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# A Facile Synthesis of Polysubstituted Pyrroles

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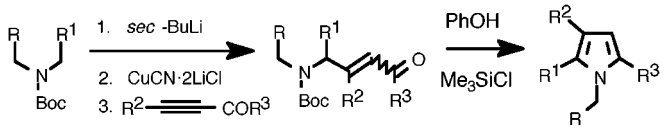
## ABSTRACT




**α-Aminoalkylcuprates prepared from CuX·2LiCl (X = Cl, CN) and 1 equiv of an α-lithiocarbamate undergo conjugate addition reactions to α,β-alkynyl ketones in moderate to good yields, affording *E*:*Z* mixtures of α,β-enones. Treatment of the conjugate adducts with PhOH/TMSCl in $CH_2Cl_2$ effected carbamate deprotection and cyclization to afford a flexible two-step synthesis of substituted pyrroles.**

Pyrroles represent an important class of heterocyclic compounds,[1,2] and numerous synthetic routes exist for their preparation.[3] Many procedures, however, provide limited access to pyrroles in terms of substituents and substitution patterns. One broad strategy employs 1,4-conjugate addition reactions to construct the carbon skeleton of the pyrrole framework followed by cyclization reactions. Conjugate addition reactions of α-aminoketones to acetylenic esters, enamines to chloroacrylonitrile, betaines to activated alkynes, α-amino acid derivatives to α,β-unsaturated esters or nitriles, and α-azido esters to malononitriles[4] afford pyrroles with a wide range of substitution patterns.[3a] With the exception of the chloroacrylonitrile procedure which affords 2,3-disubstituted pyrroles, these conjugate addition routes lead to pyrroles containing electron-withdrawing groups (EWG) at the 3-position (e.g., CN, CHO, $CO_2R$, etc.). The conjugate addition of isocyanide-derived carbanions stabilized with an additional EWG to a variety of α,β-unsaturated functional groups (e.g., ester, ketone, nitro, and sulfone) provides a general route to substituted pyrroles containing an EWG.[5] In some instances the EWG can be removed in a subsequent step. Polysubstituted pyrroles are also available from transition metal intermediates (e.g, W,[6a−c] Cr,[6c−d] Zr,[6e] Ti[6f]), reductive couplings,[7] and aza Wittig reactions[8] and by several

(1) For biologically important pyrroles see: (a) Lainton, J. A. H.; Huffman, J. W.; Martin, B. R.; Compton, D. R. *Tetrahedron Lett.* **1995**, *36*, 1401. (b) De Leon, C. Y.; Ganem, B. *Tetrahedron* **1997**, *53*, 7731. (c) Jacobi, P. A.; Coutts, L. D.; Guo, J. S.; Hauck, S. I.; Leung, S. H. *J. Org. Chem.* **2000**, *65*, 205. (d) Gupton, J. T.; Krumpe, K. E.; Burnham, B. C.; Dwornik, K. A.; Petrich, S. A.; Du, K. X.; Bruce, M. A.; Vu, P.; Vargas, M.; Keertikar, K. M.; Hosein, K. N.; Jones, C. R.; Sikorski, J. A. *Tetrahedron* **1998**, *54*, 5075.

(2) (a) For the chemistry of macrocycles containing pyrrole units, see: Sessler, J. L.; Weghorn, S. J. *Expanded, Contracted & Isomeric Porphyrins*; Elsevier Science Ltd: Oxford, 1997. For pyrrole based dyes, see: Thoresen, L. H.; Kim, H.; Welch, M. B.; Burghart, A.; Burgess, K. *Synlett* **1998**, 1276.

(3) (a) Bean, G. P. In *The Chemistry of Heterocyclic Compounds*; Jones, A. R., Ed.; Wiley: New York, 1990; Vol. 48, Part 1, Chapter 2, p 105. (b) Gilchrist, T. L. *J. Chem. Soc., Perkin. Trans. 1* **1998**, 615.

(4) Marco, J. L.; Martinez-Grau, A.; Martin, N.; Seoane, C. *Tetrahedron Lett.* **1995**, *36*, 5393.

(5) For use of active methylene compounds containing an electron-withdrawing group (EWG) and an isocyanide group, see: (a) Trudell, M. L.; Pavri, N. P. *J. Org. Chem.* **1997**, *62*, 2649 (b) Katrizky, A. R.; Cheng, D.; Musgrave, R. P. *Heterocycles* **1997**, *44*, 67. (c) Adamczyk, M.; Reddy, R. E. *Tetrahedron Lett.* **1995**, *36*, 7983 and 9121. (d) Dijkstra, H. P.; ten Have, R.; van Leusen, A. M. *J. Org. Chem.* **1998**, *63*, 5332. (e) Ono, N.; Miyagawa, H.; Ueta, T.; Ogawa, T.; Tani, H. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1595. (f) Abel, v. Y.; Haake, E.; Haake, G.; Schmidt, W.; Struve, D.; Walter, A.; Montforts, F.-P. *Helv. Chem. Acta* **1998**, *81*, 1978. (g) Di Santo, R.; Costi, R.; Massa, S.; Artico, M. *Synth. Commun.* **1998**, *28*, 1801.

(6) For use of transition metal intermediates in polysubstituted pyrrole synthesis, see: (a) Iwasawa, N.; Maeyama, K.; Saitou, M. *J. Am. Chem. Soc.* **1997**, *119*, 1486. (b) Iwasawa, N.; Ochiai, T.; Maeyama, K. *J. Org. Chem.* **1998**, *63*, 3164. (c) Aumann, R. *Chem. Ber.* **1993**, *126*, 2325. (d) Danks, T. N.; Velo-Rego, D. *Tetrahedron Lett.* **1994**, *35*, 9443. (e) Dekura, F.; Honda, T.; Mari, M. *Chem. Lett.* **1997**, 825. (f) Gao, Y.; Shirai, M.; Sato, F.; *Tetrahedron Lett.* **1996**, *37*, 7787.

(7) (a) Fürstner, A.; Weintritt, H.; Hupperts, A. *J. Org. Chem.* **1995**, *60*, 6637. (b) Quiclet-Sire, B.; Thévenot, I.; Zard, S. Z. *Tetrahedron Lett.* **1995**, *36*, 9496.

(8) Katritzky, A. R.; Jiang, J.; Steel, P. J. *J. Org. Chem.* **1994**, *59*, 4551.

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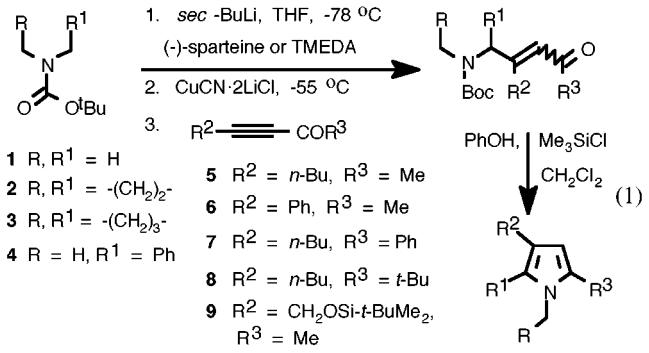
useful multistep pathways.[9] Conjugate addition of α-aminoalkylcuprates to alkynyl ketones followed by amine deprotection and cyclization (eq 1) provides a potential synthetic

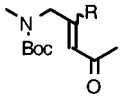
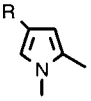
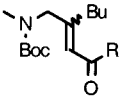
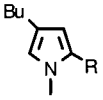
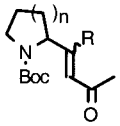
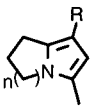
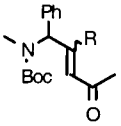
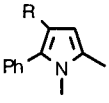
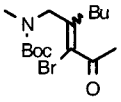
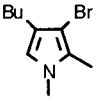



route to polysubstituted pyrroles. Inability to control olefin stereochemistry in the γ-amino-α,β-enone adduct could pose serious problems unless both stereoisomers can be cyclized to the corresponding pyrrole. In conjunction with our work on *N*-Boc-protected α-aminoalkylcuprates,[10] we have developed a versatile two-step synthesis of pyrroles that overcomes these problems and that can accommodate a variety of substituents and substitution patterns.

The alkynyl ketones **5**−**8** are readily available from terminal acetylenes via reaction of alkynyl organozinc reagents with acid chlorides.[11] Lithiation of the *tert*-butyldimethylsilyl ether of propargyl alcohol, quenching with acetaldehyde, and subsequent oxidation [$MnO_2$ (10 equiv), $CH_2Cl_2$, 25 °C] of the resultant alcohol afforded alkynyl ketone **9**.[12] The availability of several methods for the preparation of α,β-alkynyl ketones allows for the introduction of a wide range of substituents at positions 3 and 5 of the pyrrole ring system.

The first step in this synthetic protocol involves the conjugate addition of α-aminoalkylcuprates to alkynyl ketones. Initial studies employing CuCN and 2 equiv of the α-lithiocarbamate, generated via Beak's deprotonation procedure[13] [*sec*-BuLi, THF, −78 °C, 1 h], gave modest yields of conjugate adducts as 1:1 to 3:1 mixtures of *E*:*Z* diastereomers. Higher yields of conjugate adducts were obtained with the cyanocuprate reagent (RLi + CuCN·2LiCl) or an organocopper reagent prepared from CuCl·2LiCl and 1 equiv of the α-lithio carbamate (Table 1). Presumably the latter reagent involves either a chlorocuprate reagent (i.e., RCuClLi) or is analogous to the RCu/TMEDA reagent reported by Johnson.[14] α-Aminoalkylcuprates prepared from *tert*-butoxycarbonyl (Boc) protected *N*,*N*-dimethylamine, pyrrolidine, and piperidine underwent clean high yield conjugate additions to methyl alkynyl ketones (Table 1, entries 1−2 and 6−9) but gave little to no conjugate addition with a corresponding phenyl ketone (entry 5). The successful

**Table 1.** Reaction of α-Aminoalkylcuprates with α,β-ynones Followed by Deprotection and Cyclization to Pyrroles

| entry | Boc[a] | ynone | R | CuX[b] | γ-aminoenone[c] | % yield[d] | *E* : *Z* [e] | pyrrole[f] | % yield[d] |
|---|---|---|---|---|---|---|---|---|---|
| 1 | **1** | **5** | Bu | CuCl |  | 64 (80)[g] | 71:29 |  | 79 |
| 2 | **1** | **6** | Ph | CuCl | | 66 | 57:43 | | 66[h] |
| 3 | | | | CuCl | | 57[i] | 58:42 | | 67[j] |
| 4 | | | | CuCN | | 56[i] | 59:41 | | 66[k] |
| 5 | **1** | **7** | Ph | CuCN |  | 0 | - |  | - |
| 6 | **1** | **8** | *t*-Bu | CuCN | | 75 | 74:26 | | 66 |
| 7 | **2** | **5** | Bu | CuCl |  | 81 | 24:76 |  | 81[l] |
| 8 | **2** | **6** | Ph | CuCl | | 69 | 27:73 | | 85[l] |
| 9 | **3** | **5** | Bu | CuCN | | 65 | 27:73 | | 60[m] |
| 10 | **4** | **5** | Bu | CuCN |  | | |  | 41[n,o] |
| 11 | | **6** | Ph | CuCN | | | | | 50[n,p] |
| 12 | **1** | **5** | - | CuCN |  | | 50:50 |  | 41[n,q] |

[a] Boc-protected amines were deprotonated [*sec*-BuLi, THF, sparteine or TMEDA, −78 °C, 1 h] to form α-lithiocarbamates (RLi). [b] Treatment of RLi with CuX·2LiCl (X = Cl, CN, −78 °C, 1 h, 1.0 equiv) gave the cuprate RCuXLi. [c] Enones generated from α-aminoalkylcuprates and alkynyl ketones [THF, −78 °C to room temperature]. [d] Yields based upon isolated products purified by flash column chromatography unless otherwise noted. [e] *E*:*Z* isomer ratio was determined by $^1$H NMR integration ratio and/or $^{13}$C peak heights. [f] Pyrroles were formed upon treatment of Boc-protected γ-aminoketones with PhOH (30 equiv) and TMSCl (10 equiv) in $CH_2Cl_2$ at room temperature and gave satisfactory NMR, and $^{13}$C NMR, data. [g] Performed on a 5 mmol scale. [h] See ref 17. [i] Yields determined by NMR using $CH_2Cl_2$ as internal standard. [j] Yield obtained from pure (*E*)-enone. [k] Yield obtained from pure (*Z*)-enone. [l] *n* = 1. [m] *n* = 2. [n] Yield corresponds to the overall yield for conjugate addition and pyrrole formation. [o] Present as the major isomer in a 69:31 ratio with *N*-benzyl-2-methyl-4-butylpyrrole. [p] Present as the major isomer in a 70:30 ratio (obtained in both THF and PhMe/THF) with *N*-benzyl-2-methyl-4-phenylpyrrole. [q] Enolate anion generated by the conjugate addition reaction was quenched with *N*-bromosuccinimide (NBS).

conjugate addition to a *tert*-butyl ynone (entry 6) suggests that the failure with phenyl ynones lies in electronic factors. Steric factors did play a role with 4-trimethylsilyl-3-butyn-2-one which failed to react with the cuprate derived from **1**. Although alkynyl ketone **9** gave modest yields (i.e., 46%) of the conjugate adduct with the cuprate derived from **1**, 5-chloro-3-butyn-2-one gave low yields (10%) of the 1,4-addition product and the major products appeared to arise via $S_N2'$ substitution of the propargyl chloride. α-Aminoalkylcuprates prepared from Boc-protected benzylic amines also undergo a conjugate addition reaction to α,*β*-alkynyl ketones (entries 10−11), permitting introduction of an aromatic substituent at C2. Benzyl methyl carbamate **4** underwent competitive deprotonation at the methyl group, giving a 70:30 mixture of the *N*-methyl and *N*-benzyl pyrroles in both THF and toluene/THF (entries 10−11), although previous reports noted a solvent dependence for the regioisomeric deprotonation.[15] Although these conjugate addition reactions produced mixtures of *E* and *Z* diastereomers that varied from experiment to experiment, the desired *Z* isomer could not be selectively formed under a variety of reaction conditions. The stereochemistry of the conjugate adducts was established by difference NOE experiments on the addition product of **1** and **6** (entry 2) and the configuration of the other enones was assigned by analogy with the chemical shifts of the olefinic protons.[16] The proton absorption between $\delta$ 6.01−6.50 was assigned to the *Z* diastereomer while the absorption between $\delta$ 5.87−6.07 was assigned to the *E* diastereomer, consistent with previous observations and consistent with the NOE experiments performed on the isolated *E* and *Z* diastereomers obtained from carbamate **1** and ynone **6**.

Several efforts to effect Boc deprotection and pyrrole formation were unsuccessful, giving either trace amounts of product and starting material [$CH_2Cl_2$, concentrated HCl, 1−2 drops or anhydrous HCl (10 mol %) from AcCl and MeOH] or complex mixtures containing no pyrrole [TMSOTf (1.2 equiv), $CH_2Cl_2$, −20 °C, 4 h and acetyl bromide (1.2 equiv), MeOH (5.0 equiv), $CH_2Cl_2$]. Treatment of the conjugate adducts with PhOH/TMSCl[18] in methylene chloride effected deprotection of the amine and subsequent cyclization to afford the desired pyrrole. When deprotonation of carbamate **4** occurred competitively at both the benzylic and methyl carbons, both regioisomeric pyrroles were obtained, illustrating the effectiveness of the PhOH/TMSCl carbamate deprotection−cyclization sequence. Elegant studies by Merrifield and co-workers has established that Boc deprotection under these conditions is not effected by HCl which is only slowly generated from PhOH/TMSCl and then largely from the water present in commercial phenol. The addition of $Me_3SiCl$ to PhOH in $CH_2Cl_2$ lowers the $pK_a$ from 10 (1 M PhOH in $CH_2Cl_2$) to 2 and the acidity of this medium contributes to Boc cleavage which is second order in phenol. Although Boc cleavage generates HCl as a byproduct in the reaction medium, control experiments[19] revealed that anhydrous HCl in $CH_2Cl_2$ (from AcCl and MeOH, 10 mol %, 4 h) did not effectively promote Boc cleavage. Although traces of HCl are sufficient to effect isomerization of α,*β*-unsaturated ketones, the underlying mechanism of this cyclization process which effectively converts both the *E* and *Z* diastereomers to pyrroles remains to be elucidated.[19] The use of excess PhOH/TMSCl (30:10 equiv) posed difficulties in the workup and isolation of the pyrrole products. Subsequent experimentation revealed that the deprotection and cyclization could be effected with reduced quantities of PhOH/TMSCl in identical yields. Procedurally, the *γ*-amino enone (1 mmol) was dissolved in dry $CH_2Cl_2$, PhOH (10 equiv) and TMSCl (3 equiv) were added at room temperature, and the mixture was stirred at room temperature (3 h). The reaction mixture was diluted with ether and washed with 10% KOH to remove the phenol, and the KOH washings were extracted with ether. Combination of the organic phases and concentration afforded the crude products which were purified by flash chromatography (silica gel). Reactions performed on a 6−7 mmol scale generally gave higher yields than the 1 mmol scale reported in Table 1. The relatively high yields of these cyclization reactions suggested that both the *Z* and *E* diastereomers were undergoing cyclization to the pyrrole under the reaction conditions. This was confirmed by isolation of the individual *E* and *Z* diastereomers obtained from **1** and **6** and conversion of each isomer to the same pyrrole in nearly identical yields (entries 3−4). These results indicate that the α,*β*-enones are much more prone to isomerization under these reaction conditions than the corresponding α,*β*-enoates.[10c,19] The PhOH/TMSCl protocol readily converted all of the *γ*-amino

(9) (a) Arcadi, A.; Rossi, E. *Tetrahedron* **1998**, *54*, 15253. (b) Yasuda, M.; Morimoto, J.; Shibata, I.; Baba, A. *Tetrahedron Lett.* **1997**, *38*, 3265. (c) Aoyagi, Y.; Mizusaki, T.; Ohta, A. **1996**, *37*, 9205. (d) Barluenga, J.; Tomás, M.; Kouznetsov, V.; Suárez-Sobrino, A.; Rubio, E. *J. Org. Chem.* **1996**, *61*, 2185. (d) Katritzky, A. R.; Li, J. *J. Org. Chem.* **1996**, *61*, 1624. (e) Nagafuji, P.; Cushman, M. *J. Org. Chem.* **1996**, *61*, 4999. (f) Hamby, J. M.; Hodges, J. C. *Heterocycles* **1993**, *35*, 843.

(10) For conjugate addition reactions of α-aminoalkylcuprates, see: (a) Dieter, R. K.; Alexander, C. W. *Tetrahedron Lett.* **1992**, *33*, 5693. (b) Dieter, R. K.; Alexander, C. W. *Synlett* **1993**, 407−409. (c) Dieter, R. K.; Velu, S. E. *J. Org. Chem.* **1997**, *62*, 3798−3799. (d) Dieter, R. K.; Lu, K. *Tetrahedron Lett.* **1999**, *40*, 4011. (e) Dieter, R. K.; Alexander, C. W.; Nice, L. E. *Tetrahedron* **2000**, *56*, 2776.

(11) Verkruijsse, H. D.; Heus-kloos, Y. A.; Brandsma, L. *J. Organomet. Chem.* **1988**, *338*, 289.

(12) Obrecht, D. *Helv. Chim. Acta* **1989**, *72*, 447.

(13) (a) Beak, P.; Lee, W. K. *Tetrahedron Lett.* **1989**, *30*, 1197. (b) Beak, P.; Lee, W. K. *J. Org. Chem.* **1993**, *58*, 1109. (c) For a review, see: Beak, P.; Basu, A.; Gallagher, D. J.; Park, Y. S.; Thayumanavan, S. *Acc. Chem. Res.* **1996**, *29*, 552.

(14) Johnson, C. R.; Marren, T. J. *Tetrahedron Lett.* **1987**, *28*, 27.

(15) (a) Park, Y. S.; Boys, M. L.; Beak, P. *J. Am. Chem. Soc.* **1996**, *118*, 3757. (b) Schlosser, M.; Limat, D. *J. Am. Chem. Soc.* **1995**, *117*, 12342. (c) Voyer, N.; Roby, J. *Tetrahedron Lett.* **1995**, *36*, 6627. (d) The isomeric pyrroles were confirmed by GC-mass spectral analysis. Although appearing as a single spot on TLC, *N*-benzyl-2-methyl-4-phenylpyrrole was cleanly separated from its regioisomer by GC chromatography and displayed a parent molecular ion at *m*/*z* 247 and a fragement ion at 91 *m*/*z* for the benzyl cation. A $^{13}C$ absorption at $\delta$ 50.5 was also observed for the benzylic $CH_2$ group.

(16) Dieter, R. K.; Silks, L. A., III.; Fishpaugh, J. R.; Kastner, M. E. *J. Am. Chem. Soc.* **1985**, *107*, 4679.

(17) Adachi, I.; Harada, K.; Miyazaki, R.; Kano, H. *Chem. Pharm. Bull.* **1974**, *22*, 61.

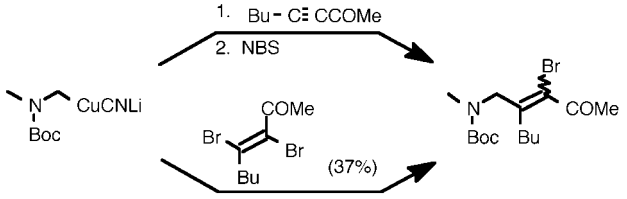
(18) Kaiser, E.; Sr.; Picart, F.; Kubiak, T.; Tam, J. P.; Merrifield, R. B. *J. Org. Chem.* **1993**, *58*, 5167.

(19) While a referee suggested the possibility of *E* to *Z* isomerization via sequential phenol 1,4-conjugate addition−elimination, control experiments revealed that while anhydrous HCl ($CH_2Cl_2$, 10 mol %) failed to cleave the Boc protecting group the *E*:*Z* ratio of the *γ*-amino-α,*β*-enone from **1** and **6** changed from 71:29 to 37:63. Thus, the generation of HCl during Boc deprotection appears sufficient to effect *E* to *Z* isomerization.

enones to pyrroles in modest to good yields (Table 1), with the exception of the conjugate adduct of alkynyl ketone **9** and the cuprate derived from **1** which gave only trace amounts of the desired pyrrole.

This synthetic route to pyrroles provides opportunities for introducing substituents at positions 1, 2, 3, and 5 of the pyrrole ring (eq 1). Trapping of the intermediate allenyl enolate would allow for the introduction of substituents at the 4-position. Reaction of the α-aminoalkylcuprate derived from **1** with ynone **5** followed by trapping with *N*-bromosuccinimide afforded the α-bromo enone (Scheme 1) which

**Scheme 1**




could be cyclized to the bromopyrrole in 41% overall yield (entry 12). Alternatively, bromination of ynone **5** [$Br_2$, $CH_2Cl_2$, −78 °C] afforded the *trans*-1,2-dibromoenone (76% yield) which reacted with the α-aminoalkylcuprate to give the same conjugate adduct in 37% yield. The bromopyrroles may be used in a variety of transition metal coupling reactions (e.g., Pd, Ni, Zn, Cu) or converted to lithium and Grignard reagents for introduction of alkyl, aryl, alkenyl, or alkynyl substituents at the bromine-bearing carbon atom.

The recent development of α-aminoalkylcuprate chemistry and the ready availability of ynones provides an efficient two-step synthesis of polysubstituted pyrroles. This synthetic strategy provides a rapid and efficient synthesis of 1,2-di-, 1,2,4-tri-, 1,2,5-tri-, and 1,2,3,5-tetrasubstituted pyrroles. Trapping of the intermediate allenyl enolate generated in the conjugate addition reaction leads to the bromopyrrole, allowing substitution at all five positions of the pyrrole ring. Utilization of ynals or monoprotected carbamates of primary amines (leading to 1-unsubstituted pyrroles) are under investigation and would increase the range of pyrrole substitution patterns accessible by this methodology. The only current limitation of this method for simple alkyl and aryl substituents appears to be the synthesis of 2,5-diarylpyrroles and the use of alkynyl ketones derived from propargyl derivatives (e.g., propargyl halides and silyl ethers).

**Acknowledgment.** This work was generously supported by the National Institutes of Health (GM-60300-01). Several initial experiments on the conjugate addition of α-aminoalkylcuprates to alkynones were performed by Dr. Lois E. Nice and are gratefully acknowledged.

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