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Highly flexible and efficient synthesis of the $GABA_B$ enhancer 4-(2-hexylsulfanyl-6-methyl-pyrimidin-4-ylmethyl)-morpholine

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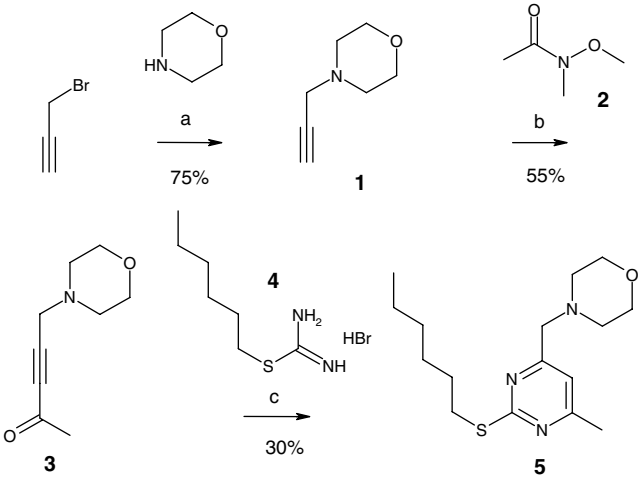
Abstract—In the course of establishing a flexible synthesis of 2,4,6-substituted pyrimidines, we discovered that 2-hexyl-isothiourea hydrobromide reacts at ambient temperature and in a mildly exothermic fashion with 5,5-diethoxy-pent-3-yn-2-one upon treatment with 2 equiv of triethylamine in tetrahydrofuran to afford 4-diethoxymethyl-2-hexylsulfanyl-6-methyl-pyrimidine in 80% isolated yield. The methodology was developed in the search for an improved synthesis of the $GABA_B$ enhancer 4-(2-hexylsulfanyl-6-methyl-pyrimidin-4-ylmethyl)-morpholine.

The non-fused pyrimidine ring is an important scaffold in medicinal chemistry. According to the *Derwent World Drug Index*® close to 100 drugs with a non-fused pyrimidine ring have been launched in the pharmaceutical market and several of these drugs have reached blockbuster status including trimethoprim, buspirone, bosentan, and imatinib. The vitamin thiamine belongs to the same structural class.

The chemistry of the non-fused pyrimidines has been exhaustively reviewed in monographs.[1,2] Many publications of more recent solution[3–6] and solid phase syntheses[7] have appeared in the literature.

In the course of a medicinal chemistry program aimed at the discovery of novel $GABA_B$ receptor enhancers,[8] we were in need of a flexible synthesis of 2,4,6-substituted pyrimidines. We opted for a previously reported method[9] which uses the condensation of a alkynone with a thiuronium salt.

In order to resynthesize our lead compound **5**, we first chose the pathway shown in Scheme 1. Morpholine was readily alkylated with propargyl bromide and potassium carbonate in methanol to afford the propargyl amine **1**,[10] which was purified on large scale directly by distillation. Propargyl amine **1** was treated with isopropyl magnesium chloride at low temperature which led to the formation of the corresponding acetylenic Grignard reagent under the liberation of propane. The Grignard reagent was cannulated slowly into a cold solution of the commercial Weinreb amide **2**.[11] The purification of the resulting acetylenic ketone **3** proved to be difficult and unreacted starting material could not



Scheme 1. Reagents and conditions: (a) K_2CO_3, MeOH, 0–20 °C; (b) (i) *i*-PrMgCl (1 equiv), THF, −20 °C, (ii) AcNMeOMe, THF, −10 °C (inverse addition); (c) DIPEA (4 equiv), DMF, 24 h, 20 °C.

Keywords: 2,4,6-Substituted pyrimidines; 2-Hexyl-isothiourea hydrobromide; 5,5-Diethoxy-pent-3-yn-2-one; Modular pyrimidine synthesis; $GABA_B$ enhancer.
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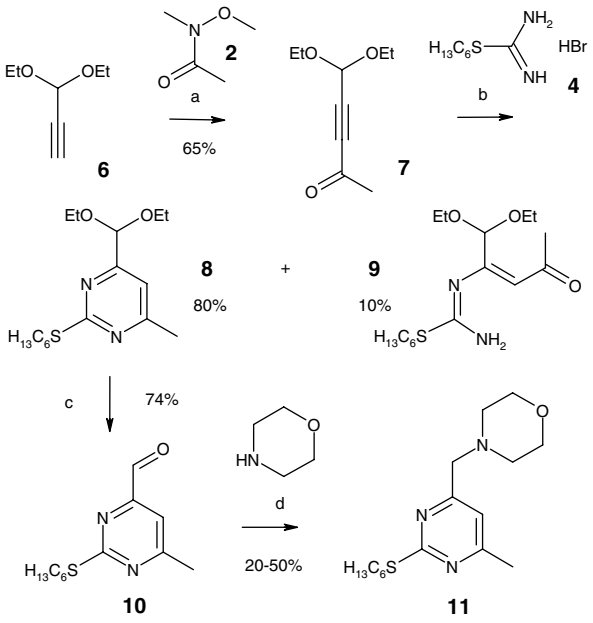
be removed by chromatography. Therefore the acetylenic ketone **3** was purified by Kugelrohr distillation, but it soon became apparent that the intermediate **3** had limited chemical stability. Probably as a consequence, the condensation of **3** with the thiuronium salt **4** with Hünig's base in DMF proceeded in low yield.[9]

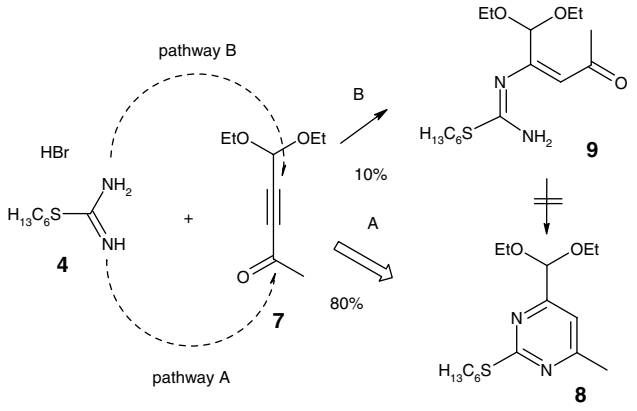
Despite the shortness of this pathway, a better synthesis (Scheme 2) was imperative in view of the preparation of libraries with ample variation of the substituents in 2-, 4-, and 6-position of the pyrimidine. Since we planned to incorporate a wide variety of amines via reductive amination, we chose a protected aldehyde as intermediate, which in the end turned out to be highly beneficial.

Luckily, 5,5-diethoxy-pent-3-yn-2-one (**6**), a commercial item, could also be obtained on larger scale. Grignard formation and inverse addition to a solution of the Weinreb amide **2** proceeded in 70% yield. The resulting acetylenic ketone **7** proved to be a stable synthetic intermediate. On a small scale, screening of solvents and bases for the condensation reaction of **7** with the thiuronium salt **4** indicated that triethylamine in THF was the best choice. On a large scale (15 g), the reaction was mildly exothermic (30 °C) and afforded pyrimidine **8** at ambient temperature in 80% yield. This transformation was accompanied by formation of by-product **9**, which could be isolated in 10% yield. Refluxing of the reaction mixture did not convert by-product **9** into pyrimidine **8**. Formation of by-product **9** occurred via Michael addition of the thiuronium salt **4** to acetylenic ketone **7** (pathway B, Scheme 3), while main product **8** was formed via carbonyl addition (pathway A, Scheme 3).

This behavior triggered the interesting thought that the high yield observed in this reaction may be due to the



Scheme 2. Reagents and conditions: (a) (i) *i*-PrMgCl (1.1 equiv), (ii) AcNMeOMe, THF, −20 to 0 °C, 2 h; (b) TEA (2.2 equiv), THF, 5 h, 20 °C; (c) 4 N H_2SO_4, THF, 24 h, 50 °C; (d) $NaBH_3CN$, EtOH/AcOH 10:1, 24 h, 20 °C.



Scheme 3.

fact that the diethoxy acetal function sterically and electronically suppresses the Michael addition pathway B and thus favors the carbonyl addition pathway A (Scheme 3). Furthermore, we speculate that the Michael addition occurred in *syn* fashion and therefore led to *E*-geometry of the double bond in by-product **9** precluding subsequent cyclization to pyrimidine **8**.

Moreover, we found that the thiuronium salt **4** with its long lipophilic tail was the best nucleophile. Thiuronium salts with shorter lipophilic appendices (e.g., Me only), resulted in lower yield. The role of the hexyl chain may be two-fold: first it increases the solubility of the thiuronium salt **4**, and secondly, it enhances the nucleophilicity of the azathioenol ether substructure. Thus in retrospect, a number of unanticipated features contributed to the optimal outcome of the originally planned reaction.

Acetal **8** was cleaved with 4 N sulfuric acid in THF at 50 °C overnight to afford aldehyde **10** in 74% yield. The latter was reductively aminated with a range of secondary amines. In the case of morpholine, Borch reduction[12] or pyridine borane reduction[13] was convenient for parallel chemistry with direct purification of the products by preparative HPLC, but with more sterically demanding secondary amines, the $Ti(OiPr)_4$–$NaBH_3CN$ method[14] was necessary to bring about efficient coupling of the reaction partners. The yields of the reductive aminations were not optimized. Detailed experimental procedures for the preparation of compounds **1**–**10** are listed in Ref. 15.

In conclusion we have discovered a flexible and high yielding synthesis of 2,4,6-trisubstituted pyrimidines which proceeds through the utilization of 5,5-diethoxy-pent-3-yn-2-one as the key building block, and we have gained mechanistic insight into the factors governing the maximally achievable yield of the addition of 2-hexyl-isothiourea to this key intermediate.

Acknowledgments

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References and notes

1. Brown, D. J. *The Pyrimidines* **1962**.
2. Brown, D. J.; Evans, R. F.; Cowden, W. B.; Fenn, M. D. *The Chemistry of Heterocyclic Compounds*, Vol. 16, *The Pyrimidines*, 1985.
3. Herrera, A.; Martinez-Alvarez, R.; Chioua, R.; Chioua, M. *Tetrahedron Lett.* **2003**, *44*, 2149–2151.
4. Herrera, A.; Martinez-Alvarez, R.; Chioua, R.; Benabdelouahab, F.; Chioua, M. *Tetrahedron* **2004**, *60*, 5475–5479.
5. Stanetty, P.; Hattinger, G.; Schnuerch, M.; Mihovilovic, M. D. *J. Org. Chem.* **2005**, *70*, 5215–5220.
6. Zanatta, N.; Flores, D. C.; Madruga, C. C.; Flores, A. F. C.; Bonacorso, H. G.; Martins, M. A. P. *Tetrahedron Lett.* **2006**, *47*, 573–576.
7. Pathak, R.; Roy, A. K.; Kanojiya, S.; Batra, S. *Tetrahedron Lett.* **2005**, *46*, 5289–5292.
8. Malherbe, P.; Masciadri, R.; Prinssen, E.; Spooren, W.; Thomas, A. W. U.S. Patent 2005197337, 2005; *Chem. Abstr.* **2005**, 266950.
9. Chucholowski, A.; Masquelin, T.; Obrecht, D.; Stadlwieser, J.; Villalgordo, J. M. *Chimia* **1996**, *50*, 525–530.
10. Verkruijsse, H. D.; Bos, H. J. T.; De Noten, L. J.; Brandsma, L. *Rec. Trav. Chim. Pays-Bas* **1981**, *100*, 244–246.
11. Williams, J. M.; Jobson, R. B.; Yasuda, N.; Marchesini, G.; Dolling, U.-H.; Grabowski, E. J. J. *Tetrahedron Lett.* **1995**, *36*, 5461–5464.
12. Borch, R. F.; Hassid, A. I. *J. Org. Chem.* **1972**, *37*, 1673.
13. Moormann, A. E. *Synth. Commun.* **1993**, *23*, 789–795.
14. Mattson, R. J.; Pham, K. M.; Leuck, D. J.; Cowen, K. A. *J. Org. Chem.* **1990**, *55*, 2552–2554.
15. *Experimental procedures:* 4-Prop-2-ynyl-morpholine (**1**). Morpholine (100 mL, 1.148 mol) was dissolved in MeOH (1 L) and cooled in ice under nitrogen, then potassium carbonate (120 g, 0.63 mol) and propargyl bromide (124 mL, 1.148 mol) were added while stirring in ice. Stirring without cooling was continued for 4 h. The white suspension was filtered through paper and the solids were washed with MeOH (100 mL), and MeOH was carefully evaporated. The white precipitate was suspended in DCM (400 mL), filtered through paper, and carefully evaporated. Finally the oil was distilled at 60 °C/16 mbar. One obtained 100 g (70%) of a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.27$ (t, $J = 2.4$ Hz, 1H, CCH), 2.57 (t, $J = 4.5$ Hz, 4H, CH_2N), 3.29 (d, $J = 2.4$ Hz, 2H, $CCCH_2$), 3.75 (t, $J = 4.5$ Hz, 4H, CH_2O).
N-Methoxy-*N*-methyl-acetamide (**2**). *N*,*O*-Dimethylhydroxylamine HCl (100 g, 1025 mmol) was suspended under nitrogen in DCM (1000 mL) and cooled in ice. Triethylamine (300 mL, 2152 mmol) was added slowly, then acetyl chloride (76.5 mL, 1076 mmol) was added slowly, and the temperature reached 20 °C despite ice cooling and slow addition. Stirring without cooling was continued for 30 min. Extraction: 1 × DCM, 1 × 1 N HCl, 2 × saturated NaCl solution. Distillation at 42 °C/20 mbar gave 69 g (65%) of a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.13$ (s, 3H, $COCH_3$), 3.18 (s, 3H, $CONCH_3$), 3.69 (s, 3H, OCH_3).
5-Morpholin-4-yl-pent-3-yn-2-one (**3**). 4-Prop-2-ynyl-morpholine (**1**) (22 g, 176 mmol) was dissolved under nitrogen in THF (40 mL) and cooled to −40 °C. Then a 2 M solution of isopropyl magnesium chloride in THF (97 mL, 193 mmol) was added while keeping the temperature below −20 °C. Stirring at −40 °C to −30 °C was continued for 30 min. In a separate flask, *N*-methoxy-*N*-methyl-acetamide (20 g, 193 mmol) was dissolved under nitrogen in THF (40 mL) and cooled to −10 °C in ice/MeOH. The Grignard solution prepared above was transferred to the Weinreb amide solution at −10 °C via Teflon tubing under slightly positive nitrogen pressure. There was no exotherm. Stirring at −10 °C to 0 °C was continued for 2 h. The resulting white suspension was poured on a 1:1 mixture of ice and saturated NH_4Cl solution (400 mL). Extraction: 2 × AcOEt, 1 × saturated NaCl solution. One obtained yellow oil (26.1 g, 89%). Chromatography on silica gel in heptane/ethyl acetate 1:2 gave 19.4 g (66%) of a brown oil which was distilled in the Kugelrohr at 130 °C/0.2 mbar. One obtained 15.8 g (53%) of a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.36$ (s, 3H, $COCH_3$), 2.58 (t, $J = 4.8$ Hz, 4H, CH_2N), 3.47 (s, 2H, $CCCH_2$), 3.74 (t, $J = 4.8$ Hz, 4H, CH_2O); MS (ISP): $m/z = 168$ (M+H).
2-Hexyl-isothiourea hydrobromide (**4**). *Caution*: Because of its pungent odor, all manipulations with this reagent should be run in a well ventilated laboratory hood, and all glassware that has been in contact with this reagent should be rinsed with 10% sodium hypochlorite solution before putting into the washing machine. Thiourea (50 g, 657 mmol) and 1-bromohexane (119 mL, 723 mmol) were heated at reflux under nitrogen in ethanol (500 mL) for 20 h. Ethanol was evaporated, and the thick oil stirred in diethyl ether (500 mL). The product precipitated spontaneously. After filtration one obtained 144.5 g (91%) of white crystals, mp 75 °C.
4-(2-Hexylsulfanyl-6-methyl-pyrimidin-4-ylmethyl)-morpholine (**5**). 5-Morpholin-4-yl-pent-3-yn-2-one (**3**) (1 g, 6 mmol) and 2-hexyl-isothiourea hydrobromide (**4**) (1.06 g, 7 mmol) were dissolved under nitrogen in DMF (10 mL), then *N*-ethyldiisopropylamine (4.1 mL, 24 mmol) was added and stirring at the room temperature continued for 18 h. DMF was evaporated. The product was extracted with AcOEt (2 × 50 mL), saturated solution of NH_4Cl (2 × 50 mL), dried and concentrated. The residue was purified by flash chromatography on an aminated silica gel column with a heptane/AcOEt gradient. One obtained 440 mg (24%) of a yellow liquid. ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 0.9$ (m, 3H, $S(CH_2)_5CH_3$), 1.32 (m, 4H, $SCH_2(CH_2)_4CH_3$), 1.45 (m, 2H, $SCH_2(CH_2)_4CH_3$), 1.72 (quin, $J = 7.2$ Hz, 2H, $SCH_2(CH_2)_4CH_3$), 2.44 (s, 3H, $ArCH_3$), 2.52 (m, 4H, NCH_2CH_2O), 3.14 (t, $J = 7.2$ Hz, 2H, $SCH_2(CH_2)_4CH_3$), 3.52 (s, 2H, $ArCH_2N$), 3.74 (m, 4H, NCH_2CH_2O), 6.98 (s, 1H, ArH); MS: $m/z = 310$ (M+H).
5,5-Diethoxy-pent-3-yn-2-one (**7**). Propargylaldehyde diethylacetal (40 g, 312 mmol) was dissolved in THF (200 mL) under argon and cooled to −70 °C. Then a 1.6 M solution of *n*-butyl lithium in hexane (234 mL, 374 mmol) was added and stirring continued for 30 min at −30 °C. Then *N*-methoxy-*N*-methylacetamide (38.6 g, 374 mmol) in THF (10 mL) was added. After 30 min at −30 °C, the reaction was quenched by addition of saturated NH_4Cl solution (20 mL). The product was extracted with AcOEt (2 × 200 mL), saturated solution of NH_4Cl (2 × 200 mL), dried and concentrated. Chromatography on silica gel with a heptane/AcOEt gradient 100:0 to 95:5 gave 38.5 g (72%) of a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.25$ (t, $J = 7.2$ Hz, 6H, OCH_2CH_3), 2.37 (s, 3H, $COCH_3$), 3.62 (q, $J = 7.2$, OCH_2CH_3), 3.75 (q, $J = 7.2$, OCH_2CH_3), 5.38 (s, 1H, $CH(OEt)_2$); GC/MS: $m/z = 232$(M).
4-Diethoxymethyl-2-hexylsulfanyl-6-methyl-pyrimidine (**8**)[8] and 1-((*E*)-1-diethoxymethyl-3-oxo-but-1-enyl)-2-hexyl-isothiourea (**9**). 5,5-Diethoxy-pent-3-yn-2-one (**7**) (15 g, 88 mmol) and 2-hexyl-isothiourea hydrobromide (23 g, 97 mmol) were dissolved under nitrogen in THF (150 mL). Then triethylamine (27 mL, 194 mmol) was added slowly while cooling with an ice bath to keep the temperature at 20 °C. The suspension was stirred without cooling for 5 h.

The product was extracted with AcOEt, satd NH_4Cl solution, dried, and concentrated. The residue was purified by silica gel chromatography in heptane/AcOEt 20:1. One obtained 22.3 g (80%) of **8** as colorless oil and 2.8 g (10%) of **9** as yellow oil. Compound **8**: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.89$ (t, $J = 4$ Hz, 3H, $S(CH_2)_5CH_3$), 1.25 (t, $J = 7.2$ Hz, 6H, OCH_2CH_3), 1.31 (m, 4H, $SCH_2(CH_2)_4CH_3$), 1.45 (m, 2H, $SCH_2(CH_2)_4CH_3$), 1.72 (m, 2H, $SCH_2(CH_2)_4CH_3$), 2.45 (s, 3H, $ArCH_3$), 3.15 (t, $J = 7.6$ Hz, 2H, $SCH_2(CH_2)_4CH_3$), 3.61 (m, 2H, OCH_2CH_3), 3.72 (m, 2H, OCH_2CH_3), 5.25 (s, 1H, $CH(OEt)_2$), 7.06 (s, 1H, ArH); MS (ISP): $m/z = 313$ (M+H). Compound **9**: ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 0.86$ (t, $J = 4$ Hz, 3H, $S(CH_2)_5CH_3$), 1.16 (t, $J = 7.2$ Hz, 6H, OCH_2CH_3), 1.25 (br, 2H, NH_2), 1.26 (m, 4H, $SCH_2(CH_2)_4CH_3$), 1.33 (m, 2H, $SCH_2(CH_2)_4CH_3$), 1.49 (m, 2H, $SCH_2(CH_2)_4CH_3$), 2.15 (s, 3H, $COCH_3$), 3.01 (t, $J = 7.6$ Hz, 2H, $SCH_2(CH_2)_4CH_3$), 3.48 (m, 2H, OCH_2CH_3), 3.58 (m, 2H, OCH_2CH_3), 5.16 (s, 1H, $CH(OEt)_2$), 6.56 (s, 1H, C=CH); MS (EI): $m/z = 288$ (M–$COCH_2$), 259 (M–Et), 243 (M–OEt), 213 (M–SC_6H_{13}), 103 ($CH(OEt)_2$).

2-Hexylsulfanyl-6-methyl-pyrimidine-4-carbaldehyde (**10**). 4-Diethoxymethyl-2-hexylsulfanyl-6-methyl-pyrimidine (**8**) (19 g, 60.8 mmol) was dissolved in THF (100 mL), 4 N aqueous H_2SO_4 (100 mL) was added and the mixture was heated at 50 °C for 33 h. After cooling, the reaction mixture was poured into cold 10% Na_2CO_3 solution (400 mL) and extracted with ethyl acetate and a satd solution of NaCl. The crude oil was purified by silica gel chromatography with a heptane/DCM gradient of 100:0 to 67:33. One obtained 10.7 g (74%) of a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.90$ (t, $J = 4$ Hz, 3H, $S(CH_2)_5CH_3$), 1.33 (m, 4H, $SCH_2(CH_2)_4CH_3$), 1.48 (m, 2H, $SCH_2(CH_2)_4CH_3$), 1.76 (m, 2H, $SCH_2(CH_2)_4CH_3$), 2.55 (s, 3H, $ArCH_3$), 3.21 (t, $J = 7.6$ Hz, 2H, $SCH_2(CH_2)_4CH_3$), 7.28 (s, 1H, ArH). MS (EI): $m/z = 239$ (M+H).

Library Synthesis via reductive amination: 4-(2-Hexylsulfanyl-6-methyl-pyrimidin-4-ylmethyl)-morpholine (**5**). Aldehyde **10** (0.1 g, 0.42 mmol) was dissolved in EtOH (1 mL) and AcOH (0.1 mL). Then morpholine (0.087 mL, 1 mmol) and $NaBH_3CN$ (26 mg, 0.4 mmol) were added slowly at 20 °C and stirring was continued for 24 h. The reaction mixture was evaporated to dryness and dissolved in a minimal amount of DMF (0.8 mL) and directly purified by preparative HPLC chromatography on a YMC combiprep ODS-AQ column (75 × 20 mm iD, S-5 μM, 12 nm) with an acetonitrile–water gradient. One obtained 34.7 mg (28%) of a yellow liquid. MS: $m/z = 310$ (M+H).