Pergamon

Tetrahedron Letters 39 (1998) 967–970

TETRAHEDRON
LETTERS

Mannich Reactions of Resin-Bound Substrates: 2.
A Versatile Three-Component Solid-Phase Organic Synthesis Methodology

James J. McNally, Mark A. Youngman and Scott L. Dax*

Drug Discovery, The R. W. Johnson Pharmaceutical Research Institute
Spring House, Pennsylvania 19477-0776

Received 7 October 1997; accepted 19 November 1997

Abstract: Alkynes, secondary amines and aldehydes, in the presence of a copper (I) salt, undergo Mannich reactions to afford the corresponding aminomethylalkynyl adducts on a solid support. Any member of this three-component reaction system can be immobilized on a resin providing three distinct routes for the generation of structurally diverse compound libraries.

Multi-component reaction systems are highly valued in Solid Phase Organic Synthesis (SPOS) because several elements of diversity can be introduced in a single transformation. The Passerini reaction, namely treatment of a carboxylic acid with an isonitrile and aldehyde to afford amido-esters, is an example of a three component system that has been successfully adapted for use in SPOS.[1] Similarly, the Ugi reaction (four components) has been carried out on resin-bound substrates to afford diverse libraries of bis-amides.[2]

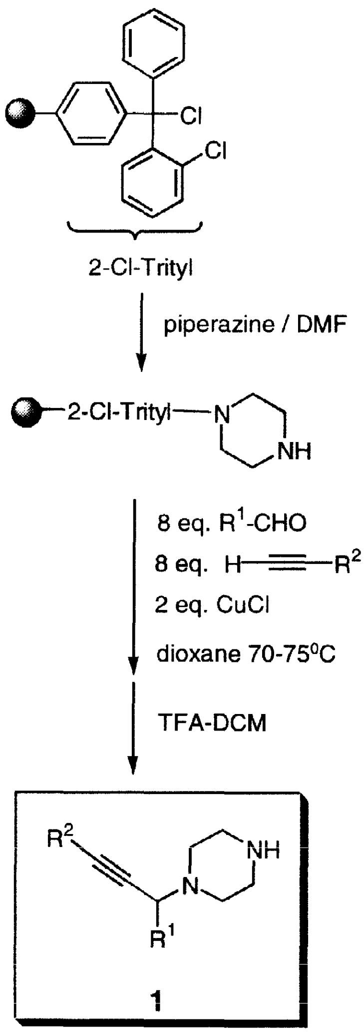
The Mannich reaction is a classic three-component system in which "hydrogen-active" substrates react with putative imine species that arise from condensation of an amine with an aldehyde.[3] Silyl enol ethers can serve as the "hydrogen-active" component and recently the Kobayashi group applied this variation to solid-phase technology.[4] In their work, resin-bound silyl enol ethers reacted with imines that were preformed via the reaction of amines with aldehydes in the presence of a Lewis acid catalyst and a dehydrating agent. Alternatively, terminal alkynes can also behave as the "hydrogen-active" Mannich partner when in the presence of a copper(I) salt.[5] We recently reported on Mannich reactions of a resin-bound alkyne without the need to preform the imine separately.[6] In this paper, we demonstrate that either of the remaining two components, namely the amine or aldehyde, when immobilized on a resin, similarly afford the desired Mannich adducts. Furthermore, we report that a variety of aldehydes smoothly react with immobilized amines thereby expanding the utility of this methodology.

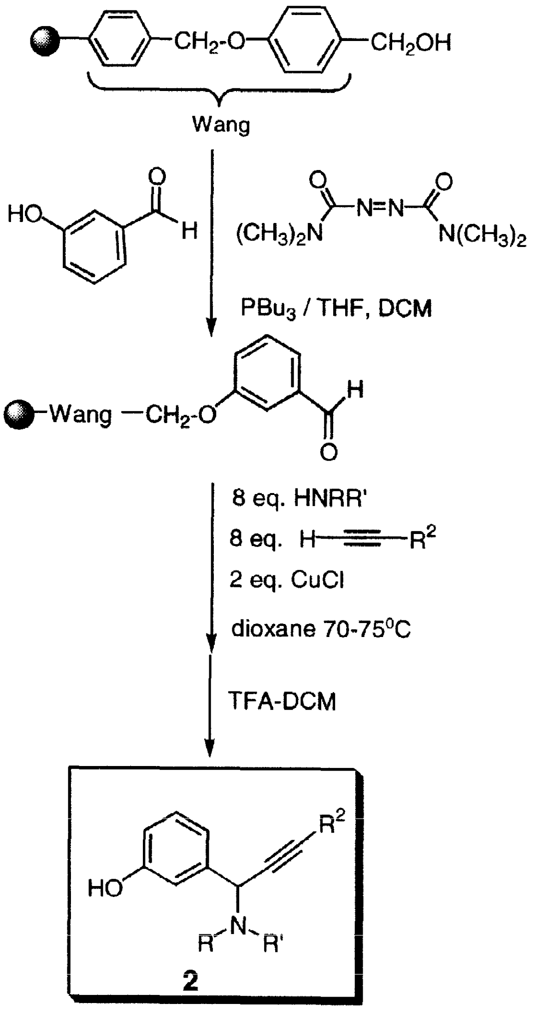
We believe that this SPOS strategy is powerful for several reasons. Any single component can be immobilized on an appropriate solid support to make the methodology very versatile from a synthetic perspective. Structurally diverse compound libraries can be readily prepared due to the numerous amines, aldehydes and alkynes that are either commercially available or easily synthesized. The alkyne moiety itself presents an opportunity for further synthetic elaboration and provides a site for the introduction of another element of diversity; progress in this area will be the subject of future reports. In this regard, it should be

0040-4039/98/$19.00 © 1998 Elsevier Science Ltd. All rights reserved.
PII: S0040-4039(97)10716-X

noted that many functional groups are tolerant to the reaction conditions.[5,6] Lastly, reactions are typically very efficient and isolated products are usually of high purity.

Commercially available 2-chlorotrityl chloride resin was treated with piperazine and washed.[7,8] The resin-bound amine was then subjected to Mannich reaction conditions. In general, the overall conversion to product is efficient (often >80%) and in most cases, the final crude products are quite pure (>80%) (Table 1). For example, a screw capped fritted glass reaction vessel was charged with the resin (0.30 g, 0.75 mmol/g, 0.225 mmol), Cu(I)Cl (45 mg, 0.45 mmol) and benzaldehyde (0.160 mL, 1.57 mmol). After shaking for 0.5 h, phenylacetylene (0.173 mL, 1.57 mmol) was added to the mixture, and the reaction vessel was heated to 85^{0}C with shaking for 3 h. The resin was filtered hot and washed thoroughly.[9] Cleavage of the desired product from the solid support was accomplished by subsequent reaction with trifluoroacetic acid (TFA)-dichloromethane (1/1; v/v) for 5 min.[9] Evaporation of the solvents under nitrogen gave the desired Mannich adduct[10] as a bis-TFA salt, 98 mg (86%) as an oil: ^{1}H NMR (DMSO-d_6) δ 2.65-2.90 (m, 4H), 3.05-3.18 (m, 2H), 3.28-3.39 (m, 2H), 5.18 (s, 1H), 7.32-7.48 (m, 6H), 7.55-7.65 (m, 4H), 8.87 (br s, 2H) and 9.43 (br s, 1H). MS: m/z 277 (MH$^+$).





Alternatively, the aldehyde component was immobilized via attachment to a resin; in this case, 3-hydroxybenzaldehyde was coupled to the Wang resin via reaction with N,N,N',N'-tetramethylazodicarboxamide and tributylphosphine.[11] The resin-bound aldehyde was then subjected to Mannich conditions and cleavage from the resin to afford the desired products (**2**) (Table 2). These preliminary results indicate that the lower yield of the Mannich adducts from the resin-bound aldehyde may be due to incomplete iminium formation.

Table 1: Mannich Adducts (1) From Resin-Bound Piperazine

R^1	R^2	Purity: HPLC	$M+H^+$
Ph	Ph	89%	277
Ph	4-Cl-Ph	78%	311
Ph	4-pentyl-Ph	52%	347
Ph	-CH_2OCH_3	90%	245
Ph	butyl	91%	257
Ph	-CH_2Ph	95%	291
3-Cl-Ph	Ph	91%	311
3-Cl-Ph	4-Cl-Ph	82%	346
3-Cl-Ph	4-pentyl-Ph	95%	382
3-Cl-Ph	-CH_2OCH_3	94%	279
3-Cl-Ph	butyl	95%	291
4-Cl-Ph	Ph	87%	311
4-Cl-Ph	4-Cl-Ph	92%	346
4-Cl-Ph	4-pentyl-Ph	89%	382
3,5-$(CF_3)_2$-Ph	Ph	77%	413
3,5-$(CF_3)_2$-Ph	4-Cl-Ph	86%	447
3,5-$(CF_3)_2$-Ph	4-pentyl-Ph	87%	483
2-naphthyl	4-Cl-Ph	75%	361
2-naphthyl	CH_2OCH_3	93%	295
2-naphthyl	butyl	94%	307
1-naphthyl	4-Cl-Ph	53%	361

Table 2: Mannich Adducts (2) From Resin-Bound Benzaldehyde

Amine (R / R')	R^2	Purity*: HPLC	$M+H^+$
phenylpiperazine	Ph	74%	369
phenylpiperazine	butyl	34%	349
phenylpiperazine	TMS-	27%	365

*-contains 10%-15% of N,N,N'N'-tetramethylhydrazodicarboxamide from coupling to resin.

Summary. In general, the Mannich reactions of resin-bound amines proceeded smoothly (Table 1) while comparable examples in which the aldehyde was immobilized were somewhat problematic (Table 2). We are currently exploring ways to improve the efficiency of this transformation. In our earlier work,[6] we demonstrated that the alkyne component can similarly be attached to a solid support and undergo Mannich condensation with amines and (para)formaldehyde with high efficiency. Collectively, these studies demonstrate a versatile three-component solid-phase methodology that is based upon the Mannich reactions of amines, aldehydes and alkynes.

Acknowledgments. We thank Bruce Maryanoff, Allen Reitz, Ralph Rivero and Alex Dyatkin for their help.

References and Notes

1. Armstrong, R. W. Patent WO 95/02566, **1995**.
2. Wipf, P.; Cunningham, A. *Tetrahedron Lett.* **1995**, *36*, 7819-7822.
3. Tramontini, M.; Angiolini, L. *Mannich Bases: Chemistry and Uses*, CRC Press Inc, Boca Raton, FL **1994**.
4. Kobayashi, S.; Moriwaki, M.; Akiyama, R.; Suzuki, S.; Hachiya, I. *Tetrahedron Lett.* **1996**, *37*, 7783-7786.
5. For example, see Cook, S. C.; Dax, S. L. *Biooorg. Med. Chem. Lett.* **1996**, *6*, 797-802.
6. Youngman, M. A.; Dax, S. L. *Tetrahedron Lett.* **1997**, *38*, 6347-6350.
7. The resin was washed: 3 x 3mL DMF, 3 x 3mL MeOH, 3 x 3mL THF, 3 x 3mL DCM.
8. Hoekstra, W. J.; Greco, M. N.; Yabut, S. C.; Hulshizer, B. L.; Maryanoff, B. E. *Tetrahedron Lett.* **1997**, *38*, 2629-2632.
9. The resin was washed: 1 x 3mL dioxane, 3 x 3mL DMF, 3 x (1 x 3mL 20% Aq. HOAc then 1 x 3mL DMF), 3 x (1 x 3mL 7M NH_4OH then 1 x 3mL DMF), 3 x 3mL MeOH, 3 x 3mL THF, 3 x 3mL DCM.
10. The identity and purity of all final products were determined by NMR and MS or HPLC and MS. Nuclear magnetic resonance spectra were obtained on a Bruker AC-300SB FT-NMR equipped with a 5 mm $^1H/^{13}C$ dual probe using DMSO-d_6 or CD_3OD for fixed frequency lock and chemical shift; HPLC were obtained on a Hewlett Packard HP1050 using a gradient (10:90 to 90:10) of acetonitrile/water with 0.1% trifluoroacetic acid as eluent and UV detection at either 217 nM or 220 nM; Mass spectra were obtained on a Micromass Platform II using electrospray ionization and probe = 4.0 kV or on a Hewlett Packard HP5989 MS Engine using particle beam chemical ionization with ammonia as reagent gas.
11. Rano, T. A.; Chapman, K. T. *Tetrahedron Lett.* **1995**, *36*, 3789-3792.