Pergamon

Tetrahedron Letters 43 (2002) 4589–4592

TETRAHEDRON LETTERS

2,2-Dimethyl-2-(*o*-nitrophenyl)acetyl (DMNA) as an assisted cleavage protecting group for amines

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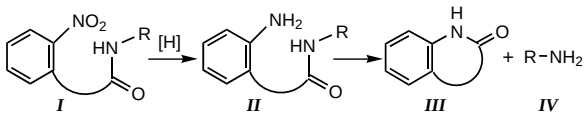
Received 6 April 2002; revised 7 May 2002; accepted 9 May 2002

Abstract—2,2-Dimethyl-2-(*o*-nitrophenyl)acetyl group (DMNA) was explored as an assisted cleavage protecting group for amines and a one-step deprotection condition was developed for its efficient removal using hydrogenation in the presence of Pd–C or PtO_2 catalyst and 10% HOAc in MeOH. DMNA was found to be especially useful for the synthesis of *gem*-diamino compounds using Hofmann rearrangement.

Amines often need to be protected in organic transformations such as peptide coupling reactions. The most commonly used protecting groups are carbamoyl groups like Z, Fmoc, and Boc.[1] These carbamoyl protecting groups work well under most circumstances. However, there are cases where carbamoyl protecting groups cannot be used and other protecting groups have to be sought to protect amines in a more stable form such as an amide.

o-Nitrophenyl amides ***I*** such as *o*-nitrophenoxyacetamide, 3-(*o*-nitrophenyl)propionamide, *o*-nitrobenzamide, and 3-(4-*tert*-butyl-2,6-dinitrophenyl)-2,2-dimethylpropionamide have been explored as assisted cleavage protecting groups for amines (Scheme 1).[1] Deprotection can be accomplished by reduction of the nitro group and the resulting amine ***II*** is sufficiently nucleophilic to undergo a facile intramolecular cyclization reaction releasing the free amine ***IV***. The first step of nitro reduction could be accomplished using zinc and ammonium chloride,[2] hydrogen transfer reduction using cyclohexene or sodium phosphinate,[3] or hydrogenation using PtO_2.[4] The second cyclization step usually proceeds under acidic conditions such as alcoholic HCl[2] or through a copper(II)-catalyzed hydrolysis of the benzamide.[4] In the case of 3-(4-*tert*-butyl-2,6-dinitrophenyl)-2,2-dimethylpropionamide, deprotection was accomplished in a one-step process using Ti^{3+} ion in an aqueous buffer of pH 7.0.[5] The availability of these mild conditions for the reduction of nitro group makes it possible to selectively remove these protecting groups in the presence of various other functional groups. The enhanced UV absorption and lipophilicity of nitrophenyl group also facilitate the separation and purification of the highly polar amino compounds they protect. In addition, *o*-nitrophenyl amides are easily prepared and stable to most reaction conditions. Besides their application as protecting groups, they have also been used as a promoiety in prodrug design.[6,7]



Scheme 1.

In our efforts to synthesize reductively activated prodrugs of FUDR, we found that 2,2-dimethyl-2-(*o*-aminophenyl)acetates cyclize very quickly with half lives in the order of seconds.[7] The two methyl groups attached to the α-position of the carbonyl were introduced to restrict the rotational freedom (the conformation) of the molecule and thus facilitate the attack on the ester carbonyl by the nucleophilic amine. The corresponding 2,2-dimethyl-2-(*o*-aminophenyl) acetamides were found to be sufficiently stable and could be isolated by flash column chromatography. Similar to other *o*-aminophenyl amides, the intramolecular cyclization reaction of 2,2-dimethyl-2-(*o*-aminophenyl) acetamides was promoted by the presence of acid leading to the cleavage of the amide bonds and the release of the free amines. Here, we describe the development of 2,2-

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0040-4039/02/$ - see front matter
PII: S0040-4039(02)00891-2

dimethyl-2-(*o*-nitrophenyl)acetyl group (DMNA) as an assisted cleavage protecting group for amines and its application in the synthesis of *gem*-diamino compounds.

DMNA protecting group can be easily introduced in high yield using the corresponding acyl chloride or other typical peptide coupling methods. In this communication, we focused mainly on the optimization of the deprotection conditions: the reduction and the subsequent cyclization release process. N^{α}-DMNA-phenylalanine methyl amide (***1***) was used as a model compound to work out the deprotection conditions. Hydrogenation using 5% Pd–C in methanol was found to efficiently reduce compound ***1*** to the corresponding amine ***2*** as shown in Scheme 1. Under the neutral hydrogenation condition, no significant cyclization was observed.[8]

We then examined the effects of four different acids (HCl, TFA, TsOH, and HOAc) on the cyclization release process of the amino compound ***2***. The cyclization reaction was very fast under acidic conditions; it was completed within 30 min after the acid was added but the amount of acid used was found to be critical with 1.5 equiv. required for the three stronger acids (HCl, TsOH, TFA) and at least 5 equiv. needed for the weaker HOAc. The product composition was similar for the acids tested with phenylalanine methyl amide (***3***) isolated in moderate yields (70–85%) and 3,3-dimethyl-1,3-dihydroindol-2-one (***4***) as the other major product in 80–90% yield (Scheme 2 and Table 1). In addition, a dehydration product, N^{α}-(3,3-dimethyl-3*H*-indole-2-yl)phenylalanine methyl amide (***5***) was observed using LC–MS and characterized using NMR after isolation.[9] Although only observed as a minor product ($\leq$10%), the dehydrated compound ***5*** was more significant for the three stronger acids than for HOAc (Table 1). Since HOAc is a mild acid and is tolerated by many other functional groups, we consider it to be the reagent of choice for the deprotection.

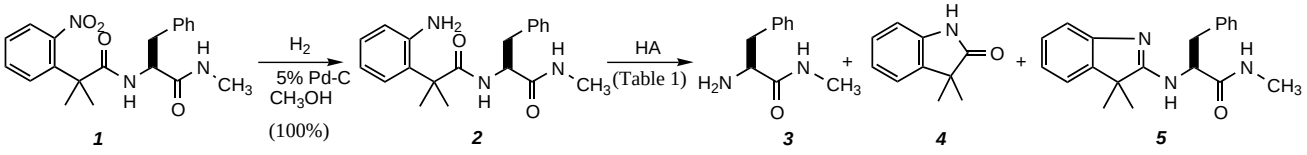
Having accomplished the deprotection of DMNA in a two-step sequence, we decided to explore a one-step deprotection process using hydrogenation in the presence of dilute HOAc (Scheme 3). When compound ***1*** was subjected to hydrogenation in the presence of 10% acetic acid in methanol, H-Phe-NH-CH_3 (***3***) was isolated in 97% yield, which is significantly higher than the two-step deprotection process described above. Under this one-step deprotection condition, two cyclized products were isolated: 3,3-dimethyl-1,3-dihydroindol-2-one (***4***) in 33% yield and 1-hydroxy-3,3-dimethyl-1,3-dihydroindol-2-one (***8***) in 57% yield. The formation of hydroxy lactam ***8*** in higher yield suggests that the intermediate in the reduction of nitro group, hydroxylamine ***6***, preferentially undergoes the desired cyclization reaction.[2] Because of its higher nucleophilicity, the cyclization of the hydroxylamine intermediate ***6*** is expected to be faster, thus decreasing the formation of the corresponding amine intermediate ***7***, which in turn reduces the formation of the dehydration side product ***8*** and improves the efficiency of deprotection.

Table 1. Effect of acid used on the yield of cyclization of ***2***[a]

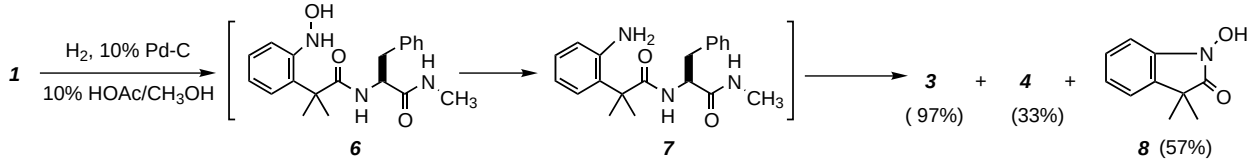
Acid	Equiv.	***3*** (%)[b]	***4*** (%)[b]	***5*** (%)[b]
TFA	1.5	70	89	10
HCl	1.5	75	80	8
TsOH	1.5	76	82	8
HOAc	5.0	85	91	<2[c]

[a] Experiments carried out with 0.05 M solution of compound ***2***.
[b] Isolated yields unless otherwise noted.
[c] Estimated based on HPLC.

The above one-step deprotection condition was used to deprotect a number of other N^{α}-DMNA-protected amino acid derivatives and dipeptides.[10] As shown in Table 2, the corresponding amines were obtained in high yields (80–97%) using our one-step deprotection procedure as compared to moderate yields (42–85%) reported using other deprotection methods.[1] In addition, our one-step deprotection of DMNA is simple and more selective. Under this mild acidic condition, Boc (***13***→***20***) and *tert*-butyl ester (***14***→***21***) were not affected. However, benzyl ester (***12***→***19***) was reductively cleaved while Z (***14***) and benzyl ether (***15***) were partially cleaved. Selectivity can be achieved in the latter case when the more selective PtO_2 catalyst was used (***14***→***21*** and ***15***→***22***). This is consistent with the



Scheme 2.

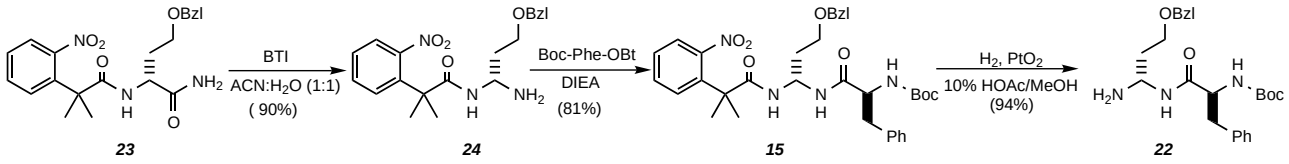


Scheme 3.

Table 2. Deprotection of DMNA-protected amino acids and peptides using the one-step deprotection process[10]

Entry	N^{α}-DMNA-protected AA or peptides	Catalyst	AA or peptides[b]	Yield (%)[c]	Yield ***4***+***8***% (***8***/***4***)[c]
1	N^{α}-DMNA-Phe-NHMe (***1***)	10% Pd–C	H-Phe-NHMe (***3***)	97	91 (1.7/1)
2	N^{α}-DMNA-Phe-Gly-NH_2 (***9***)	10% Pd–C	H-Phe-Gly-NH_2 (***16***)	88	91 (1.7/1)
3	N^{α}-DMNA-Val-Gly-NH_2 (***10***)	10% Pd–C	H-Val-Gly-NH_2 (***17***)	94	93 (0.9/1)
4	N^{α}-DMNA-Ser-OCH_3 (***11***)	10% Pd–C	H-Ser-OCH_3 (***18***)	86	89 (1.5/1)
5	N^{α}-DMNA-Ile-OBzl (***12***)	10% Pd–C	H-Ile-OH (***19***)	85	95 (1.2/1)
6	N^{α}-DMNA-Lys(Boc)-OCH_3 (***13***)	10% Pd–C	H-Lys(Boc)-OCH_3 (***20***)	80	88 (1/1)
7	N^{α}-DMNA-Lys(Z)-OBu^t (***14***)	PtO_2[a]	H-Lys(Z)-OBu^t (***21***)	81	92 (4.7/1)
8	N^{α}-Boc-Phe-gHse(OBzl)-DMNA (***15***)	PtO_2[a]	N^{α}-Boc-Phe-gHse(OBzl)-H (***22***)	94	98 (8.8/1)

[a] The Z or Bzl protecting group was partially cleaved if 10% Pd–C is used as the catalyst.
[b] All compounds were confirmed by NMR and LC–MS.
[c] Isolated yields.



Scheme 4.

fact that PtO_2 is more selective and it causes more hydrogenation than hydrogenolysis.[11] It should also be noted that the ratio of the hydroxy lactam ***8*** to lactam ***4*** isolated were increased to around 5:1 or better when PtO_2 was used as a catalyst. As expected, the DMNA protecting group is stable to conditions used to remove Boc or Fmoc.[12]

In addition to its convenient and mild deprotection conditions, DMNA protection of amines in the form of stable amides would find specific applications in cases where carbamoyl protecting groups such as Z and Boc are not suitable. One such example is the bis(trifluoroacetoxy)iodobenzene (BTI)-mediated Hofmann rearrangement of terminal α-amino acid amides we attempted recently. BTI-mediated Hofmann rearrangement is the most widely used method for the synthesis of peptide analogues containing a retro-inverso peptide bond isostere.[13] The monocarbamoyl (Z or Boc) protected *gem*-diamines lacked sufficient stability under the Hofmann rearrangement conditions.[13,14] However, when DMNA-protected D-Hse(OBzl) amide (***23***) was subjected to BTI-mediated Hofmann rearrangement, N^{α}-DMNA-D-gHse(OBzl)-NH_2 (***24***) was easily obtained in 90% yield (Scheme 4), and DMNA was successfully removed, after Boc-Phe-OH coupling, by the procedure described above to give N^{α}-Boc-Phe-gHse(OBzl)-NH_2 (***22***).[15] This example demonstrated the usefulness of DMNA in the synthesis of peptide analogs containing the retro-inverso peptide bond isostere.

In conclusion, we explored the use of 2,2-dimethyl-2-(*o*-nitrophenyl) acetyl group (DMNA) as an assisted cleavage protecting group and developed a one-step process for its efficient deprotection. We have shown that DMNA is especially useful as a protecting group for the synthesis of *gem*-diamino compounds using BTI-mediated Hofmann rearrangement reaction, where the common carbamoyl protecting groups like Z and Boc could not be used.

Acknowledgements

We gratefully acknowledge the financial support of a pilot project grant from the Gallo Prostate Cancer Center of the Cancer Institute of New Jersey.

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8. Typical procedure: To a solution of N^{α}-DMNA-phenylalanine methyl amide (***1***, 1 mmol) in methanol (20 mL) was added catalytic amount of 5% Pd–C. H_2 was introduced using a balloon and maintained for 30 min. The Pd–C catalyst was removed by filtration through Celite 545 and the filtrate was concentrated in vacuo below 20°C. The product was dried in vacuo and gave N^{α}-(2,2-dimethyl-2-(*o*-aminophenyl)acetyl) phenylalanine methyl amide (***2***) in quantitative yield.

9. Spectroscopic data for N^{α}-(3,3-dimethyl-3*H*-indole-2-yl)phenylalanine methyl amide (***5***): ^{1}H NMR (CD_3OD, 200 MHz): δ ppm 7.32–6.89 (10H, m, Ar), 4.70 (1H, dd, $J=5.8$ Hz, 9.2 Hz, CH), 3.28 (1H, dd, $J=5.8$ Hz, 13.8 Hz, Phe-CH_2), 3.05 (1H, $J=9.2$ Hz, 13.8 Hz, Phe-CH_2), 2.75 (3H, s, N-CH_3), 1.36 (3H, s, CH_3), 1.16 (3H, s, CH_3); ^{13}C NMR (CD_3OD, 200 MHz): 136.6, 128.5, 127.4, 126.8, 125.8, 120.9, 120.0, 114.3, 56.9, 37.3, 24.5, 23.3, 22.7; LC–MS (ESI): 322.0 (MH^+).
10. Typical procedure: N^{α}-DMNA-amino acid or dipeptide (1 mmol) in 10% HOAc in methanol (20 mL) was added a catalytic amount of 10% Pd–C or PtO_2. H_2 was introduced using a balloon and maintained for 30 min. The catalyst was removed by filtration through Celite 545 and the filtrate was concentrated and the product was isolated either by flash column chromatography with an initial ethyl acetate wash to remove all side products followed by methanol to elute the desired product or by a cationic exchange column eluted with 1% TEA in methanol.
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15. Spectroscopic data for N^{α}-DMNA-D-gHse(OBzl)-H (***24***): ^{1}H NMR (CD_3OD, 200 MHz) δ ppm 7.93–7.29 (m, 9H, Ar), 5.19 (t, 1H, J=6.6 Hz, CH), 4.95 (s, 2H, Bzl-CH_2), 3.66 (t, 2H, $J=6$ Hz, CH_2-O), 2.20 (dd, 2H, $J=6.6$ Hz, 6 Hz, CH_2), 1.65 (s, 3H, CH_3), 1.64 (s, 3H, CH_3); ^{13}C NMR (CD_3OD, 200 MHz): 177.3, 148.5, 137.6, 137.3, 128.2, 127.6, 127.3, 127.0, 124.7, 72.4, 64.6, 56.8, 30.9, 25.9, 25.7; LC–MS (ESI): 372.23 (MH^+), 743.42 (2M+1).
Spectroscopic data for N^{α}-Boc-Phe-gHse(OBzl)-DMNA (***15***): ^{1}H NMR ($CDCl_3$, 200 MHz): δ ppm 7.24–7.84 (m, 14H, Ar), 5.05 (m, 1H, CH), 4.44 (s, 2H, Bzl-CH_2), 4.36 (m, 1H, Phe-CH), 3.62–3.47 (m, 2H, CH_2-O), 3.25 (dd, 1H, $J=13.6$ Hz, 5.2 Hz, Phe-CH_2), 3.0 (dd, 1H, $J=13.6$ Hz, 8.6 Hz, Phe-CH_2), 2.20 (m, 2H, CH_2), 1.59 (s, 3H, CH_3), 1.54 (s, 3H, CH_3), 1.38 (s, 9H, Boc); ^{13}C NMR ($CDCl_3$, 200 MHz): 175.5, 171.6, 155.4, 149.3, 139.2, 137.9, 137.1, 133.2, 129.6, 128.7, 128.6, 128.1, 128.0, 126.8, 125.6, 79.9, 73.4, 66.5, 57.3, 55.8, 47.0, 38.2, 32.4, 28.4, 27.7, 27.4, LC–MS (ESI): 619 (MH^+).
Spectroscopic data for N^{α}-Boc-Phe-gHse(OBzl)-H·HCl (***22***): ^{1}H NMR (CD_3OD, 200 MHz): δ ppm 7.36–7.23 (m, 5H, Ar), 5.30 (m, 1H, CH), 4.53 (s, 2H, Bzl-CH_2), 4.35 (dd, 1H, $J=9.2$ Hz, 6 Hz, Phe-CH), 3.6 (m, 2H, CH_2-O), 3.1 (dd, 1H, $J=13.6$ Hz, 9.2 Hz, Phe-CH_2), 2.8 (d, 2H, Phe-CH_2), 2.2 (m, 2H, CH_2), 1.35 (s, 9H, Boc); ^{13}C NMR (CD_3OD, 200 MHz): 173.4, 155.8, 137.4, 136.6, 128.7, 128.5, 127.6, 127.5, 127.0, 126.9, 125.9, 78.9, 72.3, 64.2, 55.7, 55.4, 31.2, 26.7; LC–MS (ESI): 411 (MH^+–17), 428.18 (MH^+), 450.1 (M+Na).