MONO-ESTERIFICATION OF N-PROTECTED DI-ACIDS ASPARTIC AND GLUTAMIC BY CHLOROFORMATE ACTIVATION.

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Summary : Mono-esters of N-protected di-acids aspartic and glutamic are prepared by a one-pot activation with alkyl chloroformates or isopropenyl chloroformate and an additionnal alcohol. This process involves the intermediate internal anhydride formation.

With respect to the mono-esterification of N-protected aspartic 1 or glutamic diacid 2, the most suitable reaction already described was a multi-steps procedure that involved the partially regioselective opening of the preformed internal anhydride 3 or 4, leading predominantly to the α -isomer 7 α or 8 α 1. The internal anhydride was mostly prepared from acetic anhydride 2 or carbodilmide 3 activation of the N-protected diacid. The use of chloroformates for di-acids activation has not been investigated so far, although activation of N-protected amino acids with chloroformates has been extensively studied 4, including esterification reactions 5. We report in this paper the one-pot preparation of mono-esters of N-protected aspartic and glutamic acids, by alkyl-chloroformate activation. In this process, the ester formed corresponds to the chloroformate used and is limited by the accessibility of the reagent 5. We demonstrated in a previous communication, the efficiency of isopropenyl chloroformate activation for the esterification of N-protected aminoacids by alcohols 4. We show herein that the isopropenyl chloroformate activation in the presence of an alcohol also prouved to be suitable for mono-esterification of di-acids.

The mono-esterification was obtained by adding one equivalent of the chloroformate to the di-acid 1 or 2 neutralized with two equivalents of base (pyridine, triethylamine with or without a catalytic amount of DMAP) in dichloromethane solution, at 0° C. The mono-esterification occured directly from alkyl-chloroformates (method A) or with an additional equivalent of alcohol in the case of IPCF activation (method B). The mono-esters 7 or 8 were purified by aqueous basic extraction of the methylene chloride solution after aqueous acidic washing : the mixture of mono-esters was then extracted from acidified

1665

N-Z-Glu.
and
N-Z-ASP
Å
Nono-esterification
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IPCT cety1. TEA 2h * Zasp(OH)OCety1 64% 62-63 - IPCT BuOH TEA/DMAP 70/30 Zasp(OH)OTBu,DCha (1)7 41% 175-176 - R = Ne none TEA Zh 66/34 40% 175-176 - IPCT MeOH TEA/DMAP Zh 10/90 ZGIU(OME,DCha (e)7 63% 152-153 IPCT MeOH TEA/DMAP Zh 12/88 60% 151-152 IPCT Cety1 TEA/DMAP Zh Y ZGIU(OME,DCha (e)7 63% 152-153 IPCT Cety1 TEA/DMAP Zh Y ZGIU(OME,DCHA (e)7 63% 151-152 IPO	IPCT cety1. TEA $2h$ * ZAsp(OH)OCety1 64% 62-63 - IPCT tBuOH TEA/DMAP 70/30 ZAsp(OH)OCBU, DCha $(0)^7$ $41%$ $175-176$ - R = We none TEA Zh $66/34$ 406 $174-175$ - IPCT MeOH TEA Zh $66/34$ 406 $174-175$ - IPCT MeOH TEA Zh $66/34$ 406 $174-175$ - IPCT MeOH TEA/DMAP Zh $10/90$ ZGIU(OME, DCha $(0)^7$ $41%$ $175-153$ IPCT MeOH TEA/DMAP Zh $12/98$ 603 $152-153$ IPCT MeOH TEA/DMAP Zh $12/98$ $$ 603 $151-152$ IPCT Cety1 TEA/DMAP Zh $*$ ZGIU(ONCety1)OH $61%$ $58-59$ IPCT MeOH TEA/DMAP Zh $80/20$ $$ 608 $151-152$	IPCF cety1. TEA 2h * ZASP(OE)OCEty1 649 62-63 -11.4 IPCF tBuOH TEA/DMAR 70/30 ZASP(OE)OCEty1 649 62-63 -11.4 IPCF tBuOH TEA/DMAR 2h 67/33 ZGIU(OH)ONE,DCha (a)7 418 175-176 -11.2 IPCT MeOH TEA 2h 66/34 408 174-175 -10.9 IPCT MeOH TEA 2h 66/34 408 174-175 -10.9 IPCT MeOH TEA 2h 10/90 ZGIU(OH)ONE,DCha (e)7 63 152-152 +9.4 IPCT MeOH TEA/DMAR 1h 10/90 ZGIU(OME),DCha (e)7 63 152-152 +9.4 IPCT Cety1. <tea dmar<="" td=""> 2h 12/80 603 151-152 +9.4 IPCT Cety1.<tea dmar<="" td=""> 1h 74/26 604 151-152 +9.4 IPCT MeOH TEA 2h 74/26 604 151-152</tea></tea>	IPCF Cety1. TEA 2h * Zasp(OH)OCEty1 64% 62-63 -11.4 IPCF thuOH TEA/DMAR 70/30 Zasp(OH)Oth.Dcha (d)7 41% 175-176 -11.2 IPCT MeOH TEA/DMAR 2h 67/33 ZGIU(OH)OME,DCha (d)7 41% 175-176 -11.2 IPCT MeOH TEA/DMAR 1h 10/90 ZGIU(OH)OME,DCha (d)7 41% 175-176 -11.2 IPCT MeOH TEA/DMAR 1h 10/90 ZGIU(OH)OME,DCha (d)7 41% 175-176 -11.2 R = Me none TEA/DMAR 1h 10/90 ZGIU(OME)DCH (e)7 63% 152-152 49.4 IPCT Cety1. TEA/DMAR 2h 12/88 60% 151-152 49.4 IPCT Cety1. TEA/DMAR 2h 7 ZGIU(OCETY)OH 6.9% 58-59 -6.5 IPCT Cety1. TEA/DMAR 1h 74/26 - 20% 151-152 49.4 IPO MoH <td></td> <td>IPCF</td> <td>BZIOH</td> <td>TEA</td> <td>Zh</td> <td>76/24</td> <td></td> <td>578</td> <td>85-86</td> <td>-17.3</td>		IPCF	BZIOH	TEA	Zh	76/24		578	85-86	-17.3
IPCF EBUOH TEA/DMAP 70/30 ZASp(OH)OtEBu, DCha (C) ⁶ R = Me none TEA 2h 67/33 ZGJu(OH)OMe, DCha (d) 7 41% 175-176 - IPCT MeOH TEA 2h 65/34 40% 175-176 - IPCT MeOH TEA 2h 66/34 40% 174-175 - R = Me none TEA/DMAP 1h 10/90 ZGJu(OMe)DCha (d) 7 41% 175-153 - IPCT MeOH TEA/DMAP 2h 12/98 60% 151-152 - IPCT Cety1. TEA/DMAP 2h 12/98 60% 151-152 IPCT Cety1. TEA/DMAP 2h 12/98 60% 151-152 IPCT Cety1. TEA/DMAP 2h y ZGJu(OME)DOH 6B% 58-59 IPO MeOH TEA 2h 80/20 - 58-59	IPCF tat/DMAR 70/30 ZAsp(oH)OtBu, Dcha (c) ⁶ R = Me none TEA 2h 67/33 ZGJu(OH)OMe, Dcha (d) 7 41% 175-176 - IPCT MeoH TEA 2h 65/34 40% 174-175 - R = Me none TEA/DMAR 1h 10/90 ZGJu(OH)OMe, Dcha (d) 7 41% 175-176 - R = Me none TEA/DMAR 1h 10/90 ZGJu(OMe)OH, Dcha (d) 7 41% 175-175 - IPCT MeOH TEA/DMAR 2h 12/98 40% 152-153 IPCT Cety1. TEA/DMAR 2h 12/98 60% 151-152 IPCT Cety1. TEA/DMAR 2h 720 - 58-59 58-59 IPCT MeOH TEA 2h 80/20 - 58-59 58-59 IPON MeOH TEA 2h 85/15 - 58-59 IPON <td>IPCF tBuOH TEA/TMAP 70/30 ZASP(OH)OtBu, Dcha (c)* IU $R = Ne$ none TEA 2h $67/33$ ZGIU(OH)ONE, Dcha (d)? 41% $175-176$ -11.2 IPCT MeOH TEA 2h $66/34$ 40% $174-175$ -10.9 R = Ne none TEA/TMAP 1h $10/90$ ZGIU(OH)ONE, Dcha (d)? 41% $174-175$ -10.9 R = Ne none TEA/TMAP 2h $10/90$ ZGIU(ONE)OH, Dcha (e)? 63% $152-153$ $+9.2$ IPCT MeOH TEA/TMAP 2h $10/90$ ZGIU(OCE4Y1)OH 69% $56-59$ -6.5 None MeOH TEA 2h $80/20$ -1.22 49.4 -1.22 49.4 IPCT Cety1. TEA/TMAP 2h $10/90$ 260% $56-59$ -6.5 Wone MeOH TEA 2h $80/20$ -1.22 49.4 -1.22 49.4 IPCT Cety1. TEA $2h$ $74/26$ -1.22 49.4<td>IPCT EBUOH TEX/TMARP 70/30 ZABPC (OH) OCEBU, DCha (C)* IU R = Me none TEX 2h 67/33 ZGIU(OH) OME, DCha (d) 7 41% 175-176 -11.2 IPCT MeOH TEX 2h 67/33 ZGIU(OH) OME, DCha (d) 7 41% 175-176 -11.2 IPCT MeOH TEX Zh 2h 6/34 40% 174-175 -10.9 R = Me none TEX/DMAP 1h 10/90 ZGIU(OME) DCHa (e) 7 63% 152-152 49.4 IPCT Cety1. TEX/DMAP 2h 12/88 60% 151-152 49.4 IPCT Cety1. TEX/DMAP 2h 12/88 60% 151-152 49.4 IPCT Cety1. TEX/DMAP 2h 80/20 51.5 49.4 51.5 49.4 Iu none MeOH TEX 2h 80/20 51.5 49.4 Iu none MeOH TEX 2h 80/20 51</td><td></td><td>IPCF</td><td>cetyl.</td><td>TEA</td><td>ŝ</td><td>*</td><td>ZASP(OH)OCELY1</td><td>648</td><td>6263</td><td>+'II-</td></td>	IPCF tBuOH TEA/TMAP 70/30 ZASP(OH)OtBu, Dcha (c)* IU $R = Ne$ none TEA 2h $67/33$ ZGIU(OH)ONE, Dcha (d)? 41% $175-176$ -11.2 IPCT MeOH TEA 2h $66/34$ 40% $174-175$ -10.9 R = Ne none TEA/TMAP 1h $10/90$ ZGIU(OH)ONE, Dcha (d)? 41% $174-175$ -10.9 R = Ne none TEA/TMAP 2h $10/90$ ZGIU(ONE)OH, Dcha (e)? 63% $152-153$ $+9.2$ IPCT MeOH TEA/TMAP 2h $10/90$ ZGIU(OCE4Y1)OH 69% $56-59$ -6.5 None MeOH TEA 2h $80/20$ -1.22 49.4 -1.22 49.4 IPCT Cety1. TEA/TMAP 2h $10/90$ 260% $56-59$ -6.5 Wone MeOH TEA 2h $80/20$ -1.22 49.4 -1.22 49.4 IPCT Cety1. TEA $2h$ $74/26$ -1.22 49.4 <td>IPCT EBUOH TEX/TMARP 70/30 ZABPC (OH) OCEBU, DCha (C)* IU R = Me none TEX 2h 67/33 ZGIU(OH) OME, DCha (d) 7 41% 175-176 -11.2 IPCT MeOH TEX 2h 67/33 ZGIU(OH) OME, DCha (d) 7 41% 175-176 -11.2 IPCT MeOH TEX Zh 2h 6/34 40% 174-175 -10.9 R = Me none TEX/DMAP 1h 10/90 ZGIU(OME) DCHa (e) 7 63% 152-152 49.4 IPCT Cety1. TEX/DMAP 2h 12/88 60% 151-152 49.4 IPCT Cety1. TEX/DMAP 2h 12/88 60% 151-152 49.4 IPCT Cety1. TEX/DMAP 2h 80/20 51.5 49.4 51.5 49.4 Iu none MeOH TEX 2h 80/20 51.5 49.4 Iu none MeOH TEX 2h 80/20 51</td> <td></td> <td>IPCF</td> <td>cetyl.</td> <td>TEA</td> <td>ŝ</td> <td>*</td> <td>ZASP(OH)OCELY1</td> <td>648</td> <td>6263</td> <td>+'II-</td>	IPCT EBUOH TEX/TMARP 70/30 ZABPC (OH) OCEBU, DCha (C)* IU R = Me none TEX 2h 67/33 ZGIU(OH) OME, DCha (d) 7 41% 175-176 -11.2 IPCT MeOH TEX 2h 67/33 ZGIU(OH) OME, DCha (d) 7 41% 175-176 -11.2 IPCT MeOH TEX Zh 2h 6/34 40% 174-175 -10.9 R = Me none TEX/DMAP 1h 10/90 ZGIU(OME) DCHa (e) 7 63% 152-152 49.4 IPCT Cety1. TEX/DMAP 2h 12/88 60% 151-152 49.4 IPCT Cety1. TEX/DMAP 2h 12/88 60% 151-152 49.4 IPCT Cety1. TEX/DMAP 2h 80/20 51.5 49.4 51.5 49.4 Iu none MeOH TEX 2h 80/20 51.5 49.4 Iu none MeOH TEX 2h 80/20 51		IPCF	cetyl.	TEA	ŝ	*	ZASP(OH)OCELY1	648	6263	+'II-
R = We none TEA 2h 61/33 ZGJU(OH)OMe, DCha (d) 7 418 175–176 - IPCT MeOH TEA 2h 66/34 40% 174–175 - R = Me none TEA/DMAP 1h 10/90 ZGJU(OMe, DCha (e) 7 63% 152–153 IPCT MeOH TEA/DMAP 2h 12/88 60% 151–152 IPCT MeOH TEA/DMAP 2h 12/88 60% 151–152 IPCT Cety1. TEA/DMAP 2h 12/88 60% 151–152 IPCT Cety1. TEA/DMAP 2h 12/88 60% 151–152 IPCT Cety1. TEA/DMAP 2h * ZGJU(OPCEYJ)OH 68% 58–59 IPCT MeOH TEA 2h 80/20 16/24 151–152 IPONE MeOH TEA 2h 74/25 58–59	R = We none TEA 2h 61/33 ZGJU(OH)OMe, DCha (d)7 418 175–176 - IPCT MeOH TEA 2h 66/34 408 174–175 - R = Me none TEA/DMAP 1h 10/90 ZGJU(OMe, DCha (e)7 638 152–153 IPCT MeOH TEA/DMAP 2h 12/88 608 151–152 IPCT MeOH TEA/DMAP 2h 12/88 608 151–152 IPCT Cety1. TEA/DMAP 2h 12/88 608 151–152 IPCT Cety1. TEA/DMAP 2h * ZGJU(OCety1)OH 683 58–59 none MeOH TEA 2h 80/20 174–175 151–152 none MeOH TEA 2h 80/20 174/26 1608 58–59 none MeOH TEA 2h 86/15 16/84 1608 <t< td=""><td>Iu R = Me none TEA 2h 67/33 ZGJU(OH)OME, DCha (d)7 418 175-176 -11.2 IPCT MeOH TEA 2h 66/34 408 174-175 -10.9 R = Me none TEA/DMAP 1h 10/90 ZGJU(OME)DCha (e)7 638 152-153 49.2 IPCT MeOH TEA/DMAP 2h 12/88 608 151-152 49.4 IPCT MeOH TEA/DMAP 2h 12/88 608 151-152 49.4 IPCT Cety1. TEA/DMAP 2h 12/88 608 151-152 49.4 IPCT Cety1. TEA/DMAP 2h 12/86 608 151-152 49.4 IPCT Cety1. TEA/DMAP 1h 74/26 14/26 -6.5 -6.5 Iu None MeOH TEA/DMAP 2h 74/26 -1.5 2h.4 -6.5 -6.5 Iu None MeOH TEA/DMAP 2h</td><td>In $R = We$ none TEA 2h $67/33$ ZGIU(OMe, DCha (d)7 41% 175-176 -11.2 IPCT MeOH TEA 2h 66/34 40% 174-175 -10.9 R = Me none TEA/DMAP 1h 10/90 ZGIU(OME)OH, DCha (e)7 63 152-153 +9.2 IPCT MeOH TEA/DMAP 2h 12/98 60% 151-152 +9.4 IPCT MeOH TEA/DMAP 2h 12/98 60% 151-152 +9.4 IPCT Cety1. TEA/DMAP 2h 74 58-59 -6.5 IPCT Cety1. TEA/DMAP 2h 74/26 -</td><td></td><td>IPCF</td><td>tBuOH</td><td>TEA/DMAP</td><td></td><td>70/30</td><td>ZASP(OH)OtBu , Dcha</td><td>(c)e</td><td></td><td></td></t<>	Iu R = Me none TEA 2h 67/33 ZGJU(OH)OME, DCha (d)7 418 175-176 -11.2 IPCT MeOH TEA 2h 66/34 408 174-175 -10.9 R = Me none TEA/DMAP 1h 10/90 ZGJU(OME)DCha (e)7 638 152-153 49.2 IPCT MeOH TEA/DMAP 2h 12/88 608 151-152 49.4 IPCT MeOH TEA/DMAP 2h 12/88 608 151-152 49.4 IPCT Cety1. TEA/DMAP 2h 12/88 608 151-152 49.4 IPCT Cety1. TEA/DMAP 2h 12/86 608 151-152 49.4 IPCT Cety1. TEA/DMAP 1h 74/26 14/26 -6.5 -6.5 Iu None MeOH TEA/DMAP 2h 74/26 -1.5 2h.4 -6.5 -6.5 Iu None MeOH TEA/DMAP 2h	In $R = We$ none TEA 2h $67/33$ ZGIU(OMe, DCha (d)7 41% 175-176 -11.2 IPCT MeOH TEA 2h 66/34 40% 174-175 -10.9 R = Me none TEA/DMAP 1h 10/90 ZGIU(OME)OH, DCha (e)7 63 152-153 +9.2 IPCT MeOH TEA/DMAP 2h 12/98 60% 151-152 +9.4 IPCT MeOH TEA/DMAP 2h 12/98 60% 151-152 +9.4 IPCT Cety1. TEA/DMAP 2h 74 58-59 -6.5 IPCT Cety1. TEA/DMAP 2h 74/26 -		IPCF	tBuOH	TEA/DMAP		70/30	ZASP(OH)OtBu , Dcha	(c)e		
IFCF MeOH TEA 2h 66/34 408 174-175 R = Me none TEA/DMAP 1h 10/90 ZG1u(OMe)OH,DCha (e)7 63% 152-153 IPCT MeOH TEA/DMAP 2h 12/98 60% 151-152 IPCT MeOH TEA/DMAP 2h 12/98 60% 151-152 IPCT Cety1. TEA/DMAP 2h 12/98 60% 58-59 IPCT Cety1. TEA/DMAP 2h 80/20 × ZG1u(Ocety1)OH 68% 58-59 IPDN MeOH TEA 74/26 15/15 58-59 IPDN MeOH TEA 2h 80/20 58-59 IPDN MeOH TEA/DMAP 1h 74/26 58-59 IPDN MeOH TEA 2h 85/15 58-59 IPDN MeOH TEA 2h 56/15<	IPCF MeOH TEA 2h 66/34 406 174-175 R = Me none TEA/DMAP 1h 10/90 ZGJU(OME)DCha (e)7 63% 152-153 IPCT MeOH TEA/DMAP 2h 12/88 60% 151-152 IPCT MeOH TEA/DMAP 2h 12/88 60% 151-152 IPCT Cety1. TEA/DMAP 2h 12/88 60% 151-152 IPCT Cety1. TEA/DMAP 2h 12/88 60% 151-152 IPCT Cety1. TEA/DMAP 2h 80/20 151-152 IPCT Cety1. TEA/DMAP 2h 80/20 58-59 IPONE MeOH TEA/DMAP 1h 74/26 58-59 IPONE MeOH TEA 2h 85/15 58-59 IPONE MeOH TEA 2h 85/15 <	IPCF MeOH TEA 2h 66/34 40% 174-175 -10.9 R = Me none TEA/DMAP 1h 10/90 ZGJu(OME)OH,DCha (e)7 63% 152-153 49.4 IPCF MeOH TEA/DMAP 2h 12/86 60% 151-152 49.4 IPCF MeOH TEA/DMAP 2h * ZGJu(OME)OH,DCha (e)7 63% 152-153 49.4 IPCF Cetyl. TEA/DMAP 2h 12/86 60% 151-152 49.4 IPCF Cetyl. TEA/DMAP 2h * ZGJu(OCetyl)OH 68% 56-59 -6.5 IU none MeOH TEA/DMAP 1h 74/26 14/26 IU none MeOH TEA/DMAP 2h 15/94 4.0.1 14/26 IU none MeOH TEA/DMAP 2h 15/94 4.0.1 14/26 Iu none MeOH TEA/DMAP 2h 16/94 16/14	IPCF MeOH TEA 2h 66/34 40% 174-175 -10.9 R = Me none TEA/DMAR 1h 10/90 ZG1u(OMe)OH,DCha (e)7 63% 152-153 +9.2 IPCF MeOH TEA/DMAR 2h 12/88 60% 151-152 +9.4 IPCF cety1. TEA/DMAR 2h x ZG1u(OMe)OH,DCha (e)7 63% 152-153 +9.2 IPCF cety1. TEA/DMAR 2h 12/88 60% 151-152 +9.4 IPCF cety1. TEA/DMAR 2h x ZG1u(Ocety1)OH 68% 58-59 -6.5 sp <none< td=""> MeOH TEA 2h 80/20 74/26 lu none MeOH TEA 2h 85/15 lu none MeOH TEA 2h 85/15 none MeOH TEA 2h 85/15</none<>	z-Glu	R = Me	none	TEA	2h Zh	67/33	ZGlu(OH)OMe , Dcha	(d)7 41 8	175-176	-11.2
R = Me IDMOR TEA/DMAR ID 10/90 ZGJU(OMe)DCha (e)7 6.3 IS2-I53 IPCT MeOH TEA/DMAR 2h 12/98 60% 151-I52 IPCT Cety1. TEA/DMAR 2h 12/98 60% 151-I52 IPCT Cety1. TEA/DMAR 2h 32 SGIU(OCETY1)OH 68% 58-59 None MeOH TEA 2h 80/20 58-59 58-59 None MeOH TEA/DMAR 1h 74/26 58-59 58-59 None MeOH TEA 2h 80/20 58-59 58-59 None MeOH TEA 2h 80/20 58-59 58-59 None MeOH TEA 2h 80/20 58-59 58-59 58-59 None MeOH TEA 2h 96/20 58-59 58-59 58-59 58-59	R = Me IDMOR TEA/DMAR ID 10/90 ZGJU(OMe)OH, DCha (e)7 63 IS2-I53 IPCT MeOH TEA/DMAR 2h 12/98 60% 151-I52 IPCT Cety1. TEA/DMAR 2h 12/98 60% 151-I52 IPCT Cety1. TEA/DMAR 2h x ZGIU(OCETY1)OH 68% 58-59 None MeOH TEA 2h 80/20 51-152 None MeOH TEA 2h 80/20 58-59 None MeOH TEA 2h 80/20 58-59 None MeOH TEA 2h 80/20 58-59 None MeOH TEA 2h 85/15 58-59 None MeOH TEA 2h 95/15	R = Me none TEA/INMAP ih 10/90 ZGIU(OME)OChA (e)7 63% 152-153 +9.2 IPCT MeOH TEA/INMAP 2h 12/88 60% 151-152 +9.4 IPCT Cetyl. TEA/INMAP 2h * ZGIU(OCETY1)OH 68% 58-59 -6.5 16 None MeOH TEA 2h 80/20 58-59 -6.5 1u none MeOH TEA 2h 80/20 58-59 -6.5 1u none MeOH TEA 2h 80/20 58-59 -6.5 1u none MeOH TEA 2h 85/15	R = Me none TEA/DMAP 1h 10/90 ZG1u(OMe)OH, DCha (e) ⁷ 53 152-153 +9.2 IPCT MeOH TEA/DMAP 2h 12/88 60% 151-152 +9.4 IPCT Cetyl. TEA/DMAP 2h * ZG1u(Ocetyl)OH 68% 58-59 -6.5 Me MeOH TEA/DMAP 2h * ZG1u(Ocetyl)OH 68% 58-59 -6.5 Pone MeOH TEA 2h 80/20 * ZG1u(Ocetyl)OH 68% 58-59 -6.5 Prone MeOH TEA 2h 80/20 * 74/26 *		IPCF	MeOH	TEA	zh	66/34	ł	408	174-175	6.01 -
IPCF MeOH TEA/DMAP 2h 12/88 60% 151-152 IPCF cety1. TEA/DMAP 2h * Zdlu(Ocety1)OH 68% 58-59 none MeOH TEA/DMAP 1h 74/26 61% 58-59 none MeOH TEA/DMAP 1h 74/26 58% 58-59 none MeOH TEA/DMAP 1h 74/26 58% 58-59 none MeOH TEA/DMAP 1h 74/26 58% 58-59 none MeOH TEA 2h 85/15 58 58 none MeOH TEA 2h 16/84 58 58	IPCF MeOH TEA/DMAP 2h 12/8B 60% 151-152 IPCF cety1. TEA/DMAP 2h * Zdlu(Ocety1)OH 68% 58-59 none MeOH TEA/DMAP 1h 74/26 68% 58-59 none MeOH TEA/DMAP 1h 74/26 58 58-59 none MeOH TEA/DMAP 1h 74/26 58 58-59 none MeOH TEA/DMAP 1h 74/26 58 58-59 none MeOH TEA 2h 85/15 58 58 none MeOH TEA 2h 16/84 58 58	IPCF MeOH TEA/DMAD 2h 12/88 608 151-152 +9.4 IPCF cety1. TEA/DMAD 2h * ZGIU(Ocety1)OH 608 151-152 +9.4 IPCF cety1. TEA/DMAD 2h * ZGIU(Ocety1)OH 608 58-59 -6.5 IPCP none MeOH TEA 2h 80/20 1 74/26 Iu none MeOH TEA 2h 85/15 16/94 16/94 Iu none MeOH TEA/DMAD 2h 85/15 16/94 16/94 uated. TEA/DMAD 2h 15/94 16/94 16/94 16/94 16/94	IPCF MeOH TEA/DMAP 2h 12/8B 60% 151-152 +9.4 IPCF cety1. TEA/DMAP 2h * ZG1u(Ocety1)OH 68% 58-59 -6.5 1PCF cety1. TEA/DMAP 2h * ZG1u(Ocety1)OH 68% 58-59 -6.5 10 none MeOH TEA 2h 80/20 1 74/26 1 74/26 1		R = Me	none	TEA/DMAP	អ	06/01	ZGlu(OMe)OH, Dcha	(e) ⁷ 63%	152–153	+9.2
IPCFcetyl. TEA/DMAP2h*ZG1u(Ocetyl)OH68%58–59noneMeOHTEA2h80/20noneMeOHTEA/DMAP1h74/26noneMeOHTEA2h85/15noneMeOHTEA/DMAP2h15/84noneMeOHTEA2h85/15noneMeOHTEA/DMAP2h15/84	IPCFcetyl. TEA/DMAP2h*ZGlu(Ocetyl)OH68%58-59noneMeOHTEA2h80/20noneMeOHTEA/DMAP1h74/26noneMeOHTEA2h85/15noneMeOHTEA/DMAP2h15/94noneMeOHTEA/DMAP2h15/94	IPCF cetyl. TEA/DWAP 2h * ZGIU(Ocetyl)OH 68% 58-59 -6.5 10 Anne MeOH TEA 2h 80/20 1h 74/26 1u none MeOH TEA/DWAP 1h 74/26 1h 74/26 1u none MeOH TEA/DWAP 2h 85/15 16/84 uene MeOH TEA/DWAP 2h 16/84 16/84 16/84 uated. Anno 150-160 0C. [c] 44.9 (c] 100 84 0C. [c] -9.3 (c) 12 ACOH) 1000 100 100 1000 10000000000000000000	IPCF Cety1. TEA/DMAP 2h * ZG1u(Ocety1)OH 68% 58-59 -6.5 10 None MeOH TEA 2h 80/20 1 <td></td> <td>IPCF</td> <td>MeOH</td> <td>TEA/DMAP</td> <td>2h</td> <td>12/88</td> <td>1</td> <td>608</td> <td>151-152</td> <td>49.4</td>		IPCF	MeOH	TEA/DMAP	2h	12/88	1	608	151-152	49.4
none MeOH TEA 2h none MeOH TEA/DMAP 1h none MeOH TEA 2h none MeOH TEA 2h	none MeOH TEA 2h none MeOH TEA/DMAR 1h none MeOH TEA 2h none MeOH TEA/DMAR 2h	6 SP none MeOH TEA 2h 80/20 Iu none MeOH TEA 2h 85/15 none MeOH TEA 2h 85/15 none MeOH TEA/DMARP 2h 16/84 uated. uated.	6 SP none MeOH TEA 2h 80/20 none MeOH TEA 2h 80/20 1u none MeOH TEA 2h 85/15 none MeOH TEA 2h 85/15 none MeOH TEA/DMARP 2h 16/84 uated. uated. Cone (α) mp 159-160 °C, (α) hat (b) mp 84 °C, (α) hat (cone (con		IPCF	cetyl.		2h	¥	ZGlu(Ocetyl)OH	68\$	58-59	-6.5 -
none MeOH TEA 2h none MeOH TEA/DMAN 1h none MeOH TEA 2h none MeOH TEA 2h	none MeoH TEA 2h none MeoH TEA/DMAN 1h none MeoH TEA 2h none MeoH TEA 2h	sp none MeOH TEA 2h B0/20 none MeOH TEA/DMORP 1h 74/26 lu none MeOH TEA/DMORP 2h 85/15 none MeOH TEA/DMORP 2h 85/15 none MeOH TEA/DMORP 2h 15/94 uated. 15/94 16/94	sp none MeOH TEA 2h BO/20 none MeOH TEA/DMAR 1h 74/26 lu none MeOH TEA 2h 85/15 none MeOH TEA/DMAR 2h 85/15 none MeOH TEA/DMAR 2h 16/84 uated. 159-160 0C, [α] +4.9 (C 1 MeOH) ; (b) mp 84 0C, [α] -9.3 (C 1.2 AOOH) ;	9									
none MeOH TEA/DMAP 1h none MeOH TEA 2h none MeOH TEA/DMAP 2h	none MeOH TEA/DMARP lh none MeOH TEA 2h none MeOH TEA/DMARP 2h ted.	In none WeOH TEA/DWAP IN 74/26 Lu none WeOH TEA/DWAP 2h 85/15 none MeOH TEA/DWAP 2h 16/84 uated.	none MeOH TEA/DMAP 1h none MeOH TEA/DMAP 2h none MeOH TEA/DMAP 2h : (a) mp 159-160 oC, $[\alpha]_{D}$ +4.9 (C 1	Z-Asp	none	MeOH	TEA	zh	80/20				
none Meoh TEA 2h none Meoh TEA/DMAP 2h	none MeOH TEA 2h none MeOH TEA/DMARP 2h	lu none MeOH TEA 2h 85/15 none MeOH TEA/DWARP 2h 16/84 uated. ncea (a) mp 159-160 of [c] 44.9 (c 1 MeOH) ((h) mp 84 of [c] -9.3 (c) 2 AcOH)	lu none MeOH TEA 2h 85/15 none MeOH TEA/DMARP 2h 16/84 uated. nces : (a) mp 159-160 °C, [α] _D +4.9 (c 1 MeOH) ; (b) mp 84 °C, [α] _D -9.3 (c 1.2 AcOH) ;		none	MeOH	TEA/DMAP	ЧT	74/26				
none MeOH TEA/DMAP 2h	none MeoH TEA/DWAP 2h	none MeOH TEA/DWAP 2h 16/84 uated. ncea (a) mn 159-160 0C [g1] +4.9 (c1] MeOH) ; (h) mn 84 0C. [g1] -9.3 (c1.2 AcOH) ;	none MeOH TEA/DMAPP 2h 16/84 uated. $\label{eq:2}$ uated. $\label{eq:2}$ nces : (a) mp 159-160 °C, [\alpha]_D +4.9 (c 1 MeOH) ; (b) mp 84 °C, [\alpha]_D -9.3 (c 1.2 AcOH) ; \\	Π	none	NeOH	TEA	zh	85/15				
	uated.	uated. ncea · (a) mp 159-160 oC. [g] +4.9 (c] MeOH) · (h) mp 84 oC. [g] -9.3 (c] 2 AcOH) ·	uated. nces : (a) mp 159-160 °C, [α] _D +4.9 (c 1 MeOH) ; (b) mp 84 °C, [α] _D -9.3 (c 1.2 AcOH) ;		none	MeOH	TEA/DWAP	2h	16/84				
uated.		nces · (a) mb 159-160 of. [α] +4.9 (c 1 MeOH) · (h) mb 84 of. [α] -9.3 (c 1.2 AcOH) ·	nces : (a) mp 159-160 °C, [α] _D +4.9 (c 1 MeOH) ; (b) mp 84 °C, [α] _D -9.3 (c 1.2 AcOH) ;	uateđ									

(e) mp 149-151 °C, $[\alpha]_{D}$ +10.1 (c 1 EtoH).

1666

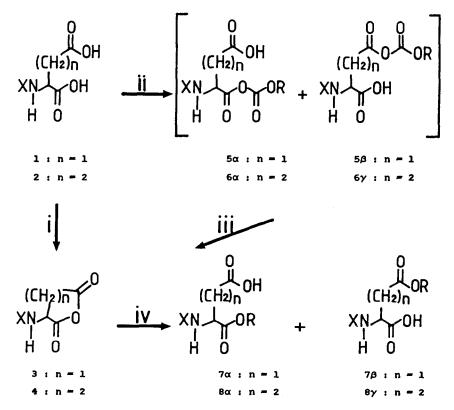
aqueous solution. The isomeric ratio was quantified by n.m.r..

The α -isomer of aspartic ester 7 was isolated, either as its di-cyclohexylamine salt precipitated from the crude mixture, or by column chromatography. The α and γ -isomers of glutamic esters 8 were separated on a silicagel column. The results of these experiments are listed in the table.

The following points emerged from these data : first, both methods (A and B) were comparable in terms of reaction time, total and relative yields of mono-esters formed (table, compare entries 1 and 2 ; 5 and 6 ; 9 and 10 ; 11 and 12). Moreover, the use of isopropenyl chloroformate was of particular interest when an unusual ester has to be prepared, thus preventing the preparation of the corresponding chloroformate. To illustrate this point, IPCF activation has been successfully used for the preparation of mono-esters with lipophilic properties (table, entries 7 and 13) as well as mono tertiobutyl ester (table, entry 8). Secondly, addition of DMAP largely favoured the mono-esterification of glutamic acid to the γ -position (table, entries 11, 12 and 13) whereas the general regioselectivity leading to the (7 α)-ester was observed for the aspartic acid in the same conditions (entries 4 and 8).

The activation of the N-protected di-acids with chloroformates was supposed to provide monoesterification via the internal anhydride formation.

Scheme : Mono-esterification of N-protected Asp and Giu.



i) DCC or Ac_zO ; ii) CICOOR, base; iii) - CO_z , - ROH (R = alkyl) or - acetone (R = isopropenyl); iv) ROH. The internal anhydride arises from decomposition of either or both mixed anhydrides 5α and 5β (respectively 6α and 6γ) which could not be isolated in our reaction conditions. The alcohol liberated reacted with the so formed internal anhydride. However, when isopropenyl chloroformate was used, the mixed anhydrides decomposed with liberation of acetone instead of alcohol; thus addition of an alcohol ied to the expected corresponding esters 7 or 8.

To support this pathway, we have been able to isolate internal anhydride 3 from N-Z-aspartic acid, in moderated yield, when activation with iPCF was performed in the absence of alcohol. To ascertain the formation of this intermediate 3 or 4 we reinvestigated the reactivity of the internal anhydride towards alcohol in our experimental conditions. We prepared respectively the internal anhydride of N-Z-glutamic acid and N-Z-aspartic acid by the usual DCC activation. We examinated by n.m.r. the ratio of 7 α or 8 α versus 7 β or 8 γ mono-ester formed when this internal anhydride was opened in the presence of methanol, according to the nature of the base added (table, entries 14, 15, 16 and 17). The observed regioselectivity in these conditions was identical to the one obtained when N-protected Asp or Glu was reacted with methyl chloroformate as well as with IPCF and methanol (table, entries 3, 4, 9, 10, 11 and 12) ; we noticed the high proportion of Glu- γ -ester 8 γ formed when the anhydride 3 was open in the presence of DMAP (table, entry 17), as well as by direct chloroformate activation with DMAP catalysis (table, entries 11, 12 and 13) ; these results support also the internal anhydride formation in this latter process.

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