHCH_2N$), 53.22 (CH_2N), 111.34 (C_{ortho}), 126.03 (C_{para}), 129.37 (C_{meta}), 149.91 (C_{ipso}). Mass spectrum, m/e: 203 (M^+), 119 (M^+-84), 91 (M^+-112), 65 (M^+-138).

3-Phenyl-N-(p-tolyl)azetidine (4). Melting point: 97-98.5°C. ^1H NMR (C_6D_6, 90 MHz) δ: 2.24 (s, 3 H, CH_3Ar), 3.35-3.78 (overlapped signals: dd, J = J' = 6 Hz, 2 H, $H_{2,4eq}$ and m, 1 H, PhCH), 3.95 (dd, J = J' = 6 Hz, 2 H, $H_{2,4ax}$), 6.46 (d, J = 9 Hz, 2 H, H_{ortho}), 7.11 (d, J = 9 Hz, 2 H, H_{meta}), 7.18 (s, 5 H, Ph). ^{13}C NMR (C_6D_6, 22.49 MHz) δ: 20.45 (CH_3Ar), 35.28 (C_3), 59.68 ($C_{2,4}$), 111.77 (C_{ortho}), 126.68 (C_{para}), 126.81 ($C_{para'}$), 126.99 ($C_{meta'}$), 128.55 ($C_{ortho'}$), 129.46 (C_{meta}), 142.67 ($C_{ipso'}$), 149.96 (C_{ipso}). Mass spectrum, m/e: 223 (M^+), 119 (M^+-104), 91 (M^+-132), 78 (M^+-145), 65 (M^+-158).

3,3-Dimethyl-2-methylidene-1-N-(p-tolyl)butylamine (5). Melting point: 57-59°C. ^1H NMR ($CDCl_3$, 90 MHz) δ: 1.14 (s, 9 H, $(CH_3)_3C$), 2.20 (s, 3 H, CH_3Ar), 3.52 (s, 1 H, NH), 3.69 (s, 2 H, CH_2N), 4.93 (s, 1 H, C=CHH'), 4.99 (s, 1 H, C=CHH'), 6.38 (d, J = 9 Hz, 2 H, H_{ortho}), 6.87 (d, J = 9 Hz, 2 H, H_{meta}).

N-(p-Tolyl)azetidin-2-carboxylic Acid (6). Viscous oil. ^1H NMR ($CDCl_3$, 90 MHz) δ: 2.23 (s, 3 H, CH_3Ar), 2.59 (m, 2 H, CH_2CH_2N), 3.66 (dt, J ≈ J' ≈ 8 Hz, 1 H, H_{4eq}), 3.99 (dt, J ≈ J' ≈ 7 Hz, 1 H, H_{4ax}), 4.43 (dd, J = J' = 9 Hz, 1 H, $CHCO_2$), 6.5 (d, J = 9 Hz, 2 H, H_{ortho}), 7.05 (d, J = 9 Hz, 2 H, H_{meta}), 7.8 (s, 1 H, CO_2H). ^{13}C NMR ($CDCl_3$, 90 MHz) δ: 20.39 (CH_3Ar), 21.66 (C_3), 50.04 (C_4), 63.74 (C_2), 112.59 (C_{ortho}), 128.68 (C_{para}), 129.41 (C_{meta}), 148.09 (C_{ipso}), 176.42 (CO_2H).

N-(p-Tolyl)azetidine (7). Melting point: 38-39°C (lit.[13] m.p. 38-39°C). ^1H NMR ($CDCl_3$, 90 MHz) δ: 2.14-2.55 (quintet, J = 7 Hz, 2 H, CH_2CH_2N), 2.25 (s, 3 H, CH_3Ar), 3.81 (t, J = 7 Hz, 4 H, CH_2N), 6.40 (d, J = 9 Hz, 2 H, H_{ortho}), 7.05 (d, J = 9 Hz, 2 H, H_{meta}). ^{13}C NMR ($CDCl_3$, 22.49 MHz) δ: 17.07 (C_3), 20.45 (CH_3Ar), 52.70 ($C_{2,4}$), 111.56 (C_{ortho}), 126.46 (C_{para}), 129.36 (C_{meta}), 150.43 (C_{ipso}). Mass spectrum, m/e: 147 (M^+), 119 (M^+-28), 118 (M^+-29), 91 (M^+-56), 65 (M^+-82), 39 (M^+-108).

N,N'-Bis(p-tolyl)-1,5-diazacyclooctane (8). Melting point: 114-115°C. ^1H NMR ($CDCl_3$, 60 MHz) δ: 1.8-2.18 (m, 4 H, CH_2CH_2N), 2.28 (s, 6 H, CH_3Ar), 3.48 (t, J = 6 Hz, 8 H , CH_2N), 6.67 (d, J = 9 Hz, 4 H, H_{ortho}), 7.1 (d, J = 9 Hz, 4 H, H_{meta}). ^{13}C NMR ($CDCl_3$, 22.49 MHz) δ: 20.07 (CH_3Ar), 25.22 (CH_2CH_2N), 48.50 (CH_2N), 111.34 (C_{ortho}), 124.38 (C_{para}), 129.76 (C_{meta}), 145.49 (C_{ipso}). Mass spectrum, m/e: 294 (M^+), 265 (M^+-29), 160 (M^+-134), 146 (M^+-148), 134 (M^+-160), 120 (M^+-174), 119 (M^+-175), 118 (M^+-176), 105 (M^+-189), 91 (M^+-203), 65 (M^+-229).

N,N',N'',N'''-Tetrakis(p-tolyl)-1,5,9,13-Tetraazacyclohexadecane (9). Melting point: 182-183°C. ^1H NMR ($CDCl_3$, 90 MHz) δ: 1.9 (quintet, J = 6 Hz, 8 H, CH_2CH_2N), 2.28 (s, 12 H, CH_3Ar), 3.3 (t, J = 6 Hz, 16 H, CH_2N), 6.7 (d, J = 9 Hz, 8 H, H_{ortho}), 7.07 (d, J = 9 Hz, 8 H, H_{meta}). ^{13}C NMR ($CDCl_3$, 22.49 MHz) δ: 20.24 (CH_3Ar), 26.87 (CH_2CH_2N), 50.19 (CH_2N), 114.24 (C_{ortho}), 126.42 (C_{para}), 129.72 (C_{meta}),

146.88 (C_{ipso}). Mass spectrum, m/e: 588 (M^+), 265 (M^+-323), 187 (M^+-401), 174 (M^+-414), 161 (M^+-427), 160 (M^+-428), 148 (M^+-440), 134 (M^+-454), 120 (M^+-468), 119 (M^+-489), 118 (M^+-470), 105 (M^+-483), 91 (M^+-497).

N-(p-Tolyl)pyrrolidine (10). Melting point: 39-40°C (lit.[14] b.p. 64°C/0.14 mm). ^{1}H NMR ($CDCl_3$, 90 MHz) δ: 1.85-2.11 (m, 4 H, CH_2CH_2N), 2.23 (s, 3 H, CH_3Ar), 3.09-3.40 (m, 4 H, CH_2N), 6.51 (d, J = 9 Hz, 2 H, H_{ortho}), 7.07 (d, J = 9 Hz, 2 H, H_{meta}). ^{13}C NMR ($CDCl_3$, 22.49 MHz) δ: 20.28 (CH_3Ar), 25.40 ($C_{3,4}$), 47.85 ($C_{2,5}$), 111.86 (C_{ortho}), 124.51 (C_{para}), 129.59 (C_{meta}), 146.1 (C_{ipso}). Mass spectrum, m/e: 161 (M^+), 160 (M^+-1), 118 (M^+-43), 105 (M^+-56), 91 (M^+-70), 65 (M^+-96).

N-(p-Tolyl)piperidine (11). Boiling point: 57-60°C/0.5 mm (lit.[15] 56°C/0.7 mm). ^{1}H NMR ($CDCl_3$, 90 MHz) δ: 1.4-1.94 (m, 6 H , $CH_2CH_2CH_2N$), 2.26 (s, 3 H, CH_3Ar), 2.91-3.25 (t, J = 6 Hz, 4 H, CH_2N), 6.9 (d, J = 9 Hz, 2 H, H_{ortho}), 7.11 (d, J = 9 Hz, 2 H, H_{meta}). ^{13}C NMR ($CDCl_3$, 22.49 MHz) δ: 20.31 (CH_3Ar), 24.30 ($CH_2CH_2CH_2N$), 25.90 (CH_2CH_2N), 51.21 (CH_2N), 116.83 (C_{ortho}), 128.49 (C_{para}), 129.44 (C_{meta}), 150.24 (C_{ipso}). Mass spectrum, m/e: 175 (M^+), 174 (M^+-1), 146 (M^+-29), 134 (M^+-41), 120 (M^+-55), 119 (M^+-56), 118 (M^+-57), 91 (M^+-84), 65 (M^+-110), 41 (M^+-134), 39 (M^+-136).

N-(p-Tolyl)hexahydroazepine (12). (Viscous oil). ^{1}H NMR ($CDCl_3$, 90 MHz) δ: 1.33-1.97 (m, 8 H, $CH_2CH_2CH_2N$), 2.21 (s, 3 H, CH_3Ar), 3.40 (t, J = 6 Hz, 4 H, CH_2N), 6.61 (d, J = 9 Hz, 2 H, H_{ortho}), 7.05 (d, J = 9 Hz, 2 H, H_{meta}). ^{13}C NMR ($CDCl_3$, 22.49 MHz) δ: 20.10 (CH_3Ar), 27.20 ($CH_2CH_2CH_2N$), 27.90 (CH_2CH_2N), 49.22 (CH_2N), 111.28 (C_{ortho}), 124.11 (C_{para}), 129.74 (C_{meta}), 146.86 (C_{ipso}). Mass spectrum, m/e: 189 (M^+), 188 (M^+-1), 160 (M^+-29), 146 (M^+-43), 134 (M^+-55), 120 (M^+-69), 119 (M^+-121), 118 (M^+-122), 105 (M^+-84), 91 (M^+-98), 65 (M^+-124), 41 (M^+-148), 39 (M^+-151).

1,4-Bis(p-tolyl)piperazine (13). Melting point: 188.5-190°C (lit.[16] 189.3°C). ^{1}H NMR ($CDCl_3$, 90 MHz) δ: 2.3 (s, 3 H, CH_3Ar), 3.3 (s, 8 H, CH_2N), 6.98 (d, J = 9 Hz, 4 H, H_{ortho}), 7.22 (d, J = 9 Hz, 4 H, H_{meta}). ^{13}C NMR ($CDCl_3$, 22.49 MHz) δ: 20.44 (CH_3Ar), 50.00 (CH_2N), 116.66 (C_{ortho}), 129.53 (C_{para}), 129.70 (C_{meta}), 149.20 (C_{ipso}). Mass spectrum, m/e: 266 (M^+), 251 (M^+-15), 146 (M^+-120), 120 (M^+-146), 119 (M^+-147), 118 (M^+-148), 105 (M^+-161), 91 (M^+-175), 77 (M^+-189), 65 (M^+-201).

N,N',N''-Tris(p-tolyl)phosphoramide (14). Melting point: 198-199°C. ^{1}H NMR (DMSO-d_6, 60 MHz) δ: 2.08 (s, 9 Hz, CH_3Ar), 6.87 (d, J = 9 Hz, 6 H, H_{ortho}), 7.08 (d, J = 9 Hz, 6 H, H_{meta}), 7.82 (d, J = 11 Hz, 3 H, NH). ^{13}C NMR (DMSO-d_6, 22.49 MHz) δ: 20.17 (CH_3Ar), 117.32 (d, J = 7 Hz, C_{ortho}), 128.43 (C_{para}), 129.03 (C_{meta}), 139.31 (C_{ipso}). ^{31}P NMR (DMSO, 36.23 MHz , H_3PO_4 internal reference) δ: -4.45. Mass spectrum, m/e: 365 (M^+), 258 (M^+-107), 241 (M^+-124), 107 (M^+-258), 79 (M^+-286), 77 (M^+-288).

1,3-Dioxolan-2-one-4-N-(p-tolyl)methanamine (15). Melting point: 50-51°C. ^{1}H NMR ($CDCl_3$, 90 MHz) δ: 2.23 (s, 3 H, CH_3Ar), 3.31-3.59 (m, 2 H, CH_2N), 3.80 (bs, 1 H, NH), 4.28 (dd, $J_{gem} \approx {}^3J_{cis}$ = 7 Hz, 1 H, OCHH'CH), 4.52 (dd, $J_{gem} \approx J_{trans}$ = 7 Hz, 1 H, OCHH'CH), 4.85-5.08 (m, 1 H, CH), 6.60 (d, J = 9 Hz, 2 H, H_{ortho}), 7.05 (d, J = 9 Hz, 2 H, H_{meta}). ^{13}C NMR ($CDCl_3$, 22.49 MHz) δ: 20.33 (CH_3Ar), 46.20 (CH_2N), 67.13 (CH_2O), 75.43 (CH), 113.38 (C_{ortho}), 127.98 (C_{para}), 129.93 (C_{meta}), 144.71 (C_{ipso}), 154.85 (C=O). Mass spectrum, m/e: 207 (M^+), 121 (M^+-86), 120 (M^+-87), 91 (M^+-116), 65 (M^+-142).

ACKNOWLEDGMENTS

We are grateful to Miss Guadalupe Arceo for technical assistance, to Mr. Guillermo Uribe for recording the ^{13}C and ^{31}P NMR spectra, to Mr. Luis Velasco for recording the mass spectra at Instituto de Química, UNAM, to Laboratories Prosalud for partial financial support, and to Prof. William F. Bailey for a useful discussion.

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