Pergamon

Tetrahedron Letters 40 (1999) 683–686

TETRAHEDRON LETTERS

A Novel, Thioacetal Based Linker for Solid-Phase Synthesis

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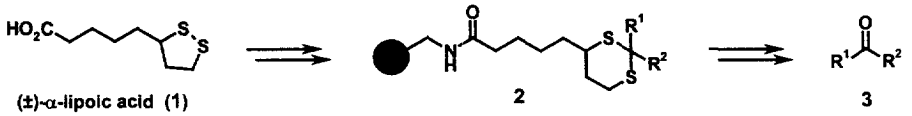
Received 28 October 1998; accepted 19 November 1998

Abstract: Commercially available (±)-α-lipoic acid was employed as a novel, chemically robust linker for the immobilization of ketones. The utility of this thioacetal based linker in solid-phase synthesis was demonstrated by synthesizing several 4-acetylbiphenyls and 4-alkoxyacetophenones *via Suzuki* and *Mitsunobu* reactions, respectively. The products were easily cleaved from solid support by treatment with [bis(trifluoroacetoxy)iodo]benzene.

Keywords: combinatorial chemistry, solid-phase synthesis, thioacetals.

The development of solid-phase synthesis[1] into a widely applicable technique of organic synthesis has to a large extent been driven by the paradigm shift in pharmaceutical industry, which is more and more focusing on synthesizing and testing combinatorial compound libraries[2] instead of single compounds. Therefore, a number of linkers has been developed in order to immobilize substrates on a solid support, thus allowing automated parallel multistep syntheses while using excess reagents, but avoiding the need for intermittent purification. However, there still is a need for novel linker systems, which on the one hand are sufficiently stable under a variety of reaction conditions, but on the other hand are selectively removable using, ideally, unique conditions. Surprisingly, while oxoacetal based linkers have been reported a long time ago,[3] to our knowledge the utilization of thioacetals as linking functionalities, offering a wide range of tolerated chemistries, has not been described in the literature so far. Herein, we report the utilization of commercially available (±)-α-lipoic acid[4] (**1**) as a linker for the immobilization of ketones (*Scheme 1*).

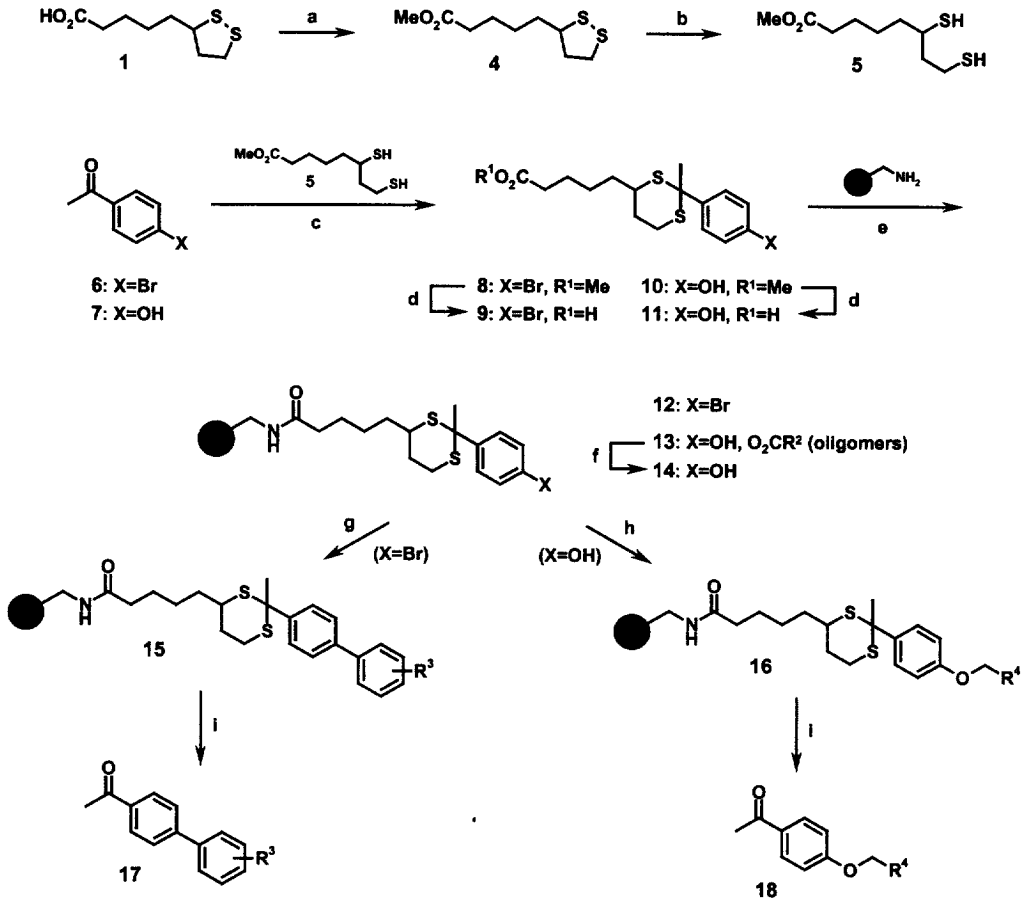


Scheme 1. (±)-α-lipoic acid as a linker for the solid-phase synthesis of substituted ketones.

In order to validate the utility of this thioacetal based linker in solid-phase synthesis, two transformations widely used on solid support, *Suzuki*[5] and *Mitsunobu*[6] reactions, were chosen. Thus, starting from 4-bromoacetophenone and 4-hydroxyacetophenone, a solid-phase synthesis[7] of several 4-acetylbiphenyls and 4-alkoxyacetophenones was performed, respectively (*Scheme 2*, *Table 1*). In order to obtain high polymer loadings, we decided to immobilize the pre-formed thioacetal based on a reliable amide bond formation. Therefore, (±)-α-lipoic acid (**1**) was transformed into its methyl ester **4** using *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (EDC) and *N*-hydroxybenzotriazole (HOBT) in MeOH/DMF 1:1 at r.t. (98% crude yield), thereby eliminating the need for further purification of the crude product after aqueous work-up. Reduction of the disulfide moiety in **4** ($NaBH_4$, MeOH, r.t.), followed by aqueous work-up then yielded a methylene chloride solution of dithiol **5**, which was directly used for the thioacetalization step. Treatment of 4-bromoacetophenone (**6**) and 4-hydroxyacetophenone (**7**) with this dithiol solution in the presence of excess $BF_3 \cdot Et_2O$ at r.t., followed by chromatographic purification, then gave thioacetals **8** and **10** in 67% and 91% yield, respectively.[8] Saponification (NaOH, H_2O, THF, r.t.) of the methyl ester group led to carboxylic acids **9**

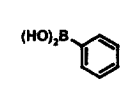
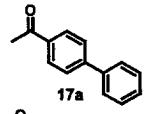
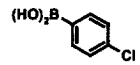
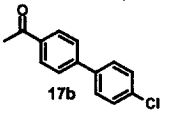
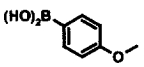
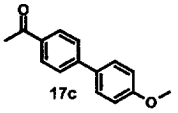
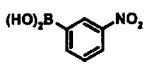
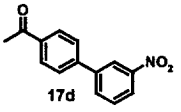
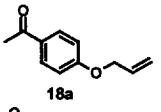
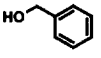
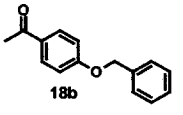
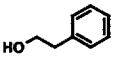
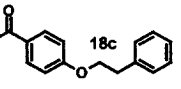
PII: S0040-4039(98)02580-5

and **11**, which were used for the immobilization step without further purification. Reaction of **9** (X=Br, 1.5 eq.) and **11** (X=OH, 2 eq.) with commercially available aminomethyl polystyrene resin, diisopropylcarbodiimide, and HOBT in DMF at r.t. gave rise to resins **12** (~0.8 mmol/g)[9] and **13**, the latter being contaminated with a small amount of oligomers produced by ester formation at the phenolic hydroxyl group during the amide formation step, as detected by solid-phase IR (KBr, shoulder at ~1725 cm^{-1}). Saponification of these phenolic esters by treatment of **13** with NaOMe in MeOH/THF at r.t.[10] removed this impurity (signal disappeared from IR spectrum), yielding resin **14** (~0.9 mmol/g).[9] Reaction[11] of bromo compound **12** and hydroxy derivative **14** with several boronic acids (*Suzuki* conditions[5]) and alcohols (*Mitsunobu* conditions[6]) afforded resins **15** and **16**, respectively.



Scheme 2. Reagents and conditions: (a) EDC, HOBT, MeOH, DMF, r.t., 22 h (98% crude); (b) $NaBH_4$, MeOH, r.t., 1.5 h (dried CH_2Cl_2 solution from aqueous work-up directly used for next step); (c) **5**, $BF_3{\cdot}Et_2O$, CH_2Cl_2, r.t. (**8**: 5 eq. **5**, 5 d, 67%; **10**: 2 eq. **5**, 4 d, 91%); (d) NaOH, H_2O, THF, r.t. (**9**: 24 h, **11**: 2 d; ~100%); (e) aminomethyl polystyrene resin, DIC, HOBT, DMF, r.t. (**12**: 0.67 eq. resin, 4 d, ~0.8 mmol/g; **13**: 0.5 eq. resin, 2 d); (f) NaOMe, MeOH, THF, r.t., 22 h (**14**: ~0.9 mmol/g); (g) 1. $R^3C_6H_4B(OH)_2$ (*Table 1*), $Pd(PPh_3)_4$, Na_2CO_3, H_2O, DMF, DME, 80 °C, o/n; 2. repeat; (h) 1. R^4CH_2OH (*Table 1*), DEAD, PPh_3, CH_2Cl_2, THF, r.t., o/n; 2. repeat; (i) $PhI(Tfa)_2$, CH_2Cl_2, EtOH, H_2O, r.t., 30 min.

Table 1. Products synthesized on solid support using the novel thioketal based linker.

Building Block	Product	Yield
	 17a	31%
	 17b	33%
	 17c	28%
	 17d	34%
	 18a	37%
	 18b	59%
	 18c	36%

Among the many published procedures for the cleavage of thioacetals,[12] the methods involving [bis-(trifluoroacetoxy)iodo]benzene[13] ($PhI(Tfa)_2$) or anhydrous periodic acid[14] (H_5IO_6) appeared to be the most promising for the application in solid-phase synthesis. While both procedures succeeded in cleaving the prepared thioacetals in a few minutes at r.t., we found that $PhI(Tfa)_2$ generated less side products compared to anhydrous H_5IO_6. Thus, treatment of resins **15** and **16** with $PhI(Tfa)_2$ (~2.5 eq., CH_2Cl_2/EtOH/H_2O 4.5/4.5/1) for 30 min. at r.t.[15] afforded, after chromatographic purification, 4-acetylbiphenyls **17** and 4-alkoxyacetophenones **18** in 28-59% overall yield[16] (*Table 1*).

In conclusion, we have introduced a novel, thioacetal based linker for the immobilization of ketones. The linker is easily obtained from commercially available, racemic α-lipoic acid and immobilized ketones can be recovered by treatment of the resins with [bis(trifluoroacetoxy)iodo]benzene at room temperature. The synthesis of several 4-acetylbiphenyls and 4-alkoxyacetophenones in reasonable yields using *Suzuki* and *Mitsunobu* reactions, illustrated the utility of the novel linker in solid-phase synthesis. Further applications of the thioacetal based linker described herein, *e.g.*, the immobilization of aldehydes and the preparation of combinatorial libraries, are under current investigation.

Acknowledgements. This work was supported by BMBF (Grant 03D0037E8). The authors wish to thank Ms. J. Krumnow and Mr. M. Thiel for assistance.

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7. Compounds **4**, **8**, **10**, **17 a-d**, and **18 a-c** were characterized by ^{1}H NMR, ^{13}C NMR, and MS. Spectroscopic data of selected compounds are given in notes.[8,15]
8. Compound **10**: freshly prepared **4** (7.27 g, 33 mmol) was dissolved in dry MeOH (100 mL) and stirred in an ice-bath for 10 min. to give a yellow, turbid solution. To this mixture was then added $NaBH_4$ (5.35g, excess) portionwise while stirring in an ice-bath and the resultant colorless solution was stirred at r.t. for 30 min. after which the pH was adjusted to 2 (1 M HCl in H_2O). This mixture was extracted with 400 mL CH_2Cl_2, the organic layer was separated, dried (Na_2SO_4) and filtered into a three-necked flask equipped with a rubber septum and a nitrogen source. To this solution was added 4-hydroxyacetophenone (**7**, 2.25 g, 16.5 mmol) and $BF_3{\cdot}Et_2O$ (33 mL, excess), and stirring was continued for 4 d at r.t., after which 400 mL CH_2Cl_2 were added. The mixture was washed with NaOH solution (10% in H_2O), H_2O, and brine, dried (Na_2SO_4) and evaporated. The residue was purified by flash-chromatography on silica using EtOAc/hexanes 1:4 to 1:1 to give **10** (5.10 g, 91%) as a yellowish oil. ^{1}H NMR (300 MHz, $CDCl_3$, two diastereomers in 0.7:0.3 ratio): δ/ppm = 1.42-1.70 (m, 7H), 1.69 (s, 0.7×3H), 1.96 (ddd, 0.7×1H, J=3/5.5/14 Hz), 2.18 (s, 0.3×3H), 2.22 (m, 0.3×1H), 2.30 (t, 0.3×2H, J=7 Hz), 2.32 (t, 0.7×2H, J=7 Hz), 2.60 (m, 0.7×1H), 2.68 (m, 0.7×2H), 2.87 (ddd, 0.3×1H, J=3/4.5/14.5 Hz), 3.14 (m, 0.3×1H), 3.20 (ddd, 0.3×1H, J=2.5/12.5/14.5 Hz), 3.67 (s, 0.3×3H), 3.68 (s, 0.7×3H), 5.08 (broad s, 1H), 6.81 (dbr, 2H, J=8.5 Hz), 7.67 (dbr, 0.3×2H, J=8.5 Hz), 7.80 (dbr, 0.7×2H, J=8.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ/ppm = 24.4, 25.6, 25.8, 28.7, 29.0, 32.4, 32.7, 33.9, 34.1, 35.4, 41.4, 41.7, 51.7, 53.0, 56.1, 115.2, 115.3, 128.4, 129.3, 135.4, 136.3, 154.5, 155.5, 174.5; HR-MS (EI): calcd 340.1167, found 340.1163. Compound **8**: prepared as described for **10** using **4** (1.47 g, 6.66 mmol), MeOH (50 mL), $NaBH_4$ (1.07 g, excess), 4-bromoacetophenone (**6**, 0.33 g, 1.65 mmol), and $BF_3{\cdot}Et_2O$ (3.3 mL, excess) to give, after flash-chromatography on silica using EtOAc/hexanes 1:9 to 1:4, **8** (0.44 g, 67%) as a yellowish oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ/ppm = 1.40-1.72 (m, 7H), 2.18 (s, 3H), 2.24 (dddd, 1H, J=2.5/2.5/5/14 Hz), 2.30 (t, 2H, J=7 Hz), 2.88 (ddd, 1H, J=3/5/14.5 Hz), 3.15 (m, 1H), 3.19 (ddd, 1H, J=2.5/12.5/14.5 Hz), 3.66 (s, 3H), 7.48 (dbr, 2H, J=8.5 Hz), 7.68 (dbr, 2H, J=8.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ/ppm = 24.7, 25.8, 28.5, 29.0, 32.5, 33.3, 35.4, 41.6, 51.5, 53.0, 122.1, 128.8, 131.4, 142.6, 174.0; HR-MS (EI): calcd 402.0323, found 402.0322 (^{79}Br).
9. Polymer loadings determined gravimetrically, *i.e.*, calculated from the observed change of resin mass and compared to theoretical values in order to obtain conversion percentages.
10. Procedure for the removal of ester oligomers: resin **13** (3.17 g) was suspended in dry THF (37 mL), NaOMe solution (8 mL, ~30% in MeOH) was added, the mixture stirred at r.t. for 22 h and filtered. The resin was washed with THF/H_2O 4:1, THF and CH_2Cl_2 and dried *in vacuo*. Examination of the solid-phase IR spectrum (KBr) of this material showed disappearance of the signal at ~1725 cm^{-1}.
11. All derivatization reactions[5,6] were performed using 300 mg loaded resin (**12**, **14**).
12. For example, see: Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 2nd ed., John Wiley & Sons, Inc., New York (1991).
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14. Shi, X.-X.; Khanapure, P.; Rokach, J. *Tetrahedron Lett.* **1996**, *37*, 4331.
15. Typical procedure for the deprotection step using $PhI(Tfa)_2$: resins from *Suzuki* and *Mitsunobu* steps (**15**, **16**) were suspended in CH_2Cl_2/EtOH 1:1 (2.2 mL), H_2O (0.57 mL) and [bis-(trifluoracetoxy)]iodobenzene solution (2.8 mL, 300 mg in 3 mL CH_2Cl_2/EtOH 1:1), the mixture was stirred at r.t. for 30 min. and filtered. The resins were then washed several times with THF and CH_2Cl_2, the combined filtrates were evaporated to dryness and the residues were purified by flash-chromatography on silica using EtOAc/hexane mixtures to give compounds **17 a-d** and **18 a-c** in 28-59% total yield (17-37 mg quantities).[16] Spectroscopic data of selected compounds: **17d**: ^{1}H NMR (300 MHz, $CDCl_3$): δ/ppm = 2.66 (s, 3H), 7.65 (t, 1H, J=8 Hz), 7.72 (dbr, 2H, J=8.5 Hz), 7.95 (ddd, 1H, J=1/1.5/8 Hz), 8.08 (dbr, 2H, J=8.5 Hz), 8.25 (ddd, 1H, J=1/2/8 Hz), 8.48 (dd, 1H, J=1.5/2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ/ppm = 26.7, 122.1, 122.9, 127.9, 129.2, 130.0, 133.1, 136.9, 141.5, 143.0, 148.8, 197.5; HR-MS (EI): calcd 241.0739, found 241.0739. **18c**: ^{1}H NMR (300 MHz, $CDCl_3$): δ/ppm = 2.55 (s, 3H), 3.12 (t, 2H, J=7 Hz), 4.24 (t, 2H, J=7 Hz), 6.92 (dbr, 2H, J=9 Hz), 7.22-7.37 (m, 5H), 7.92 (dbr, 2H, J=9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ/ppm = 26.8, 35.6, 68.9, 114.2, 126.7, 128.6, 129.0, 130.4, 130.6, 137.8, 162.7, 196.8; HR-MS (EI): calcd 240.1150, found 240.1147.
16. Overall yield for the steps immobilization, derivatization, cleavage and purification, referred to theinitial loading of the aminomethyl resin given by the supplier (Rapp Polymere GmbH, Tübingen).