

Synthesis of Mono and Unsymmetrical Di- and Triesters and Amides by High Dilution Technique

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Synthesis of a number of useful mono and unsymmetrical diamides, di- and triesters (1-18) from diamines or di- and trihydroxy compounds has been achieved by chemoselective derivatisation of diamines and diols or triols by application of high dilution technique. This method avoids the conventional use of a large excess of one component to the other and also allows the preparation of differentially protected trihydric alcohol like glycerol.

INTRODUCTION

Efficient and selective hetero coupling and differential protection of identical functional groups are important organic reactions and difficult synthetic problems. In the area of molecular recognition, unsymmetrical hydrogen bond donor or acceptor groups are often required to be incorporated in the design of synthetic receptors¹. For the synthesis of unsymmetrical amides or esters² there is no systematic efficient method except the multistep procedures in some cases involving a number of protection and deprotection steps. One conventional way is to use one component in large excess (generally five to ten times) with respect to the other and sometimes it is a difficult problem if the compound is not commercially available. Also the separation of the excess starting component from the product mixture is not always easy without sacrificing the recovery of the materials.

High dilution technique was first applied by Ruggli³ in Strasbourg in formation of cyclic amides. Subsequently the method of high dilution was developed and widely used by Ziegler⁴ and Luttringhaus. A recent review has also been published⁵. High dilution technique is commonly used for macrocyclisation reaction. To achieve preferential formation of mono derivatised product we simply took advantage of the high dilution technique of using a large excess of solvent rather than one component. Very slow addition of the derivatising agent in very diluted solution from a high dilution funnel to the substrate (identical polyhydroxy and polyamino compound) solution gave good yield of the mono derivatised product predominantly along with a little of the further derivatised product which can be separated without much difficulty. The remaining functionalities can then

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be sequentially converted to the other desired derivatives according to their reactivity or steric factors following a similar technique or if there is only one remaining functional group, it can be easily converted to the desired derivative by conventional way without high dilution.

It is difficult to synthesise pure isomer of mixed esters, *e.g.*, pure synthetic mixed triglycerides free of isomers. The ease of migration of acyl groups^{2, 6, 7} (acyl transfer) from 1 or 2 position of glycerol is a common problem⁸⁻¹⁰ which is also commonly encountered in the case of synthetic carbohydrate chemistry¹¹. However cleavage of a symmetrical polyester protected carbohydrate¹² can be selectively hydrolysed to monohydroxyl ester due to the reactivity difference. In the case of silyl protection, during fluoride cleavage of *t*-butyldimethylsilyl ether (protecting the secondary hydroxyl group in glycerol) an acyl group (protecting the primary hydroxyl group) undergoes migration. Examples have been reported in other substrates, *e.g.*, nucleosides^{13, 14}, carbohydrates¹⁵ and prostaglandins¹⁶. In the chemistry of lipids and fatty polyhydric alcohols¹⁷ there has been a lot of work for the synthesis of monoglycerides¹⁸⁻²¹, symmetrical diglycerides^{19, 21}, triglycerides and mixed glycerides, *e.g.*, synthetic triglycerides² of the Dilaurin series.

We report here the synthesis and spectral data of the following monoesters and unsymmetrical (mixed or hetero) *bis* and *tris* esters (**1-11**, Chart 1) in pure forms by high dilution technique. An interesting observation was made when the 1-butyrylglycerol (**3**) was treated with benzoylchloride some 1,3-dibenzoylglycerol was isolated. We also report here the synthesis of mono and heteroamides (**11-17**, Chart 2) as well as the unsymmetrical diamide **18** from the symmetrical isophthaloylchloride by following the similar high dilution technique.

EXPERIMENTAL

The IR spectra were measured in KBr disk with a Perkin-Elmer (Model 883) spectrophotometer. The NMR spectra were obtained on a 200 MHz Bruker NMR instrument using CDCl₃ (for all compounds in Table-1 and compounds, **11**, **12**, **13**, **15**, **18**) and CDCl₃ along with d₆DMSO (compounds **14**, **16**, **17**). MS were determined on a Jeol D-300 mass spectrometer.

1-Benzoylglycerol (4): To a solution of glycerol (1 g, 10.8 mmol) in dry THF (120 mL) in a two-necked flask (500 mL) an equivalent amount of dry triethylamine (1.5 mL, 10.8 mmol) was added. The mixture was cooled in an ice bath to 5°C with stirring and a very dilute solution of benzoylchloride (1.23 mL, 10.8 mmol) in dry THF (200 mL) was added dropwise by a high dilution funnel controlling precisely the drop rate. The reaction was allowed to attain room temperature. After addition was complete (24 h), the reaction mixture was evaporated to dryness under reduced pressure. The crude product was dissolved in chloroform and washed with sodium bicarbonate (5%) followed by water (three times). The organic layer was dried over anhydrous magnesium sulfate and concentrated to give oily residue. The major product (the desired monoester, 1.5 g, 70%, R_f 0.52, 2% ethylacetate) was separated in pure state by column chromatography.

graphy using 2% ethylacetate in chloroform from the diester (R_f 0.75, 2% ethylacetate in chloroform).

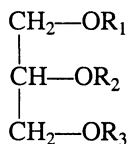
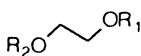
1-Benzoyl, 3-butyrylglycerol (5): To a solution of 1-benzoylglycerol (500 mg, 2.55 mmol) in dry THF (100 mL) and triethylamine (0.4 mL, 2.8 mmol) in a two-necked flask, butyrylchloride (271 mg, 2.55 mmol) was added (at 0°C and then stirred at room temperature) dropwise from a high dilution funnel. After the usual work-up, compound (5) (540 mg, 80%) was isolated.

1-Benzoyl, 2-acetyl, 3-butyrylglycerol (6): To a solution of 1-benzoyl, 3-butyrylglycerol (5) (270 mg, 0.75 mmol) was added acetic anhydride (0.15 mL) and pyridine (0.5 mL) and stirred at 70°C for 3 h. Excess pyridine and acetic anhydride was removed by distillation under reduced pressure and washed (5% sodium bicarbonate followed by copper sulphate to remove pyridine) to afford pure 6 (260 mg, 83%).

2-Benzoylamino, 6-aminopyridine (11): To a solution of 2,6-diaminopyridine (436 mg, 4 mmol) and triethylamine (0.55 mL) in dry THF (25 mL) was added very slowly a solution of benzoylchloride (0.46 mL, 4 mmol) in 100 mL dry THF and the mixture was stirred for 12 h. Usual work-up and single chromatography afforded pure product (11) (600 mg, 70%, m.p. 137–9°C).

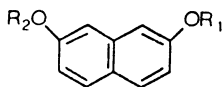
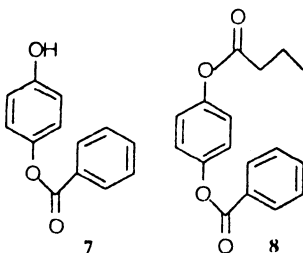
2-Benzoylamino, 6-acetylamino pyridine (12): To a stirred solution of 11 (398 mg, 2 mmol) in dry methylene chloride (25 mL) and triethylamine (0.28 mL, 2 mmol) was added a solution of acetylchloride (0.14 mL, 2 mmol) in dry methylene chloride (25 mL) dropwise and stirred for 4 h. Usual work up and crystallisation afforded pure product (12) (405 mg, 85%, m.p. 195°C [Analysis: calcd. C: 66.65, H: 5.13, N: 16.9%; found C: 66.21, H: 5.09, N: 16.47%]).

1,3-Bis [(6-aminopyrid-2-yl), 3-phenyl] carbonyl] benzene (18): To a stirred



1. $R_1 = H, R_2 = \text{COC}_6\text{H}_5$
2. $R_2 = \text{COCH}_3, R_2 = \text{COC}_6\text{H}_5$

3. $R_1 = \text{COC}_3\text{H}_7, R_2 = R_3 = H$
4. $R_1 = \text{COC}_6\text{H}_5, R_2 = R_3 = H$
5. $R_1 = \text{COC}_6\text{H}_5, R_2 = H,$
 $R_3 = \text{CO}(\text{CH}_2)_2\text{CH}_3$
6. $R_1 = \text{COC}_6\text{H}_5, R_2 = \text{COCH}_3,$
 $R_3 = \text{CO}(\text{CH}_2)_2\text{CH}_3$



9. $R_1 = H,$
 $R_2 = \text{CO}(\text{CH}_2)_2\text{CH}_3$
10. $R_1 = \text{COC}_6\text{H}_5,$

Chart 1. Monoesters and unsymmetrical di and triesters prepared

solution of isophthaloyl dichloride (406 mg, 2 mmol) a solution of 2-amino-6-methyl pyridine (0.216 g, 2 mmol) and dry triethylamine (0.205 mL) in dry methylenechloride (100 mL) was added dropwise and very slowly from a high dilution funnel at 0°C. After 1 h, a solution of aniline (186 mg, 2 mmol) and triethylamine in dry methylenechloride was added dropwise to the mixture and stirred for 8 h. Then the mixture was washed with sodium bicarbonate solution (5%) followed by water several times. The organic layer separated was dried (anhydrous sodium sulfate) and concentrated under reduced pressure to give white

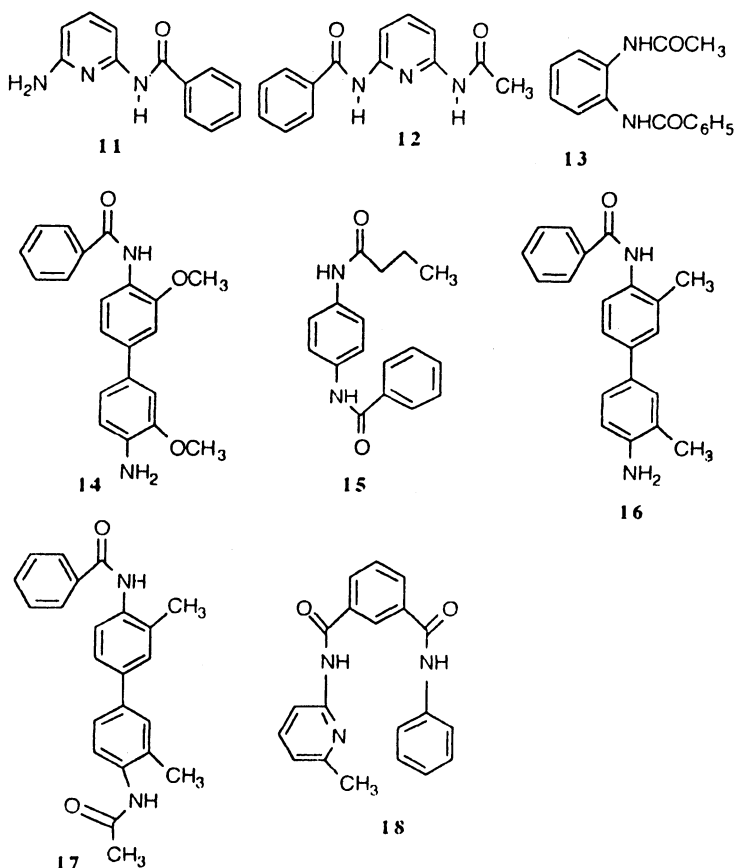


Chart 2. Monoamides and unsymmetrical bisamides prepared

solid residue. The desired heterodiamide (**18**) was obtained in pure state by preparative TLC (10% ethylacetate in chloroform, 430 mg, 65%, m.p. 280°C).

Tables-1 and 2 show the series of the mixed esters and amides synthesised by this technique along with their available NMR and Mass spectral data.

TABLE-I
SPECTRAL DATA OF MONOESTER AND UNSYMMETRICAL DI AND TRI ESTERS
PREPARED

Compd.	m.p. (°C)	IR (ν_{\max} cm^{-1})	^1H NMR (200 MHz, CDCl_3) and mass
1	—	3467 $\nu(\text{OH})$, 2924, 1688 $\nu(\text{ester CO})$, 1419, 1288	8.06 (d, $J = 6$ Hz, 2H) 7.61–7.40 (m, 3H), 4.46 (t, 5 Hz, 2H), 3.96 (t, 4 Hz, 2H), 2.23 (bs, 1H)
2	—	2960, 1731 $\nu(\text{ester CO})$, 1278, 1235	8.06 (d, $J = 6$ Hz, 2H) 7.58–7.39 (m, 3H), 4.46 (t, $J = 5$ Hz, 2H), 4.23 (t, $J = 4$ Hz, 2H), 2.08 (s, 3H)
3	—	3418 b, $\nu(\text{OH})$, 2967, 1736 $\nu(\text{ester CO})$, 1258, 1181	4.11 (m, 2H), 3.70 (d, $J = 4$ Hz, 2H), 3.29 (m, 1H), 2.66 (bs, 1H), 2.28 (t, $J = 4$ Hz, 2H), 1.64 (m, 2H), 0.93 (t, $J = 4$ Hz, 3H)
4	—	3474 b, $\nu(\text{OH})$, 2955, 1718 $\nu(\text{ester CO})$, 1274, 1110	8.06 (d, $J = 2$ Hz, 1H), 8.02 (d, $J = 2$ Hz, 1H), 7.53 (t, $J = 2$ Hz, 1H), 7.37–7.47 (m, 2H), 4.52 (d, $J = 4$ Hz, 2H), 4.40 (m, 1H), 3.85 (d, $J = 6$ Hz, 2H), 2.07 (bs, 1H)
5	—	3455 $\nu(\text{OH})$, 2965, 2929, 1728 $\nu(\text{ester CO})$, 1264, 1108	8.03 (d, $J = 2$ Hz, 1H), 7.99 (d, $J = 2$ Hz, 1H), 6.70 (bs, 1H), 7.56–7.40 (m, 3H), 4.55 (m, 5H), 2.43 (t, $J = 6$ Hz, 2H), 1.66 (m, 2H), 0.95 (t, $J = 4$ Hz, 3H)
6	—	2926, 1730 $\nu(\text{ester CO})$, 1267, 1173, 1106	8.00 (d, $J = 2$ Hz, 1H), 7.99 (d, $J = 2$ Hz, 1H), 7.56–7.38 (m, 3H), 5.56 (m, 1H), 4.57 (m, 4H), 2.28 (m, 2H), 2.09 (s, 3H), 1.60 (m, 2H), 0.89 (t, $J = 4$ Hz, 3H)
7	162–3	3453 $\nu(\text{OH})$, 2969, 1720 $\nu(\text{ester CO})$, 1266, 1186	8.20 (d, $J = 10$ Hz, 2H), 7.64–7.39 (m, 3H), 7.03 (d, $J = 10$ Hz, 2H), 6.84 (d, $J = 10$ Hz, 2H), 3.56 (bs, 1H)
8	—	2969, 1750 $\nu(\text{ester CO})$, 1259, 1174	8.16 (d, $J = 8$ Hz, 2H), 7.62–7.35 (m, 3H), 7.20 (d, $J = 10$ Hz, 2H), 7.12 (d, $J = 10$ Hz, 2H), 2.30 (t, $J = 8$ Hz, 2H), 1.70 (m, 2H), 0.99 (t, $J = 4$ Hz, 3H)
9	133–4	—	7.72 (d, $J = 8$ Hz, 1H), 7.65 (d, $J = 8$ Hz, 1H), 7.31 (d, $J = 2.2$ Hz, 1H, peri H ortho to butyrate), 7.06–7.00 (m, 2H), 6.98 (d, $J = 2.2$ Hz, 1H, peri H ortho to OH), 2.60 (t, $J = 6$ Hz, 2H), 1.83 (sextet, $J = 6$ Hz, 2H), 1.08 (t, $J = 2$ Hz, 3H)
10	70	—	8.25 (d, $J = 7$ Hz, 1H), 8.19–8.14 (m, 2H) 7.92–7.85 (m, 1H), 7.72–7.62 (m, 2H), 7.56–7.50 (m, 2H), 7.49–7.47 (m, 1H), 7.33 (dd, $J = 6$ Hz, $J = 2$ Hz, 1H), 7.22 (dd, $J = 6$ Hz, $J = 2$ Hz, 1H), 2.60 (t, $J = 6$ Hz, 2H), 1.82 (sextet, $J = 6$ Hz, 2H), 1.06 (t, $J = 8$ Hz, 3H)

TABLE-2
SPECTRAL PROPERTIES OF MONO AND DIAMIDES PREPARED

Compd.	m.p. (°C)	IR (ν_{\max} cm^{-1})	^1H NMR (200 MHz in $\text{CDCl}_3/\text{DMSO}-d_6$) and mass
11	137-9	3440 $\nu(\text{NH}_2)$, 3320, 3270 (amide NH), 1665 $\nu(\text{amide CO})$, 1615, 1570, 1263	8.75 (bs, 1H, NHCOPh), 7.95-7.64 (m, 2H), 7.54-7.15 (m, 5H, Ar), 6.25 (dd, $J_{\text{ortho}} = 1.8$ Hz, $J_{\text{ortho}} = 1.7$ Hz, Py-H-4), 4.85 (b, NH_2), M^+ 213
12	195	3319, 3268 $\nu(\text{amide NH})$, 1667 $\nu(\text{amide CO})$, 1586, 1449, 1262	8.32 (bs, 1H, NHCOPh), 8.05 (d, $J = 8$ Hz, 2 H), 7.91 (bs, 1H, NHCOCH_3), 7.80, $J = 8$ Hz, 1H), 7.74 (t, $J = 10$ Hz, 1H), 7.60-7.44 (m, 3H), 2.19 (s, 3H), M^+ 255
13	192-4	3269 $\nu(\text{NH})$, 2915, 1655 $\nu(\text{amide CO})$, 1523, 1263	9.60 (s, 1H, NHCOPh), 7.90 (d, $J = 6$ Hz, 2H), 7.71 (s, 1H, NHCOCH_3), 7.55-7.46 (m, 6H), 2.41 (s, 3H, CH_3 , NHCOCH_3)
14	175	3480 $\nu(\text{NH}_2)$, 3273 $\nu(\text{amide NH})$, 1659 $\nu(\text{amide CO})$, 1506, 1264, 1174	8.8 (bs, 1H, NHCOPh), 7.90-7.60 (m, 3H, 7.4 (s, 2H), 7.2-7.6 (m, 6H), 3.9 (s, 3H, OCH_3 a to amide), 3.2 (s, 3H, OCH_3 a to amine), M^+ 348
15	210	3311 $\nu(\text{NH})$, 2939, 1650 $\nu(\text{amide CO})$, 1547, 1394	9.38 (s, 1H, NHCOPh), 8.95 (s, 1H, NHCOR), 7.67 (d, $J = 2$ Hz, 1H), 7.63 d, $J = 2$ Hz, 1H), 7.45 (d, $J = 10$ Hz, 2H), 7.27 (d, $J = 10$ Hz, 2H), 7.22-7.11 (m, 3H), 2.02 (t, $J = 6$ Hz, 2H), 1.5 (m, 2H), 0.66 (t, $J = 4$ Hz, 3H), M^+ 316
16	162	3477 $\nu(\text{NH})$, 3270 $\nu(\text{CONH})$, 1648	9.7-9.4 (bs, 1H, NHCO), 8.05-7.65 (4H, Ar), 7.60-7.30 (7H Ar), 7.25-7.10 (bs, 2H, NH_2), 2.25 (s, 3H, CH_3) 2.1 (s, 3H, CH_3)
17	247	3270 $\nu(\text{NH})$, 2932, 1645 $\nu(\text{amide CO})$, 1509, 1317	8.96 (s, 1H, PhCONH), 8.49 (s, 1H, HNCOCH_3), 7.61 (d, $J = 6$ Hz, 1H), 7.16-7.02 (m, 9H, Ar), 2.67 (s, 6H, ArCH_3), 2.01 (s, 3H, HNCOCH_3)
18	280	3424 $\nu(\text{NH})$, 3254 $\nu(\text{NH})$, 3128, 1643 $\nu(\text{amide CO})$, 1543, 1332, 703	12.71 (s, 1H, PhNHCO), 9.51 (s, 1H, CONHPy), 9.20 (s, 1H, Ar), 8.78 (d, 1H, $J = 10$ Hz), 8.42 (d, 1H, $J = 8$ Hz), 8.22 (t, 1H), 8.05 (d, 1H, $J = 8$ Hz), 7.69 (t, 1H, $J = 8$ Hz), 7.24-7.40 (m, 5H, Ar), 7.11 (d, 1H, $J = 8$ Hz), 2.17 (s, 3H)

ACKNOWLEDGEMENTS

We thank Department of Science and Technology, Government of India, for financial support. Thanks to Central Drug Research Institute, Lucknow (for some mass and NMR spectra) and also to Indian Association for Cultivation of Science, Calcutta (for elemental analysis).

REFERENCES

1. O.E. McElroy and C.G. King, *J. Am. Chem. Soc.*, **56**, 1191 (1934).
2. P. Ruggli, *Ann.*, **392**, 92 (1912); **399**, 174 (1913); **412**, 1 (1917).
3. K. Ziegler, *Methoden der Organischen Chemie (Houben Weyl)*, Georg Thieme Verlag, Stuttgart, p. 729 (1955).
4. L. Rossa and F. Vogtle, *Topics in Current Chemistry*, **113**, 1 (1983); P. Knops, N. Sendhoff, H.B. Meikelburger and F. Vogtle, *ibid.*, **161**, 1 (1991).
5. B. Serdarevich, *J. Am. Oil Chem. Soc.*, 381 (1967).
6. E. Fischer, *Ber.*, **53**, 1621 (1920).
7. F.G.F. Menzies and S.L. Wright, *J. Am. Chem. Soc.*, **43**, 2312 (1921).
8. H.P. Averill, J.N. Roche and C.G. King, *J. Am. Chem. Soc.*, **52**, 365 (1930); **51**, 86 (1929).
9. H.E. Robinson, J.N. Roche and C.G. King, *J. Am. Chem. Soc.*, **54**, 705 (1932).
10. V. Amarnath and A.D. Broom, *Chem. Rev.*, **77**, 183 (1977).
11. C.B. Reese, *Tet.*, **34**, 3143 (1978).
12. Y. Ishido, N. Nakazake and N. Sakairi, *J. Chem. Soc. Perkin Trans.*, 208 (1979).
13. G.H. Dodd, B.T. Golding and P.V. Ioannou, *J. Chem. Soc. Chem. Com.*, 249 (1975).
14. K.K. Ogilvie, S.L. Beaucage, A.H. Schiffman, N.Y. Theriault and K.L. Sadana, *Canad. J. Chem.*, **56**, 2768 (1978).
15. S.S. Jones and C.B. Reese, *J. Chem. Soc. Perkin Trans.*, 2762 (1979).
16. F. Franke and R.D. Geethrie, *Aust. J. Chem.*, **31**, 1285 (1978).
17. Y. Torisawa, M. Shibasaki and S. Ikegami, *Tet. Lett.*, 1865 (1979).
18. B.T. Golding and P.V. Ioannou, *Synthesis*, 423 (1977).
19. A.E. Tomas III, J.E. Scharoun and H. Ralston, *J. Am. Oil Chem. Soc.*, 789 (1965).
20. H.A. Schuette and J.T. Hale, *J. Am. Chem. Soc.*, **52**, 1978 (1930).
21. P.V. Ioannou, G.H. Dodd and T.G. Bernard, *Synthesis*, 939 (1979).

(Received: 28 May 1998; Accepted: 30 January 1999)

AJC-1683