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A Simple Preparation of a (Pyridonyl-1)propargylacetic Acid Derivative

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Abstract:

(Pyridonyl-1)propargyl malonate 7 was prepared through two consecutive alkylations of pyridone 2 with ethyl bromomalonate and propargyl bromide in one pot in nearly quantitative yields. Malonate 7 was hydrolyzed to give racemic acid (±)-1, which was then resolved with (−)-norephedrine to give (*S*)-1. The recovered acid, which was enriched with undesired (*R*)-1, was activated with CDI, and a complete racemization was achieved in the presence of triethylamine at room temperature. Malonate 7 was also treated with LiBr and underwent selective monodecarboxylation to give (pyridonyl-1)propargylacetic ester 6, an enzymatic resolution substrate, directly in 87% yield.

Introduction

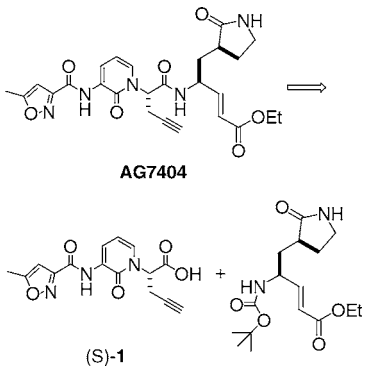
Chiral (pyridonyl-1)propargylacetic acid (*S*)-**1** is a key intermediate in the synthesis of **AG7404** (Scheme 1), which is a selective irreversible inhibitor of human rhinovirus (HRV) 3C protease.[1] Initially, (*S*)-**1** was synthesized through alkylation of pyridone **2** with triflate **3**, followed by a chemical resolution (Scheme 2). The synthesis is lengthy and involves expensive propargylglycine and hazardous diazotization. Although a chiral version of the synthesis starting from enantiopure propargylglycine was demonstrated on laboratory scales,[1a] racemization control in both the alkylation and subsequent hydrolysis proved to be difficult.

Results and Discussion

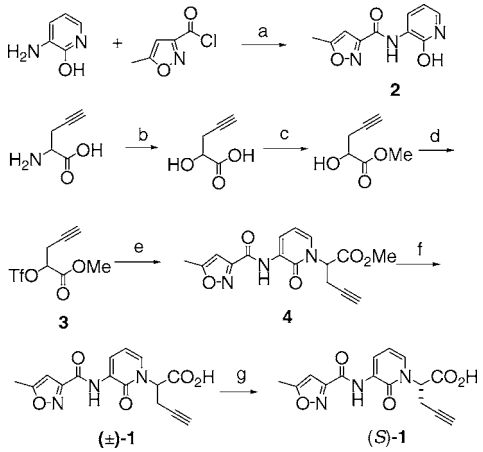
A two-step alkylation approach with bromoacetate and propargyl bromide was explored initially (Scheme 3). While the first alkylation with bromoacetate proceeded smoothly, the second one with propargyl bromide was not clean due to dialkylation. To avoid dialkylation, a bromomalonate alkylation approach was investigated (Scheme 4). Compound **2** was first alkylated with ethyl bromomalonate and then with propargyl bromide in the presence of tetrabutylammonium bromide and powdered potassium carbonate. Since both alkylations were clean, high yielding, and under identical conditions, a one-pot process was then developed. Crude **7** was obtained in >98% yield over two steps with >97% HPLC purity. **7** was easily hydrolyzed to form acid **1** with lithium hydroxide in THF, and the latter was resolved with (−)-norephedrine to give chiral acid (*S*)-**1** in 33% chemical yield and >95% ee.

Attempts to racemize the recovered acid, enriched with the undesired (*R*)-**1**, under either basic or acidic conditions

Scheme 1



Scheme 2 [a]



[a] Reagents and conditions: (a) NEt_3, THF, 87%; (b) 1 M H_2SO_4, $NaNO_2$; (c) 4 M HCl/dioxane, MeOH, 60% over two steps; (d) Tf_2O, 2,6-lutidine, 70%; (e) **2**, NaHMDS, THF, 80%; (f) aq LiOH, THF, 91%; (g) (i) (−)-norephedrine; (ii) 1 M HCl, 33%.

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(1) For similar HRV 3C protease inhibitors and recent development, see: (a) Dragovich, P. S.; Prins, T. J.; Zhou, R.; Johnson, T. O.; Hua, Y.; Luu, H. T.; Sakata, S. K.; Brown, E. L.; Maldonado, F. C.; Tuntland, T.; Lee, C. A.; Fuhrman, S. A.; Zalman, L. S.; Patick, A. K.; Matthews, D. A.; Wu, E. Y.; Guo, M.; Borer, B. C.; Nayyar, N. K.; Moran, T.; Chen, L.; Rejto, P. A.; Rose, P. W.; Guzman, M. C.; Dovalsantos, E. Z.; Lee, S.; McGee, K.; Mohajeri, M.; Liese, A.; Tao, J.; Kosa, M. B.; Liu, B.; Batugo, M. R.; Gleeson, J.-P. R.; Wu, Z. P.; Liu, J.; Meador, J. W., III; Ferre, R. A. *J. Med. Chem.* **2003**, *46*, 4572−4585. (b) Dragovich, P. S.; Prins, T. J.; Zhou, R.; Brown, E. L.; Maldonado, F. C.; Fuhrman, S. A.; Zalman, L. S.; Tuntland, T.; Lee, C. A.; Patick, A. K.; Matthews, D. A.; Hendrickson, T. F.; Kosa, M. B.; Liu, B.; Batugo, M. R.; Gleeson, J.-P. R.; Sakata, S. K.; Chen, L.; Guzman, M. C.; Meador, J. W., III; Ferre, R. A.; Worland, S. T. *J. Med. Chem.* **2002**, *45*, 1607−1623. (c) Dragovich P. S. *Expert Opin. Ther. Pat.* **2001**, *11*, 177−184.

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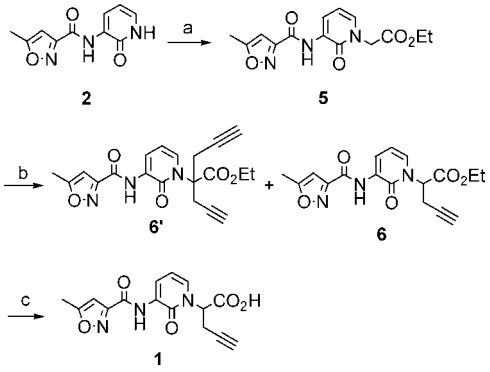
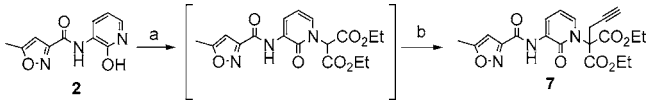
10.1021/op0600916 CCC: $33.50

Scheme 3 [a]



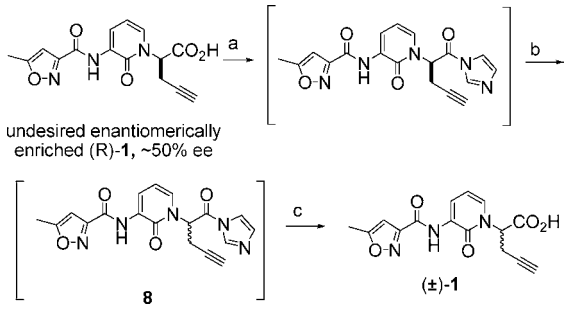
[a] Reagents and conditions: (a) DBU, ethyl bromoacetate, THF, 95%; (b) LiHMDS, propargyl bromide, DMPU/THF, 70% **6** isolated yield; (c) aq LiOH, THF, 93%.

Scheme 4 [a]



[a] Reagents and conditions: (a) Bu_4NBr, powdered K_2CO_3, ethyl bromomalonate, acetone; (b) propargyl bromide, >98% over two steps.

Scheme 5 [a]

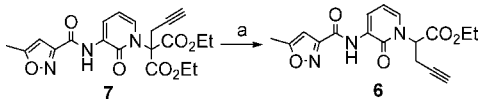


[a] Reagents and conditions: (a) CDI, EtOAc, 20 °C; (b) NEt_3, 20 °C, 3 h; (c) 2 N HCl.

resulted only in decomposition. A practical in situ activation/racemization sequence was developed (Scheme 5). The recovered **1** was treated with CDI in the presence of triethylamine. A complete racemization was achieved within 3 h at room temperature. The mixture was then quenched with 2 N HCl, and imidazolide **8** was hydrolyzed to give (±)-**1**.

Because a more selective and efficient enzymatic hydrolysis of ester **6** had been developed,[2] direct conversion of malonate **7** to mono-ester **6** became more desirable. As expected, conventional hydrolysis failed to provide selectivity, but monodecarboxylation in the presence of an alkali metal halide did give relatively clean reactions.[3] Among the salts tested, LiBr gave the best results. A large excess of LiBr was necessary to achieve a reasonable reaction rate at mild temperatures. DMPU and DMA proved to be good solvents. A relatively large solvent volume (about 20 volumes) was crucial to avoid bimolecular side reactions.[4] Under current conditions (10 equiv of LiBr, 20 volumes of DMA, 85 °C), **6** was obtained in 87% yield with >98% HPLC purity (Scheme 6).

Scheme 6 [a]



[a] Reagents and conditions: (a) LiBr, DMA, 87%.

Conclusions

A simple and efficient synthesis of malonate **7** starting from pyridone **2** and ethyl bromomalonate was developed. Malonate **7** was hydrolyzed to give acid (±)-**1**, which was resolved to give (*S*)-**1**. The recovered acid, enriched with the undesired (*R*)-**1**, was racemized using an in situ activation/racemization process in the presence of CDI and triethylamine at room temperature. A direct monodecarboxylation to convert malonate **7** to monoester **6**, an enzymatic resolution substrate, was developed, and **6** was obtained in 85% from **2**.

Experimental Section

Diethyl [3-{[(5-Methylisoxazol-3-yl)carbonyl]amino}-2-oxopyridin-1(2*H*)-yl](prop-2-yn-1-yl)malonate (7). Compound **2** (75.0 g, 0.342 mol), powdered potassium carbonate (142 g, 1.03 mol), and Bu_4NBr (11.0 g, 0.034 mol) were suspended in acetone (600 mL). The mixture was heated to 40 °C and stirred for 30 min. Diethyl bromomalonate (67.0 mL, 0.393 mol) was added at 40−50 °C. The suspension was then stirred at 40 °C for 30 min and cooled to 20 °C. Propargyl bromide (50.0 mL, 0.455 mol) was added at 20−30 °C. The mixture was stirred at 25 °C for 20 h. Acetic acid (30 mL, 0.52 mol) was added slowly at 20−30 °C. Water (1.2 L) was added carefully at 20−30 °C, and the resulting mixture was stirred for 2 h under house vacuum (~30 mmHg). The suspension was filtered to afford crude **7** as a tan solid (140.5 g, 98.8% yield, 97.3% HPLC purity). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.52 (s, br, 1H), 8.52 (dd, J = 7.4, 1.6 Hz, 1H), 7.53 (dd, J = 7.4, 1.6 Hz, 1H), 6.50 (s, 1H), 6.35 (t, J = 7.4 Hz, 1H), 4.36 (m, 4H), 3.46 (d, J = 2.6 Hz, 2H), 2.53 (s, 3H), 2.07 (t, J = 2.6 Hz, 1H), 1.33 (t, J = 7.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.7, 165.1, 159.1, 158.0, 157.6, 130.4, 128.8, 123.6, 105.8, 101.5, 83, 78.2, 73.0, 63.4, 24.7, 14.2, 12.5; HRMS (CI) *m*/*z* 416.1476 (416.1485 calcd for $C_{20}H_{22}N_3O_7$, MH^+).

2-(3-(5-Methylisoxazole-3-carboxamido)-2-oxopyridin-1(2*H*)-yl)pent-4-ynoic acid (1). Crude **7** (20.0 g, 48.1 mmol) was suspended in THF (50 mL), and 2 N LiOH (96.5 mL, 193 mmol) was added at 20 °C. The mixture was stirred for 2 h. A clear solution formed initially and soon became a white suspension subsequently. The mixture was acidified with 6 N HCl (~35 mL, 210 mmol) to pH = 3, was filtered and washed with water, and dried under vacuum (~30 mmHg) at 50 °C to give acid **1** as a tan solid (12.8 g, 84% yield, 98% HPLC purity). ^{1}H NMR (300 MHz, DMSO-d_6)

(2) Martinez, C. A.; Yazbeck, D. R.; Tao, J. *Tetrahedron* **2004**, *60*, 759−764.
(3) Krapcho, A. P.; Weimaster, J. F.; Eldridge, J. M.; Jahngen, E. G. E.; Lovey, A. J.; Stephens, W. P. *J. Org. Chem.* **1978**, *43*, 138−147.
(4) An unknown impurity with a molecular weight of about twice that of compound **6** was detected in an appreciable amount in concentrated reaction mixture.

δ 13.30 (br s, 1 H), 9.45 (s, 1 H), 8.32 (dd, J = 7.4, 1.6 Hz, 1 H), 7.55 (dd, J = 7.0, 1.6 Hz, 1 H), 6.73 (d, J = 0.8 Hz, 1 H), 6.43 (t, J = 7.2 Hz, 1 H), 5.29 (dd, J = 10.7, 4.5 Hz, 1 H), 3.20 (ddd, J = 17.5, 10.7, 2.6 Hz, 1 H), 2.97 (ddd, J = 17.4, 4.5, 2.7 Hz, 1 H), 2.86 (t, J = 2.5 Hz, 1 H), 2.51, (s, 3 H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 172.92, 169.32, 158.77, 157.10, 156.67, 133.41, 127.54, 123.56, 105.82, 101.67, 80.06, 73.99, 61.16, 19.07, 12.30; HRMS m/z 316.0945 (316.0933 calcd for $C_{15}H_{14}N_3O_5$, MH^+).

Chemical Resolution of (±)-1. (±)-**1** (30.0 kg, 95.2 mol) and (1*R*,2*S*)-(−)-norephedrine (7.19 kg, 47.6 mol) were suspended in EtOH (52 L), and the resulting mixture was heated to reflux to form a solution. A solution of (1*R*,2*S*)-(−)-norephedrine (3.60 kg, 23.8 mol) in EtOH (8 L) was added at above 75 °C. Ethyl acetate (300 L) was added in four equal portions over 2 h at 70 ± 5 °C. The mixture was cooled to 5 ± 5 °C over 3 h and was then cooled to −10 ± 5 °C and stirred for 3 h. The precipitate was isolated and washed with ethyl acetate (60 L) and dried at 50 °C to afford (*S*)-**1**·(*1R*,*2S*)-(−)-norephedrine salt (14.6 kg, yield 33%) as a snow-white solid with 95.8% ee by chiral HPLC.[5] ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.50 (br, 1H), 8.25 (dd, J = 7.3, 1.7 Hz, 1H), 8.2 (br, 3H), 7.47 (dd, J = 7.1, 1.7 Hz, 1H), 7.34 (m, 3H), 7.26 (m, 2H), 6.71 (s, 1H), 6.45 (br, 1H), 6.31 (dd, J = 7.2, 7.2 Hz, 1H), 5.21 (dd, J = 7.2, 7.2 Hz, 1H), 4.95 (d, J = 2.7 Hz, 1H), 3.37 (m, 1H), 2.98 (m, 2H), 2.69 (t, J = 2.6 Hz, 1H), 2.50 (s, 3H), 0.87 (d, J = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 171.1, 168.5, 157.1, 155.3, 155.2, 140.1, 130.9, 126.6, 125.7, 125.3, 124.4, 120.7, 102.9, 99.9, 80.1, 71.1, 69.8, 59.1, 50.2, 19.6, 10.5, 10.1; HRMS m/z 316.0944 (316.0933 calcd for free acid $C_{15}H_{14}N_3O_5$, MH^+).

Racemization of Undesired Enantiomerically Enriched (*R*)-1. The enantiomerically enriched (*R*)-**1**[6] (30.0 kg, 95.2 mol) and CDI (18.5 kg, 114 mol) were suspended in ethyl acetate (450 L). Triethylamine (14.6 L, 104.6 mol) was added. The mixture was stirred for 3 h and quenched with 2 N HCl (250 L). The organic solution was washed with saturated NaCl and dried azeotropically. The solution was concentrated to about 100 L, and heptane (200 L) was added. The resulting suspension was stirred at 0 ± 5 °C for 15 h and filtered. The wet cake was dried under vacuum at 50 °C to give racemate (±)-**1**. (28.6 kg, 95% yield).

Ethyl 2-[3-{[(5-Methylisoxazol-3-yl)carbonyl]amino}-2-oxopyridin-1(2*H*)-yl]pent-4-ynoate (6). Crude **7** (140.4 g, 0.338 mol) and LiBr (293.5 g, 3.38 mol) were suspended in *N*,*N*-dimethylacetamide (2.8 L). The mixture was heated to 85 °C and stirred for 16 h. The reaction mixture was cooled to room temperature, treated with charcoal (21 g), and filtered. Water (3 L) was added at below 45 °C, and the suspension was stirred at 20 °C for 6 h. The suspension was filtered to afford **6** as a brown solid (101.1 g, 87% yield, 99.5% HPLC purity). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.60 (s, br, 1H), 8.51 (dd, J = 7.4, 1.7 Hz, 1H), 7.21 (dd, J = 7.0, 1.7 Hz, 1H), 6.35 (t, J = 7.2 Hz, 1H), 5.22 (dd, J = 9.4, 4.6 Hz, 1H), 4.28 (q, J = 7.13 Hz, 2H), 3.22 (ddd, J = 17.5, 9.5, 2.7 Hz, 1H), 3.07 (ddd, J = 17.5, 4.6, 2.7 Hz, 1H), 2.53 (s, 3H), 2.04 (t, J = 2.7 Hz, 1H), 1.29 (t, J = 7.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8, 167.9, 159.2, 158.1, 157.4, 130.5, 129.0, 123.5, 106.4, 101.5, 79.0, 72.2, 62.6, 60.3, 20.7, 14.4, 12.5; HRMS (CI) m/z 344.1267 (344.1273 calcd for $C_{17}H_{18}N_3O_5$, MH^+).

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(5) Chiral HPLC analyses were performed with a Chiralcel OJ-R 3μm column (4.6 mm × 100 mm), 25 °C, 0.5 mL/min flow rate, an isocratic solvent system consisting of 25 mM NaH_2PO_4, pH 4.0 (60%) and acetonitrile (40%), and a total run time of 35 min.

(6) The undesired enantiomerically enriched (*R*)-**1** was obtained in >95% recovery and ~50% ee through acid−base extractive workup.