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1,2-Dimethoxy-4,5-dimethylene: A new protecting group for acyclic amino acid derivatives prepared by Stevens rearrangement

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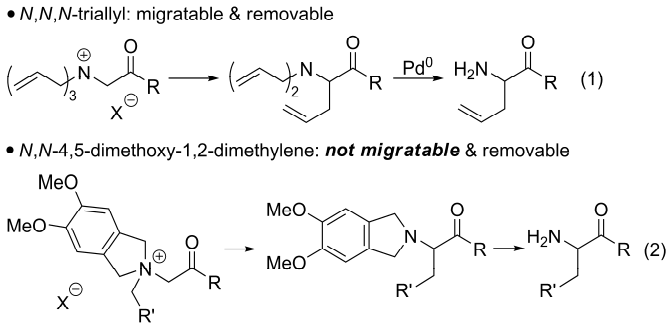
ABSTRACT

A new protecting group, 1,2-dimethoxy-4,5-dimethylene, for acyclic amino acid derivatives could be introduced by *N*,*N*-dialkylation with 1,2-bis(bromomethyl)-4,5-dimethoxybenzene (**1**) and removed via amine de-alkylation with acyl chlorides. The method can be used with base-induced [2,3] and [1,2] Stevens rearrangement products.

As part of the study of base-induced Stevens and Sommelet–Hauser rearrangements, we required a new protecting group for amino acid derivatives because the rearrangements of acyclic amino acid-derived tetraalkylammonium ylides produce the *N*,*N*-dialkyl amino acid derivatives as the products,[1] and efficient methods to remove the *N*,*N*-dialkyl substituents from nitrogen are limited.[2] Two successful examples were reported by Workman[3a] or Arboré.[3b] Their groups performed palladium-catalysed de-allylation of an *N*,*N*-diallyl α-amino acid derivative prepared by [2,3] Stevens rearrangement. However, the *N*-allyl substituent also functions as a reactive migrating group, which restricts the scope and limits the rearrangement products to α-allyl amino acid derivatives (Scheme 1, eq 1). Thus, we have been looking for a new *N*,*N*-dialkyl-type protecting group for amino acid derivatives that can be alkylated with alkyl halides to yield the corresponding tetraalkylammonium salts and that do not migrate under the rearrangement conditions. Herein, we report a new protecting group, 1,2-dimethoxy-4,5-dimethylene, for acyclic α-amino acid derivatives (Scheme 1, eq 2). This group could be introduced by *N*,*N*-dialkylation with 1,2-bis(bromomethyl)-4,5-dimethoxybenzene (**1**), can be removed via amine de-alkylation with acyl chlorides,[4,5] and does not affect the base-induced Stevens rearrangement.

A protecting reagent, 1,2-bis(bromomethyl)-4,5-dimethoxybenzene (**1**), was prepared by the bisbromomethylation of 1,2-dimethoxybenzene.[6] *N*,*N*-Dialkylation of representative L-α-amino acid methyl esters **2** with **1** afforded the corresponding isoindoline derivatives **3** in moderate yields (Table 1, entries 1–6, 50–86%).



Scheme 1 Removal of *N*,*N*-dialkyl substituents from Stevens rearrangement product

First, we examined the conversion of the 5,6-dimethoxyisoindoline derivatives **3** into the *N*-ethoxycarbonyl-α-amino acid methyl esters **5** via amine de-alkylation (Table 2). Treatment of **3a–3e** with ethyl chloroformate as a de-alkylation reagent in 1,2-dichloromethane under reflux gave the ring-opening products **4a–4e** in 73–92% yields (entries 1–5). The reaction of the phenylglycine derivative **3f** resulted in a lower yield (entry 6, 30%) because of the formation of methyl 2-chlorophenylacetate (**4f'**) as a side product (34%, 31% ee, *R*) resulting from substitution at the α-position of the ester-carbonyl.[7] The *N*-2-chloromethyl-4,5-dimethoxybenzyl substituents, as in **4**, were removed by treatment with trifluoroacetic acid (TFA) at room temperature to produce **5a–5f** in 71% to quantitative yields with minimal racemization.[8]

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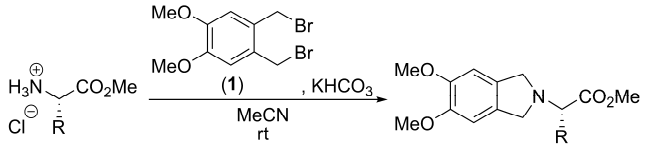
Table 1 *N*,*N*-Dialkylation of representative L-α-amino acid esters **2** with **1**[a]

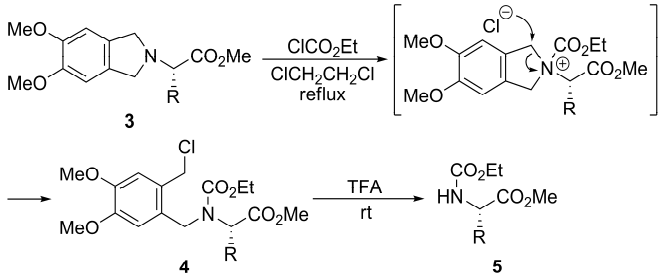


2 **3**

Entry	R		**3** (%)[b]
1	CH_2Ph	**a**	77
2	Me	**b**	50
3	*i*-Bu	**c**	60
4	*i*-Pr	**d**	67
5	(*S*)-*sec*-Bu	**e**	56
6	Ph	**f**	86

[a] Reaction conditions: **1** (1.0 equiv), **2** (1.0–1.2 equiv), $KHCO_3$ (3–6 equiv), MeCN (0.1–0.2 M), rt, 12–18 h. [b] Isolated yield.

Table 2 Conversion of **3** into *N*-ethoxycarbonyl-α-amino acid methyl esters **5**[a]



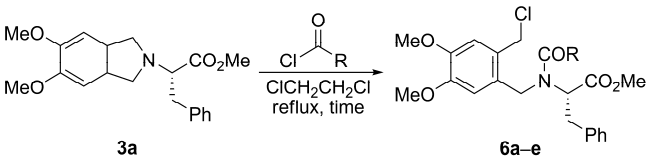
Entry	R		**4** (%)[b,c]	**5** (%)[b]	ee of **5** (%)
1	CH_2Ph	**a**	88	91	>99[d]
2	Me	**b**	84	79	99[e]
3	*i*-Bu	**c**	92	89	>99[e]
4	*i*-Pr	**d**	73	93	99[e]
5	(*S*)-*sec*-Bu	**e**	75	quant.	94[e]
6	Ph	**f**	30[f]	71	91[d]

[a] Reaction conditions: **3** (1.0 equiv), $ClCO_2Et$ (1.2–3.0 equiv), 1,2-dichloroethane (0.1 M), reflux, 2–3 days; **4** (1.0 equiv), TFA (0.1 M), rt, 48 h. [b] Isolated yield. [c] The products may contain a small amount of impurities because of the difficulty of purification. [d] Determined by HPLC analysis using a chiral column. [e] Determined by the comparison of the specific rotation with that of the authentic sample prepared from L-amino acids. [f] Methyl 2-chlorophenylacetate (**4f'**) was obtained with 34% yield.

With these results in hand, we investigated the amine de-alkylation of **3a** using various types of acyl chloride to obtain *N*-(2-chloromethyl-4,5-dimethoxy)benzyl derivatives **6a**–**6e** (Table 3). Both *N*,*N*-substituents, as in **6a**–**6e**, were easily removable by previously reported methods.[2] Treatment of **3a** with benzyl (Cbz-Cl), allyl (Alloc-Cl), and *p*-nitrophenyl chloroformate[9] resulted in lower yields of **6** (entries 1–3, **6a**–**6c**: 12–36%). Fortunately, when the reaction was carried out with 2,2,2-trichloroethyl chloroformate (Troc-Cl), the de-alkylated **6d** was obtained in 86% yield (entry 4). The use of trichloroacetyl chloride did not give the corresponding product **6e** (entry 5).

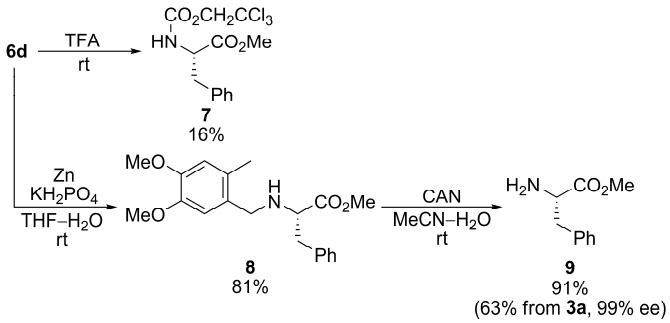
To obtain the non-*N*-protected α-amino acid ester **9** from **6d**,[10] we tried to remove the *N*-benzylic substituent, as in **6d**, by treatment with TFA under the same conditions as for **4a** described in Table 2 (Scheme 2). Unfortunately, the expected de-benzylated product **7** was obtained in only 16% yield. Thus, we changed the deprotection process; first, the *N*-Troc group, as in **6d**, was removed by reductive elimination with zinc[11] to give 4,5-dimethoxy-2-methylbenzyl derivative **8** with 81% yield. The remaining *N*-benzylic substituent was removed by oxidative cleavage with ceric ammonium nitrate (CAN)[12] to afford **9** in 91% yield. The enantio-purity of **9** thus obtained was 99% ee. Racemization was not observed during this process (**2a** to **9**).

Table 3 Amine de-alkylation of **3a** using various types of acyl chloride



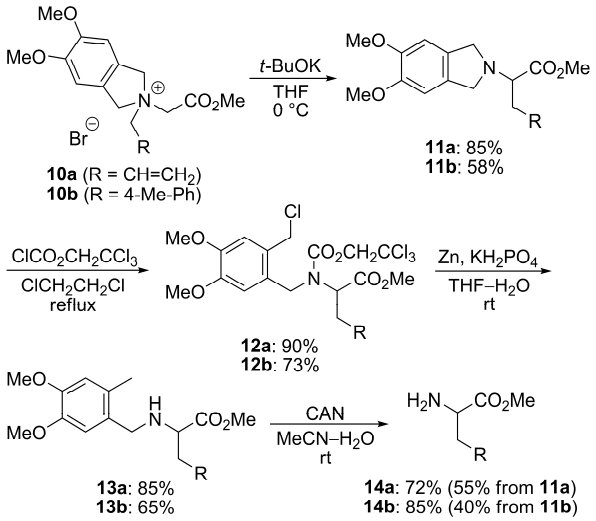
Entry	R		time (h)	**6** (%)[a]
1	OCH_2Ph	**a**	52	12[b]
2	$OCH_2CH{=}CH_2$	**b**	71	34[c]
3	O-*p*-NO_2-Ph	**c**	63	36
4	OCH_2CCl_3	**d**	62	86
5	CCl_3	**e**	60	messy

[a] Isolated yield. [b] Recovered **3a** in 75% yield. [c] Recovered **3b** in 41% yield.



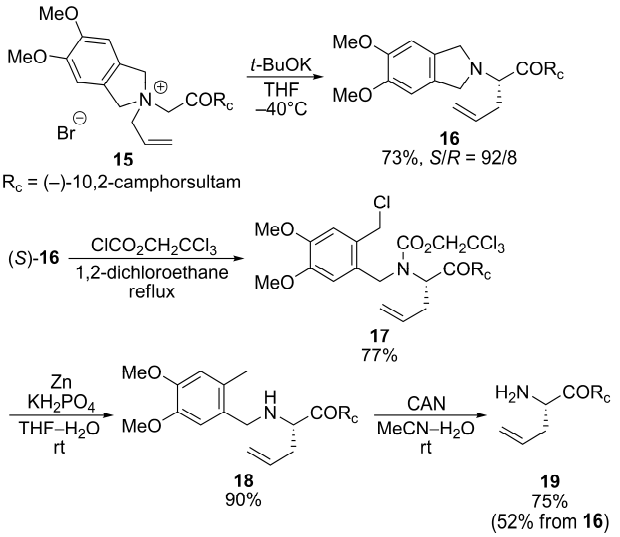
Scheme 2 Preparation of non-*N*-protected α-amino acid ester **9** from **6d** by reductive elimination and oxidative cleavage

We applied this synthetic method to prepare non-*N*-protected unnatural α-amino acid esters **14** via the base-induced [2,3] or [1,2] Stevens rearrangements (Scheme 3). Treatment of ammonium salts **10** (**10a**: R = CH=CH_2, **10b**: R = 4-Me-Ph) with potassium *tert*-butoxide in THF at 0 °C afforded **11** as rearrangement products (**11a**: 85%, **11b**: 58%). The 1,2-dimethoxy-4,5-dimethylene group, as in **11**, was removed to afford the desired products **14** by the procedures described in Scheme 1.



Scheme 3 Preparation of non-*N*-protected α-amino acid esters **14** via [2,3] or [1,2] Stevens rearrangements

Similarly, this method was applied to the asymmetric [2,3] Stevens rearrangement developed by Workman et al. (Scheme 4).[3a] When the reaction of ammonium salt **15** with potassium *tert*-butoxide was carried out in THF at –40 °C for 17 h, the corresponding α-allylglycine derivative **16** was obtained in 73% yield (*S*/*R* = 92/8).[13,14] The removal of the *N*,*N*-substituents, as in **16**, by the same procedures described in Scheme 2 and 3, gave **19** in 52% overall yield without epimerization.



Scheme 4 Preparation of non-*N*-protected α-amino acid ester **19** via the asymmetric [2,3] Stevens rearrangement of **15**

In conclusion, we have reported a new protecting group, 1,2-dimethoxy-4,5-dimethylene, for acyclic amino acid esters. This group could be introduced via *N*,*N*-dialkylation with 1,2-bis(bromomethyl)-4,5-dimethoxybenzene (**1**) and removed via amine de-alkylation with acyl chlorides, reductive elimination, and oxidative cleavage. The method can be used with base-induced [2,3] and [1,2] Stevens rearrangement products.

Acknowledgments

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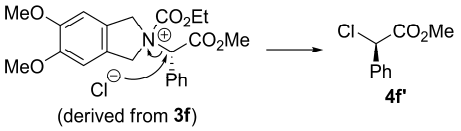
References and notes

1. For reviews: (a) Sweeney, J. B. *Chem. Soc. Rev.* **2009**, *38*, 1027–1038; (b) *Nitrogen, Oxygen, and Sulfur Ylide Chemistry*; Clark, J. S. Ed.; Oxford University Press; Oxford, 2002; (c) Markó, I. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I. Eds.; Pergamon: Oxford, 1991; Vol. 3, Chap. 3.10.
2. For a review: Wuts, P. G. M.; Greene, T. W. In *Green's Protective Groups in Organic Synthesis, 4th edition*; Wiley: Hoboken, 2006; Chap. 7.
3. (a) Workman J. A.; Garrido, N. P.; Sançon, J.; Roberts, E.; Wessel, H. P.; Sweeney, J. B. *J. Am. Chem. Soc.* **2005**, *127*, 1066–1067; (b) Arboré, A. P. A.; Cane-Honeysett, D. J.; Coldham, I.; Middleton, M. L. *Synlett* **2000**, 236–238.
4. For a review: Cooley, J. H.; Evain, E. J. *Synthesis* **1989**, 1–7.
5. Representative studies about de-alkylation of amines using acyl halide derivatives: (a) Bhat, R. G.; Ghosh, Y.; Chandrasekaran, S. *Tetrahedron Lett.* **2004**, *45*, 7983–7985; (b) Dave, P. R.; Kumar, K. A.; Duddu, R.; Axenrod, T.; Dai, R.; Das, K. K.; Guan, X.-P.; Sun, J.; Trivedi, N. J.; Gilardi, R. D. *J. Org. Chem.* **2000**, *65*, 1207–1209; (c) Miller, M. W.; Vice, S. F.; McCombie, S. W. *Tetrahedron Lett.* **1998**, *39*, 3429–3432; (d) Ferguson, J. R.; Lumbard, K. W.; Scheinmann, F.; Stachulski, A. V.; Stjernlöf, P.; Sundell, S. *Tetrahedron Lett.* **1995**, *36*, 8867–8870; (e) Yang, B. V.; O'Rourke, D.; Li, J. *Synlett* **1993**, 195–196.
6. Diederich, F.; Jonas, U.; Gramlich, V.; Herrmann, A.; Ringsdorf, H.; Thilgen, C. *Helv. Chim. Acta* **1993**, *76*, 2445–2453.
7. The α-position of the ester-carbonyl, as in **3f**, was reactive for substitution because of benzylic. We found that **4f'** is easily racemized under various conditions.



8. The formation of *N*-acylammonium intermediate derived from **3f** might cause racemization because of high acidity of the α-proton.
9. Examples of amine de-alkylation using *p*-nitrophenyl chloroformate: (a) Jones, A. D.; Zelle, R. E.; Silverman, I. R. PCT Int. Appl. WO 2009035652 **2009**; (b) Kopach, M. E.; Fray, A. H.; Meyers, A. I. *J. Am. Chem. Soc.* **1996**, *118*, 9876–9883.
10. We attempted to prepare **9** by hydrogenolysis of **3a** (Pd-C, H_2, EtOAc, rt, 5.5 h); however, the reaction did not proceed with the recovery of **3a** in quantitatively.
11. Just, G.; Grozinger, K. *Synthesis* **1976**, 457–458.
12. Bull, S. D.; Davies, S. G.; Kelly, P. M.; Gianotti, M.; Smith, A. D. *J. Chem. Soc., Perkin Trans 1* **2001**, 3106–3111. Removal of 4,5-dimethoxy-2-methylbenzyl substituent as in **8** with TFA did not proceed at all. Hydrogenolysis of **8** (5 mol% Pd-C, 0.3 MPa H_2, EtOAc, rt, 41 h) gave **9** in 23% yield (99% ee) with the recovery of **8** in 65% yield.
13. The *S*/*R* configuration was assigned tentatively by the analogy with ref. 3a.
14. We attempted the [1,2] Stevens rearrangement of *N*-(4-methylbenzyl)ammonium salt; however, the stereoselectivity was lower (dr = 6/4 to 8/2).

Supplementary Material

Supplementary data associated with this article can be found, in the online version, at XXX.