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Original reaction of *p*-nitrobenzyl chloride with aldehydes using tetrakis(dimethylamino)ethylene (TDAE)

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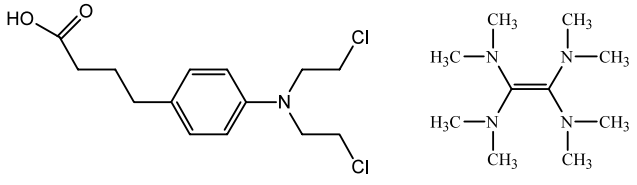
Abstract—A series of disubstituted diarylethanols was prepared in moderate to good yields by reaction of *p*-nitrobenzyl chloride (**1**) with various aromatic aldehydes (**2**–**12**) in presence of tetrakis(dimethylamino)ethylene (TDAE).

Chlorambucil or 4-(*N*,*N*-bis(2-chloroethyl)amino-phenylbutyric acid is a bifunctional aromatic derivative of nitrogen mustard (Scheme 1). Alkylating agents, such as chlorambucil, are extensively used in the treatment of neoplastic diseases, but their effectiveness is often limited by the emergence of drug resistant tumor cells. Its mode of action has not, as yet, been entirely clarified. Previously, researchers attributed chlorambucil's cytotoxicity solely to its inhibitory effects on DNA synthesis.[1] More recent studies have revealed that chlorambucil indirectly affects the synthesis of DNA.[2] Biochemical studies have found that chlorambucil affects other cellular constituents as well,[3] especially nuclear proteins.[4]

Single electron transfer methodology is emerging as an exciting new technology for mild and practical synthesis of a large number and highly branched compounds via $S_{RN}1$, bis-$S_{RN}1$, $E_{RC}1$, LD-$S_{RN}1$... mechanisms.[5] Reductive dehalogenation reactions of α-halogenated ketones using Rongalite®,[6] sodium dithionite ($Na_2S_2O_4$)[7] led to the formation of an anion via a SET. Tetrakis(dimethylamino)ethylene (TDAE) (Scheme 1) is also one of these reducing agents and we have shown that it could generate, under mild conditions, remarkably stabilized difluoromethyl and trifluoromethyl anions, in anhydrous DMF and other solvents.[8]



Scheme 1. Structures of chlorambucil and TDAE.

In continuation of our program directed toward the study of single electron transfer (SET) reactions[5,9] of bioreductive alkylating agents and the development of new analogs of chlorambucil as anticancer agents, we report herein the synthesis of disubstituted diarylethanol derivatives from reaction of *p*-nitrobenzyl chloride with various aromatic aldehydes using the TDAE methodology. The diarylethanol compounds could be suitable intermediates of the synthesis of chlorambucil analogs after reduction of nitro and alkylation. Generally, these derivatives were prepared via the reaction of benzylmagnesium bromide or chloride with various aromatic aldehydes.[10] Moreover, Tanaka[11] reported a new combination of TDAE, as organic reducing agent, and transition metal catalysts (Cr, Ni) for allylation of aldehydes and ketones.

In this study the only role of TDAE was found to promote a benzylation of aromatic aldehydes via a nitrobenzyl carbanion generated in situ in mild and practical conditions.

Keywords: TDAE; *p*-nitrobenzyl chloride; diarylethanol; aromatic aldehyde.

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Table 1. Reaction of *p*-nitrobenzyl chloride and aromatic aldehydes using TDAE[a]

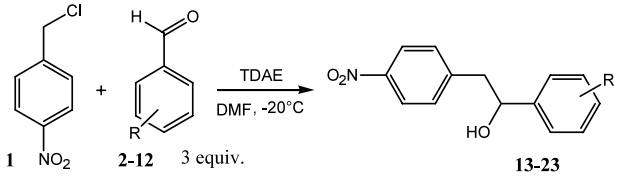
Aldehyde	R	Diarylethanol	Yield (%)[b]
Benzaldehyde **2**	H	**13**	37
p-Chlorobenzaldehyde **3**	4-Cl	**14**	62
p-Fluorobenzaldehyde **4**	4-F	**15**	51
m-Nitrobenzaldehyde **5**	3-NO_2	**16**	25
p-Nitrobenzaldehyde **6**	4-NO_2	**17**	85
o-Tolualdehyde **7**	2-CH_3	**18**	46
p-Tolualdehyde **8**	4-CH_3	**19**	34
o-Trifluoromethylbenzaldehyde **9**	2-CF_3	**20**	48
p-Trifluoromethylbenzaldehyde **10**	4-CF_3	**21**	22
Piperonaldehyde **11**	3,4-Methylenedioxy	**22**	34
6-Nitroveratraldehyde **12**	2-Nitro-4,5-dimethoxy	**23**	36

[a] All the reactions are performed using 3 equiv. of aromatic aldehydes (**2–12**), 1 equiv. of *p*-nitrobenzyl chloride (**1**) and 1 equiv. of TDAE in anhydrous DMF.

[b] % Yield relative to *p*-nitrobenzyl chloride (**1**).

The reaction of *p*-nitrobenzyl chloride (**1**) with 3 equiv. of various aromatic aldehydes (**2–12**) in presence of TDAE at −20°C for 1 h followed by 2 h at room temperature led to the corresponding diarylethanol derivatives (**13–23**) in moderate to good yields (22–85%) as shown in Table 1 (Scheme 2).[12]

The best yield of diarylethanol (85%) was observed with the *p*-nitrobenzaldehyde (**6**), and this was comparable to that obtained using the organometallic method.[10] On the other hand, no correlation could be observed representing the effect of the electronegativity of the substituents in the aromatic aldehyde on the reaction yield. However, the data reported in Table 1 show that the *p*-halo-substituted aldehydes gave good yields (R = *p*-Cl, 62% and R = *p*-F, 51%). The yields reported with *ortho* and *para* substituents seem to be higher than those with the *meta* substituted isomers. For example, the reaction with the *m*-nitrobenzaldehyde (**5**) furnished the corresponding diarylethanol (**16**) in 25% yield versus 85% with *p*-nitrobenzaldehyde (**6**). Finally, this reaction was generalized with more complex aldehydes as 3,4-methylenedioxy benzaldehyde (**11**) (piperonaldehyde) or 2-nitro-4,5-dimethoxy benzaldehyde (**12**) (6-nitroveratraldehyde) in 34 and 36% yield, respectively. However, when the reaction was treated with 1 equiv. of aromatic aldehyde, the yield of the diarylethanol was decreased and, in addition, we have observed the formation of the dimer of *p*-nitrobenzyl chloride (**1**) or 4,4′-dinitrobibenzyl. Moreover, we have realized the same reaction from benzyl chloride in place of *p*-nitrobenzyl chloride (**1**), and in such a case the reaction failed to give the corresponding diarylethanol where the starting materials were recovered unchanged. This result shows the importance of the presence of electron-withdrawing group to stabilize the benzyl anion.



Scheme 2. Reaction of *p*-nitrobenzyl chloride and aldehydes using TDAE.

In conclusion, we have shown that *p*-nitrobenzyl chloride and aromatic aldehydes react using TDAE to prepare new diarylethanol derivatives in moderate to good yields. This method, using TDAE, is an easy, original and mild method to prepare *p*-nitrobenzyl anion in situ, compared to the classical method using organometallic compounds[10] or transition metal catalysts.[11] Moreover, this method was generalized to more complex aldehydes. The pharmacological evaluation of these new diarylethanol compounds is under active investigation.

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12. General procedure for the reaction of *p*-nitrobenzyl chloride and aldehydes using TDAE. Into a two-necked flask equipped with a silica-gel drying tube and a nitrogen inlet was added, under nitrogen at −20°C, 7 mL of anhydrous DMF solution of **1** (0.52 g, 3 mmol) and aldehyde **2**–**12** (8.7 mmol, 3 equiv.). The solution was stirred and maintained at this temperature for 30 min and then was added dropwise (via a syringe) the TDAE (0.60 g, 3 mmol). A red color immediately developed with the formation of a white fine precipitate. The solution was vigorously stirred at −20°C for 1 h and then warmed up to room temperature for 2 h. After this time TLC analysis (dichloromethane) clearly showed that **1** was totally consumed. The orange–red turbid solution was filtered (to remove the octamethyloxamidinium dichloride) and hydrolysed with 80 ml of H_2O. The aqueous solution was extracted with toluene (3×40 mL), the combined organic layers washed with H_2O (3×40 mL) and dried over $MgSO_4$. Evaporation of the solvent left an orange viscous liquid as crude product. Purification by silica gel chromatography (dichloromethane) gave the corresponding diarylethanol **13**–**23**. New products: **14**; mp 116°C, ^{1}H NMR ($CDCl_3$) δ 2.04 (s, 1H); 3.09 (m, 2H); 4.92 (t, J=6.6 Hz, 1H); 7.22 (d, J=8.4 Hz, 2H); 7.29 (m, 4H); 8.11 (d, J=8.4 Hz, 2H). ^{13}C NMR ($CDCl_3$) 45.3; 74.1; 123.4; 127.1; 128.6; 130.4; 133.6; 141.6; 145.5; 146.7. Anal. calcd for $C_{14}H_{12}ClNO_3$ (277.70): C, 60.55; H, 4.36; N, 5.04. Found: C, 60.58; H, 4.31; N, 5.15. **15**; mp 101°C, ^{1}H NMR ($CDCl_3$) δ 2.08 (s, 1H); 3.09 (m, 2H); 4.93 (t, J=6.4 Hz, 1H); 7.01 (m, 2H); 7.25 (m, 2H); 7.29 (d, J=8.4 Hz, 2H); 8.11 (d, J=8.4 Hz, 2H). ^{13}C NMR ($CDCl_3$) 45.5; 74.2; 115.4; 123.4; 127.4; 130.4; 138.9; 145.6; 146.7; 165.3. Anal. calcd for $C_{14}H_{12}FNO_3$ (261.25): C, 64.36; H, 4.63; N, 5.36. Found: C, 64.35; H, 4.59; N, 5.42. **18**; mp 111°C, ^{1}H NMR ($CDCl_3$) δ 1.90 (d, J=3.0 Hz, 1H); 2.26 (s, 3H); 3.07 (d, J=6.4 Hz, 2H); 5.17 (td, J=3.0 and 6.4 Hz, 1H); 7.18 (m, 2H); 7.30 (m, 1H); 7.32 (d, J=8.4 Hz, 2H); 7.46 (m, 1H); 8.12 (d, J=8.4 Hz, 2H). ^{13}C NMR ($CDCl_3$) 18.9; 44.3; 71.1; 123.4; 125.2; 126.5; 127.7; 130.3; 130.5; 134.2; 141.4; 146.2; 146.8. Anal. calcd for $C_{15}H_{15}NO_3$ (257.28): C, 70.02; H, 5.88; N, 5.44. Found: C, 69.85; H, 5.87; N, 5.50. **19**; mp 113°C, ^{1}H NMR ($CDCl_3$) δ 2.36 (s, 3H); 2.42 (s, 1H); 3.10 (d, J=6.4 Hz, 2H); 4.87 (t, J=6.4 Hz, 1H); 7.17 (m, 4H); 7.28 (d, J=8.4 Hz, 2H); 8.08 (d, J=8.4 Hz, 2H). ^{13}C NMR ($CDCl_3$) 21.0; 45.1; 74.5; 123.2; 125.7; 129.1; 130.3; 137.6; 140.1; 146.1; 146.4. Anal. calcd for $C_{15}H_{15}NO_3$ (257.28): C, 70.02; H, 5.88; N, 5.44. Found: C, 69.86; H, 5.87; N; 5.54. **20**; mp 138°C, ^{1}H NMR ($CDCl_3$) δ 2.08 (d, J=3.1 Hz, 1H); 3.04 (m, 2H); 5.35 (m, 1H); 7.43 (m, 3H); 7.62 (m, 2H); 7.83 (m, 1H); 8.16 (d, J=8.6 Hz, 2H). ^{13}C NMR ($CDCl_3$) 45.4; 70.2; 123.6; 123.7; 125.6; 127.5; 127.9; 130.4; 132.4; 142.6; 146.0; 146.9. Anal. calcd for $C_{15}H_{12}F_3NO_3$ (311.26): C, 57.88; H, 3.89; N, 4.50. Found: C, 57.91; H, 3.91; N, 4.54. **21**; mp 140°C, ^{1}H NMR ($CDCl_3$) δ 2.25 (d, J=2.6 Hz, 1H); 3.11 (d, J=6.5 Hz, 2H); 5.01 (td, J=2.6 and 6.5 Hz, 1H); 7.31 (d, J=8.2 Hz, 2H); 7.42 (d, J=8.2 Hz, 2H); 7.59 (d, J=8.2 Hz, 2H); 8.11 (d, J=8.2 Hz, 2H). ^{13}C NMR ($CDCl_3$) 45.4; 74.1; 123.5; 124.0; 125.5; 126.1; 130.1; 130.4; 145.3; 146.8; 147.1. Anal. calcd for $C_{15}H_{12}F_3NO_3$ (311.26): C, 57.88; H, 3.89; N, 4.50. Found: C, 57.80; H, 3.89; N, 4.53. **22**; mp 104°C, ^{1}H NMR ($CDCl_3$) δ 1.97 (s, 1H); 3.08 (m, 2H); 4.84 (t, J=6.4 Hz, 1H); 5.95 (s, 2H); 6.71 (m, 2H); 6.82 (m, 2H); 7.29 (d, J=8.7 Hz, 2H); 8.11 (d, J=8.7 Hz, 2H). ^{13}C NMR ($CDCl_3$) 45.4; 74.8; 101.1; 106.2; 108.1; 119.3; 123.4; 130.4; 137.2; 145.9; 147.3; 147.9; 150.4. Anal. calcd for $C_{15}H_{13}NO_5$ (287.27): C, 62.72; H, 4.56; N, 4.88. Found: C, 62.76; H, 4.60; N, 4.97. **23**; mp 180°C, ^{1}H NMR ($CDCl_3$) δ 2.27 (s, 1H); 2.93 (d, J=13.3 Hz, 1H); 3.29 (d, J=13.3 Hz, 1H); 3.96 (s, 6H); 5.68 (m, 1H); 7.30 (s, 1H); 7.51 (s, 1H); 7.59 (d, J=8.6 Hz, 2H); 8.16 (d, J=8.6 Hz, 2H). ^{13}C NMR ($CDCl_3$) 44.6; 56.5; 70.4; 107.8; 108.9; 123.5; 130.5; 135.0; 146.2; 146.9; 148.1; 153.9. Anal. calcd for $C_{16}H_{16}N_2O_7$ (348.31): C, 55.17; H, 4.63; N, 8.04. Found: C, 55.08; H, 4.55; N, 8.04.