Solid Phase Synthesis of 1,2-Disubstituted Alkenes: A Novel Alkynyldihydropyridine to Alkenylpyridine Isomerization

Chixu Chen,* Bowei Wang, Benito Munoz

Merck Research Laboratories San Diego, 3535 General Atomics Court, San Diego, CA 92131, USA
Fax +1(858)2025743; E-mail: chixu_chen@merck.com

Received 14 August 2003

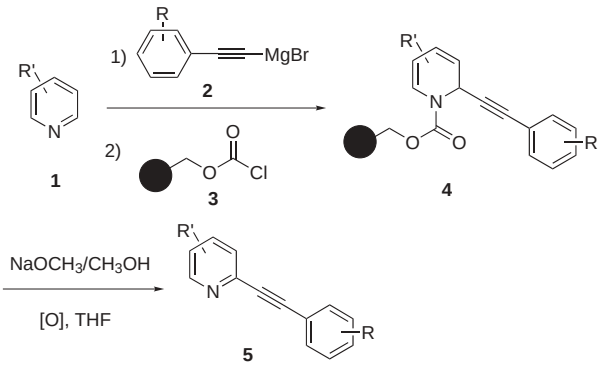
Abstract: A series of 1,2-disubstituted pyridylalkenes have been prepared using a solid-phase resin approach. This approach takes advantage of a novel alkynyldihydropyridine to alkenylpyridine isomerization.

Key words: solid-phase synthesis, 1,2-disubstituted alkenes, alkynyldihydropyridine, alkenylpyridine, isomerization

The use of solid and solution phase chemistry for the generation of non-peptidic small molecule libraries has become common practice, in both industry and academia.[1] The approach taken in our laboratories for the synthesis of such libraries has been to utilize an acyl-pyridinium complex on solid support. This novel approach, which we refer to as Resin Activation/Capture Approach or REACAP Technology, has been successful, providing a number of novel scaffolds for generation of such libraries.[2]

Continuing to elaborate on the synthetic utility of the acyl-pyridinium complex on solid support, we set forth to construct a focused library of compounds based on the potent and selective metabotropic receptor 5 (mGluR5) antagonist 2-methyl-6-(phenylethynyl)pyridine (MPEP).[3]

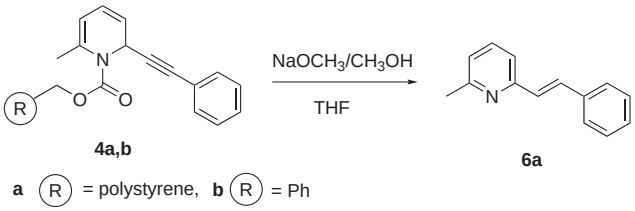
We postulated that the reaction of pyridines **1** with arylethynylmagnesium bromides **2** in the presence of support bound chloroformate **3**, should afford the resin-bound 2-arylethynyl-1,2-dihydropyridines **4**. Subsequent cleavage of the resin bound product under oxidative conditions[2d] would yield the desired 2-arylethynylpyridines **5** (Scheme 1).



Scheme 1 Proposed synthesis of 2-arylethynylpyridine

SYNLETT 2003, No. 15, pp 2404–2406
Advanced online publication: 21.11.2003
DOI: 10.1055/s-2003-43343; Art ID: S08603ST

Thus, 2-picoline (R′ = 2-Me) and phenylethynylmagnesium bromide were mixed in tetrahydrofuran (THF) and the resulting solution was allowed to react with chloroformate resin. A small sample of the resin was analyzed by FT-IR confirming the presences of both carbonyl and carbon-carbon triple bond stretches, consistent with resin-bound **4a** (Scheme 2, ® = polystyrene). Subjecting **4a** to oxidative ($NaOCH_3/CH_3OH$, THF, O_2 or H_2O_2) or general basic ($NaOCH_3/CH_3OH$, THF) cleaving conditions[2d] did not afford the desired ethynylic product. Rather, the unexpected isomeric product *E*-alkene (**6a**) was observed (Scheme 2). This result was confirmed in an analogous solution phase synthesis using benzyl chloroformate in place of the chloroformate resin (Scheme 2, ® = Ph).[4]



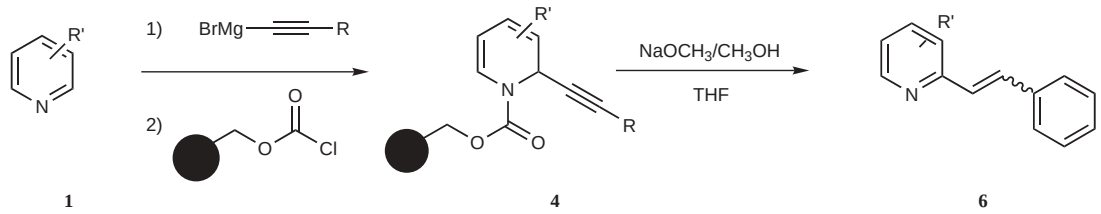
Scheme 2 Alkynyldihydropyridine to alkenylpyridine

This unexpected result led us to investigate the generality of this novel alkynyldihydropyridine to alkenylpyridine isomerization. In general, substituted pyridines **1** (neat, 1.5 mmol) were added to ethynylmagnesium bromides **2** (0.5 M, 10 mL, 5 mmol) then reacted with resin bound chloroformate **3** (1.0 g, 1.0 mmol/g) in a polypropylene tube fitted with a frit. The resulting mixtures were agitated for 15 minutes, filtered, and the resins were washed and dried. A small sample of each resin was analyzed by FT-IR to confirm the presence of both the triple bond and carbamate carbonyl.[5] The resins were re-suspended in THF (10 mL) and cleavage of the substrate from the solid support was accomplished by the addition of a sodium methoxide (25% wt. in MeOH, 0.23 mL, 1 mmol). Subsequent filtration, aqueous work-up and preparative TLC isolation, afforded the 1,2-disubstituted alkene products.[6] The results for this series of reactions are shown in Table 1.[7]

It is worth to mention that the *E*- and *Z*-isomers are the sole products from the solid-phase reactions. The cleanness and moderate yields are consistent with previous REACAP approaches.[2]

In summary, we have identified, in solution and solid phase, a novel alkynyldihydropyridine to alkenylpyridine

Table 1 Results of Synthesis of Ethenylpyridines



1 4 6

Pyridine	R′	Grignard	R			Isolated yield (%)	
						E	*Z*
1a	2-Me	**2a**	Ph	**4a**	**6a**	32	0
1c	2-Et	**2a**	Ph	**4c**	**6c**	28	0
1d	H	**2a**	Ph	**4d**	**6d**	15	11
1e	4-MeO	**2a**	Ph	**4e**	**6e**	33	19
	4-OH		Ph	**4f**	**6f**	27[b]	
1g	4-Me	**2a**	Ph	**4g**	**6g**	17	12
1h	3-MeO	**2a**	Ph	**4h**	**6h**[c]	11	16
1i	3-Me	**2a**	Ph	**4i**	**6i**[c]	15	15
1a	2-Me	**2b**	H	**4j**	**6j**	38	
1a	2-Me	**2c**	Me	**4k**	**6k**	28	20

[a] The 4-hydroxy precursor **4h** was obtained from the hydrolysis (1 M HCl/THF 1:2) of **4e**.
[b] The *E*- and *Z*-isomers were not separated and gave 27% combined yield. The *E*- to *Z*-ration, 2:1, was determined by NMR.
[c] Only 3-R′-2-phenylethynyl pyridine and no 5-R′-2-phenlyethynyl pyridine were observed.

isomerization, that has not been reported in the literature.[8] Although the rearrangement is not generally stereospecific, it works quite well with a variety of substrates, e.g. pyridines and arylethynylmagnesium bromides. The study of the rearrangement mechanism is under way and will be a separate report in due course. Overall, the approach described herein, which takes advantage of this novel alkynyldihydropyridine to alkenylpyridine isomerization, has been successfully used for the preparation of a focused library of 1,2-disubstituted alkenes.

References

(1) (a) Bhattacharyya, S. *Curr. Med. Chem.* **2001**, *8*, 1383. (b) Lou, B. *Drug Discovery Today* **2001**, *6*, 1288. (c) Sammelson, R. E.; Kurth, M. J. *Chem. Rev.* **2001**, *101*, 137. (d) Baldwin, J. J. *Comb. Chem. Mol. Diversity Drug Discovery* **1998**, 181.

(2) (a) Munoz, B.; Chen, C.; McDonald, I. A. *Biotechnology* **2000**, *71*, 78. (b) Chen, C.; Munoz, B. *Tetrahedron Lett.* **1999**, *40*, 3491. (c) Chen, C.; Munoz, B. *Tetrahedron Lett.* **1998**, *39*, 6781. (d) Chen, C.; Munoz, B. *Tetrahedron Lett.* **1998**, *39*, 3401. (e) Chen, C.; McDonald, I. A.; Munoz, B. *Tetrahedron Lett.* **1998**, *39*, 217.

(3) (a) Pin, J.-F. *Curr. Drug Targets: CNS Neurol. Disord.* **2002**, *1(3)*, 297. (b) Varney, M. A.; Cosford, N. D.; Jachec, C.; Rao, S. P.; Sacaan, A.; Lin, F.-F.; Bleicher, L. S.; Santori, E. M.; Flor, P. J.; Allgeier, H.; Gasparini, F.; Kuhn, R.; Hess, S. D.; Velicelebi, G.; Johnson, E. C. *J. Pharmacol. Exp. Ther.* **1999**, *290*, 170. (c) Gasparini, F.; Lingenhohl, K.; Stoehr, N.; Flor, P. J.; Heinrich, M.; Vranesic, I.; Biollaz, M.; Allgeier, H.; Hechendorn, R.; Urwyler, S.; Varney, M. A.; Johnson, E. C.; Hess, S. D.; Rao, S. P.; Sacaan, A. I.; Santori, E. M.; Velicelebi, G.; Kuhn, R. *Neuropharmacology* **1999**, *38*, 1493.

(4) **Benzyl 6-methyl-2-(phenylethynyl)pyridine-1(2*H*)-carboxylate (4b):** ^{1}H NMR (3:1 THF_{d8}/CD_3OD): δ = 7.43–7.25 (10 H, m), 5.98–5.93 (1 H, m), 5.89–5.87 (1 H, d), 5.75–5.70 (1 H, m) 5.54–5.52 (1 H, m), 5.25–5.16 (2 H, m), 2.17 (3 H, s). ^{13}C NMR (3:1 THF_{d8}/CD_3OD): δ = 154.55, 137.49, 136.16, 132.69, 129.51, 129.51, 129.36, 129.32, 129.20, 124.31, 124.05, 120.70, 112.79, 87.72, 83.34, 68.85, 45.78, 22.17. ESMS (M + Na^+): 352.

(5) **Resin-bound Benzyl 6-methyl-2-(phenylethynyl)pyridine-1(2*H*)-carboxylate (4a):** IR (KBr): 2221, 1714 cm^{-1}.
Resin-bound Benzyl 2-(phenylethynyl)pyridine-1(2*H*)-carboxylate (4d): IR (KBr): 2231, 1724 cm^{-1}.
Resin-bound Benzyl 4-methoxy-2-(phenylethynyl)pyridine-1(2*H*)-carboxylate (4e): IR (KBr): 2241, 1724, 1662 cm^{-1}.
Resin-bound Benzyl 4-hydroxy-2-(phenylethynyl)pyridine-1(2*H*)-carboxylate (4f): IR (KBr): 2221, 1734, 1683, 1605 cm^{-1}.
Resin-bound Benzyl 3-methoxy-2-(phenylethynyl)pyridine-1(2*H*)-carboxylate (4h): IR (KBr): 2221, 1716, 1660 cm^{-1}.
Resin-bound Benzyl 6-methyl-2-prop-1-ynylpyridine-1(2*H*)-carboxylate (4k): IR (KBr): 2240, 1719 cm^{-1}.

(6) **General Procedure for Synthesis of Ethenylpyridine; 2-Methyl-6-[(*E*)-2-phenylethenyl]pyridine (6a):** To 2-picoline (118 mg, 1.5 equiv) was added phenylethynylmagnesium bromide (0.5 M in THF, 10 mL, 5 equiv). The resulting solution was added to resin-bound chloroformate (1 g, 1 mmol/g) in polypropylene tube fitted with a frit. The tube was capped and the reaction was agitated for 15 min. The resin was filtered and washed with THF, THF/H_2O 1:1, THF, MeOH, CH_2Cl_2 and THF. The resin was re-suspended in THF and NaOMe (4.4 M in MeOH, 0.23 mL, 1 equiv) was added. The resulting suspension was agitated for 3 h. The resin was filtered and washed with THF (3×). The combined filtrates were concentrated. Prep-TLC purification gave (*E*)-2-methyl-6-(2-phenylethen-1-yl)pyridine (**6a**) in 32% yield. The yield was 46% from the corresponding solution phase reaction. Compound **6a** was converted to the HCl salt. ^{1}H NMR (CD_3OD): δ = 8.37–8.32 (1 H, t), 8.19–8.16 (1 H, d), 7.76–7.73 (2 H, m), 7.68–7.65 (1 H, d), 7.52–7.47 (3 H, m), 7.39–7.34 (1 H, d), 2.79 (3 H, s). ^{13}C NMR (CD_3OD): δ = 154.14, 151.44, 146.72, 142.34, 135.79, 131.71, 130.12, 129.29, 121.21, 121.79, 118.63, 19.65. ESMS (M + H^+): 196. HRMS (MALDI) calcd for $C_{14}H_{13}N$ (M + H) 196.1121. Found: 196.1125.

(7) **2-Ethyl-6-[(*E*)-2-phenylethenyl]pyridine (6c):** ^{1}H NMR ($CDCl_3$): δ = 7.76 (1 H, t), 7.79–7.74 (3 H, m), 7.55–7.32 (5 H, m), 7.16–7.13 (1 H, d), 3.06–2.99 (2 H, q), 1.41–1.36 (3 H, t). ^{13}C NMR ($CDCl_3$): δ = 162.14, 154.06, 138.88, 136.13, 134.79, 128.94, 128.83, 127.50, 125.67, 121.02, 119.09, 30.10, 13.91. ESMS (M + H^+): 210. HRMS (MALDI) calcd for $C_{14}H_{13}N$ (M + H): 210.1279. Found: 210.1256.

2-[(*E*)-2-phenylethenyl]pyridine (*E*-6d): ^{1}H NMR ($CDCl_3$): δ = 8.61–8.60 (1 H, d), 7.68–7.57 (4 H, m), 7.40–7.25 (4 H, m), 7.20–7.12 (2 H, m). ^{13}C NMR ($CDCl_3$): δ = 155.62, 149.72, 136.65 (2 C, overlap) 132.74, 128.79, 128.41, 127.95, 127.16, 122.20, 122.14. ESMS (M + H^+) 182. HRMS (MALDI) calcd for $C_{13}H_{11}N$ (M + H): 182.0967. Found: 182.0960.

2-[(*Z*)-2-phenylethenyl]pyridine (*Z*-6d): ^{1}H NMR ($CDCl_3$): δ = 8.59–8.57 (1 H, d), 7.46–7.40 (1 H, t), 7.27–7.20 (5 H, m), 7.17–7.15 (1 H, d), 7.10–7.06 (1 H, m), 6.86–6.82 (1 H, d), 6.71–6.67 (1 H, d). ^{13}C NMR ($CDCl_3$): δ = 156.36, 149.59, 136.66, 135.71, 133.31, 130.52, 128.92, 128.35, 127.65, 123.91, 121.83. ESMS (M + H^+): 182.

4-Methoxy-2-[(*E*)-2-phenylethenyl]pyridine (*E*-6e): ^{1}H NMR ($CDCl_3$): δ = 8.39–8.37 (1 H, d), 7.65–7.60 (1 H, d), 7.55–7.52 (2 H, d), 7.35–7.32 (2 H, t), 7.27–7.24 (1 H, t), 7.10–7.05 (1 H, d), 6.82–6.81 (1 H, d), 6.61–6.59 (1 H, m), 3.73 (3 H, s). ^{13}C NMR ($CDCl_3$): δ = 166.18, 157.06, 150.81, 136.55, 132.80, 128.76, 128.39, 127.94, 127.15, 108.39, 108.15, 55.06. ESMS (M + H^+): 212. Anal. Calcd for $C_{14}H_{13}NO$: C, 79.59; H, 6.20; N, 6.63. Found: C, 79.20; H, 6.08; N, 6.60.

4-Methoxy-2-[(*Z*)-2-phenylethenyl]pyridine (*Z*-6e): ^{1}H NMR ($CDCl_3$) δ = 8.39–8.37 (1 H, d), 7.29–7.23 (5 H, m), 6.85–6.81 (1 H, d), 6.68–6.61 (3 H, m), 3.55 (3 H, s). ^{13}C NMR ($CDCl_3$): δ = 165.62, 158.08, 150.94, 137.08, 133.74, 131.03, 129.27, 128.72, 128.01, 109.53, 109.40, 55.17. ESMS (M + H^+): 212.

4-Hydroxy-2-[(*E*)-2-phenylethenyl]pyridine [*E*-6f): ^{1}H NMR (CD_3OD): δ = 7.78–7.75 (1 H, d), 7.62–7.59 (2 H, d), 7.44–7.33 (4 H, m), 7.02–6.96 (1 H, d), 6.65–6.64 (1 H, d), 6.42–6.39 (1 H, dd). ^{13}C NMR (CD_3OD) δ = 181.75, 149.20, 140.10, 136.74, 136.54, 130.63, 130.08, 128.50, 121.61, 116.63, 115.30. ESMS (M + H^+): 198. HRMS (MALDI) calcd for $C_{13}H_{11}NO$ (M + H): 198.0913. Found: 198.0916.

4-Methyl-2-[(*E*)-2-phenylethenyl]pyridine [*E*-6g): ^{1}H NMR ($CDCl_3$) δ = 8.51–8.49 (1 H, d), 7.60–7.55 (1 H, d), 7.53–7.50 (2 H, d), 7.40–7.35 (3 H, m), 7.15–7.13 (1 H, d), 6.82–6.81 (1 H,d), 6.61–6.59 (1 H, m), 2.15 (3 H, s). ESMS (M + H^+): 196. HRMS (MALDI) calcd for $C_{14}H_{13}N$ (M + H): 196.1121. Found: 196.1125.

4-Methyl-2-[(*Z*)-2-phenylethenyl]pyridine [*Z*-6g): ^{1}H NMR ($CDCl_3$) δ = 8.57–8.55 (1 H, d), 7.29–7.23 (5 H, m), 6.85–6.81 (1 H, d), 6.75–6.71 (1 H, d), 6.68–6.61 (2 H, m), 2.12 (3 H, s). ESMS (M + H^+): 196. HRMS (MALDI) calcd for $C_{14}H_{13}N$ (M + H): 196.1121. Found: 196.1121.

3-Methoxy-2-[(*E*)-2-phenylethenyl]pyridine (*E*-6h): ^{1}H NMR ($CDCl_3$) δ = 8.22–8.20 (1 H, m), 7.80–7.75 (1 H, d), 7.64–7.61 (2 H,m), 7.62–7.57 (1 H, d), 7.38–7.33 (2 H, t), 7.29–24 (1 H, t), 7.14–7.12 (2 H, m), 3.86 (3 H, s). ^{13}C NMR ($CDCl_3$) δ = 153.09, 145.29, 141.15, 137.33, 132.69, 128.68, 128.12, 127.28, 122.81, 121.72, 117.76, 55.43. ESMS (M + H^+): 212. HRMS (MALDI) calcd for $C_{14}H_{13}NO$ (M + H): 212.7010. Found: 212.1074. Anal. Calcd for $C_{14}H_{13}NO$: C, 79.59; H, 6.20; N, 6.63. Found: C, 79.20; H, 6.09; N, 6.38.

3-Methoxy-2-[(*Z*)-2-phenylethenyl]pyridine (*Z*-6h): ^{1}H NMR ($CDCl_3$) δ = 8.14–8.12 (1 H, dd), 7.24–7.12 (7 H, m), 6.81–6.77 (1 H, d), 6.74–6.70 (1 H, d), 3.66 (3 H, s). ^{13}C NMR ($CDCl_3$) δ = 153.39, 146.50, 140.89, 137.10, 133.73, 128.95, 127.84, 127.44, 125.16, 123.14, 117.54, 55.22. ESMS (M + H^+): 212.

3-Methyl-2-[(*E*)-2-phenylethenyl]pyridine (*E*-6i): ^{1}H NMR (CD_3OD) δ = 8.32–8.33 (1 H, d), 7.62–7.57 (4 H, m), 7.43–7.27 (4 H, m), 7.18–7.14 (1 H, m), 2.43 (3 H, s). ^{13}C NMR ($CDCl_3$) δ = 153.67, 146.52, 139.00, 137.08, 134.27, 131.93, 128.74, 128.46, 127.13, 123.72, 122.52, 17.83. ESMS (M + H^+): 196. HRMS (MALDI) calcd for $C_{14}H_{13}N$ (M + H): 196.1121. Found: 196.1116. Anal. Calcd for $C_{14}H_{13}NO$: C, 86.12; H, 6.71; N, 7.17. Found: C, 86.24; H, 6.87; N, 7.17.

3-Methyl-2-[(*Z*)-2-phenylethenyl]pyridine (*Z*-6i): ^{1}H NMR (CD_3OD) δ = 8.44–8.42 (1 H, dd), 7.45–7.42 (1 H, dd), 7.15–7.08 (4 H, m), 7.05–7.01 (2 H, m), 6.80–6.76 (1 H, d), 6.70–6.66 (1 H, d), 2.10 (3 H, s). ^{13}C NMR ($CDCl_3$) δ = 156.67, 146.84, 139.68, 137.41, 134.39, 133.20, 129.42, 129.03, 128.38, 128.10, 123.58, 18.32. ESMS (M + H^+): 196.

2-Methyl-6-vinylpyridine (6j): ^{1}H NMR (CD_3OD) δ = 8.33–8.28 (1 H, t), 8.02–8.00 (1 H, d), 7.67–7.65 (1 H, d), 6.95–6.86 (1 H, dd), 6.50–6.44 (1 H, d), 5.96–5.93 (1 H, d), 2.68 (3 H, s). ^{13}C NMR ($CDCl_3$) δ = 155.00, 151.20, 147.50, 128.96, 128.27, 127.57, 122.06, 19.62. GCMS (EI): 119.

2-Methyl-6-[(1*E*)-prop-1-enyl]pyridine (*E*-6k): ^{1}H NMR (CD_3OD) δ = 8.38, 8.32 (1 H, t), 8.05–8.02 (1 H, d), 7.70–7.67 (1 H, d), 7.24–7.16 (1 H, m), 6.77–6.72 (1 H, d), 2.78 (3 H, s), 2.09 (3 H, d). ^{13}C NMR ($CDCl_3$) δ = 154.18, 151.85, 147.10, 143.45, 126.24, 123.13, 121.60, 19.56, 19.40. GCMS (EI): 133.

2-Methyl-6-[(1*Z*)-prop-1-enyl]pyridine (*Z*-6k): ^{1}H NMR (CD_3OD) δ = 8.47, 8.42 (1 H, t), 7.94–7.91 (1 H, d), 7.79–7.76 (1 H, d), 6.70–6.66 (1 H, d), 6.62–56 (1 H, m), 2.81 (3 H, s), 2.07 (3 H, d). ^{13}C NMR ($CDCl_3$) δ = 158.56, 155.05, 147.21, 141.50, 126.63, 125.45, 121.66, 19.71, 15.50. GCMS (EI): 133.

(8) An isoxazolinocyclobutenone to isoxazolocyclobutanone isomerization both in solution and solid-phase was reported, see: Cheng, W.-C.; Wong, M.; Olmstead, M. M.; Kurth, M. J. *Org. Lett.* **2002**, *4(3)*, 741.