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Staudinger/aza-Wittig reaction to access N^{β}-protected amino alkyl isothiocyanates

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A unified approach to access N^{β}-protected amino alkyl isothiocyanates from N^{β}-protected amino alkyl azides through general strategy of Staudinger/aza-Wittig reaction is described.The type of protocol to access isothiocyanates depends on the availability of the precursors and also, especially in amino acid chemistry, how well the other liable groups behave towards it. Fortunately, both these factors were not of concern as precursors-azides- were prepared at ease by standard protocols and the present protocol paved the way to access title compounds without affecting Boc, Cbz and Fmoc protecting groups, and benzyl and tertiary butyl groups in the side chains. The present strategy nullifies the need of amines to obtain title compounds, thereby, making the protocol step-economical. The added advantages include retention of chirality, convenient handling and easy purification. Few hitherto unreported compounds were also prepared and all final compounds were completely characterized by IR, mass, optical rotation, ^{1}H and ^{13}C NMR studies.

Introduction

Isothiocyanates are an important class of compounds and focus of interest in contemporary organic chemistry owing to their wide range of biological activities[1] and utility as potential precursors to access thioamides, [2] thioureas[3] and various heterocyclic compounds.[4]On the application part, based on the structural desirability of the final compounds various isothiocyanates having different skeletal structure are used.

Isothiocyanates are most commonly synthesized from amines, isonitriles and azides (Fig. 1). Thiophosgene on thiocarbonyl (C=S) transfer to amines yielded isothiocyanates in excellent yields,[5a-d] however, its toxicity and intolerance towards other sensitive functional groups limits its use. Owing to this, various C=S transfer reagents were found as ideal replacements for thiophosgene to access isothiocyanates.[5e-h] Isothiocyanates were also accessed by addition of carbon disulfide (CS_2) to amines in presence of base to form dithiocarbamate salts, which on *in situ* desulfurization led to isothiocyanates. Till date, various desulfurizing agents for dithiocarbamate have been witnessed in the literature.[6]

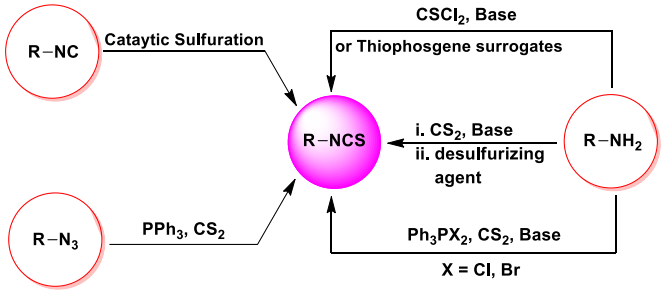

Fig. 1 Selected protocols for the synthesis of Isothiocyanates

Synthesis of isothiocyanates from amines, however, faces few setbacks as most of C=S transfer reagents are not readily available and possible contamination by the formation thioureas. In case of desulfurization of dithiocarbamates salts, electrophillic desulfurizing agents reacts with residual amines to hinder the achievements of the reaction.

There are reports where isonitriles were reacted with elemental sulfur *via* catalytic sulfuration to yield corresponding isothiocyanates.[7a-d] Boyer and Ramakrishnan demonstrated sulfuration of isonitriles using elemental sulfur and aryl isothiocyanates.[7e] And further, access of isothiocyanates were demonstrated from isocyanates,[8] nitrile oxides and hydroximoyl chlorides,[9] nitroalkanes,[10] aldoximes,[11] and alkenes and alkyl halides.[12] Bredan*et al*. demonstrated 'catch and release' strategies from polymer-bound

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thiobenzophenone[13a] and polymer-bound thiocarbonate[13b] to realize isothiocyanates.

Staudinger reaction is the reaction of azide with triphenylphosphine (PPh_3) to form iminophosphorane with evolution of nitrogen gas.[14] These iminophosphoranes can be further used as intermediates to access a wide variety of nitrogen containing organic compounds *via* aza-Wittig reaction.[15] As a result, Staudinger/aza-Wittig reaction has been put under tremendous exploitation soon after its discovery.[16] One such application is synthesis of isothiocyanates from the reaction of iminophosphorane with CS_2 and this is well established as handful of reports are available for the same.[16d-h] It is noteworthy that azaylides are also prepared by the reaction of triphenylphosphinedihalides with amines.[17]

Realm of peptidomimetics is rapidly increasing owing to the easy access and application of amino acid derived precursors.[18] Likewise amino acid derived isothiocyanates are deemed necessary precursors for various peptidomimetic achievements; they were employed to access thiourea-,[19] selenourea-,[20a] guanidine and carbodiimide-[20b] and oxadiazole-tethered peptidomimetics.[20c]

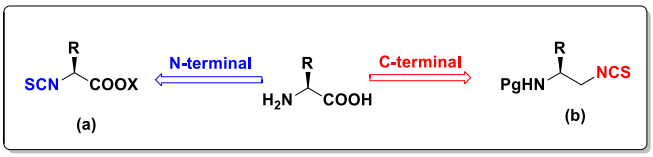
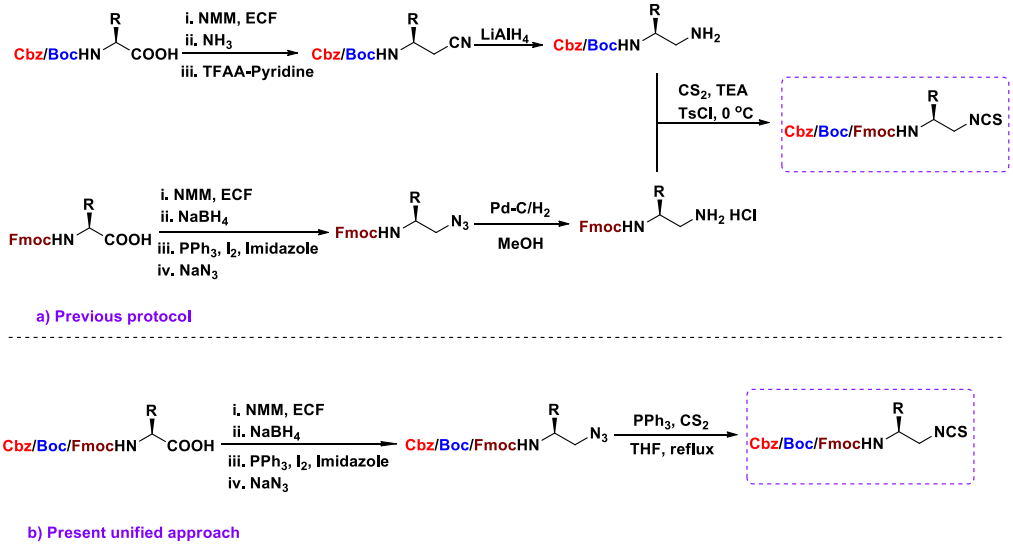


Fig. 2 (a) α-Isothiocyanato alkyl esters (b) N^{β}-protected amino alkyl isothiocyanates

Most commonly, isothiocyanato group can be inserted into amino acid at *N*-terminal (α-isothiocyanato alkyl esters, Fig. 2a) or *C*-terminal (N^{β}-protected amino alkyl isothiocyanates, Fig. 2b). Despite their importance, the literature records to access these are rather inadequate. It is understandable as the generality of the most of aforementioned reagents to amino acid chemistry fails and also the availability of amino acid derived precursors for isothiocyanates is limited. Further, undesired reactivity of sensitive groups, steric factors of side chains and possible racemization are the major concerns while synthesizing amino acid derived isothiocyanates.

A few reports are available for α-isothiocyanato alkyl esters and they involve thiocarbonylation of α-amino alkyl esters by thiophosgene,[5b-d,21a,b] and *via* desulfurization of dithiocarbamate salts.[6b, 20, 21c-e]

Interestingly, protocols for N^{β}-protected amino alkyl isothiocyanates are rather scant in the literature, in fact, the only available report to access these compounds was out from our laboratory.[19]These isothiocyanates were prepared from dithiocarbamate pathway from corresponding amines, employing tosyl chloride (TsCl) as desulfurizing agent. Therein, N^{β}-Fmoc-amino alkylamines were obtained by the reduction of corresponding azides using Pd-C/H_2. On the other hand, N^{β}-Boc/Cbz-amino alkylamines were obtained by the reduction of corresponding α-aminonitriles using lithium aluminium hydride ($LiAlH_4$). So, our previous protocol to access N^{β}-protected amino alkyl isothiocyanates employed two different routes while employing water sensitive $LiAlH_4$ and expensive Pd-C catalyst. Further, synthesis of N^{β}-Boc/Cbz-amino alkyl isothiocyanates and N^{β}-Fmoc-amino alkyl isothiocyanates is 5- and 6-step procedure respectively from corresponding N^{α}-protected amino acids. (Scheme 1a). Recently, Subhendu and Suranjan have demonstrated synthesis of side-chain isothiocyanyl amino acid derivatives employing almost a similar protocol.[22] Therein, isothiocyanates were obtained after converting azides to amines, which emphasizes the necessity of amine.



Scheme 1 Enantiopure synthesis of N^{β}-protected amino alkyl isothiocyanates: a) only protocol reported employing two separate routes b) present unified approach

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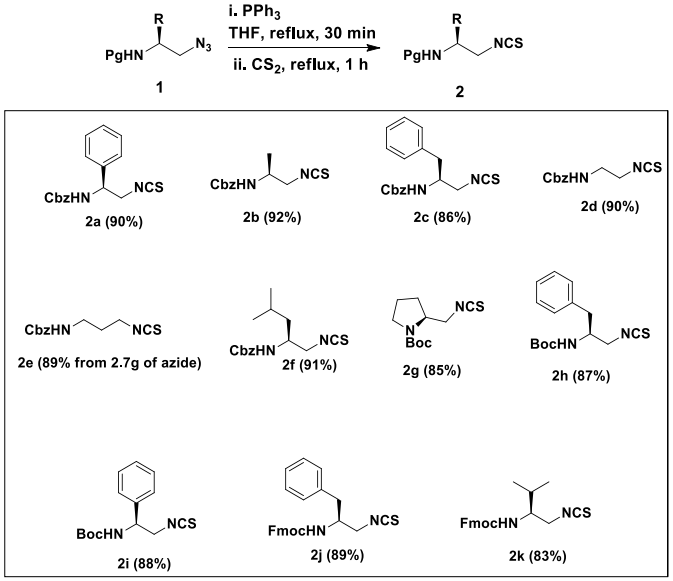
The literature dearth to access N^{β}-protected amino alkyl isothiocyanates drove us to adopt an ad hoc approach. It was found that Staudinger/aza-Wittig reaction was successfully employed to obtain sugar isothiocyanates from sugar azides.[16f] However, application of the reaction to obtain amino acid derived isothiocyanates is yet to be explored. Further, the type of protocol to be employed depends on the availability of the precursors and to our fortune, N^{β}-Boc/Cbz/Fmoc-protected alkyl azides were accessed at ease employing reported protocols, where N^{α}-protected amino acids were converted to N^{β}-protected amino alkyl iodides, which on azidolysis gave corresponding azides.[19,23] Thus, N^{β}-protected amino alkyl isothiocyanates can be prepared without the need of corresponding amines making the present protocol step-economical. So, herein, we describe an improved and unified approach to access N^{β}-protected amino alkyl isothiocyanates *via* Staudinger/aza-Wittig reaction (Scheme 1b).

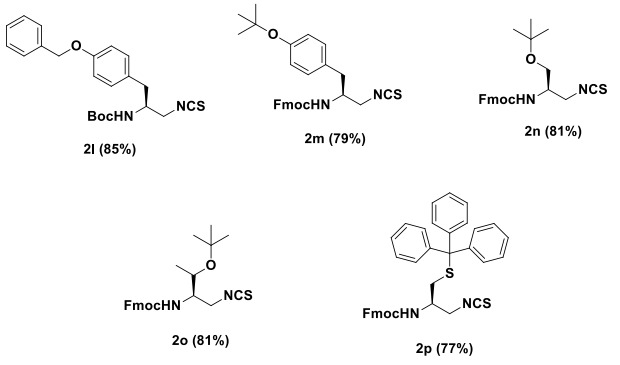
In a typical experiment, to the solution of Cbz-phg-ψ[CH_2N_3] (1a, 1.0 mmol) in dry THF was added PPh_3 (1.1 mmol) and allowed to stir at rt for 4 h. The progress of the entire reaction was monitored by thin layer chromatography (TLC). After the consumption of azide, CS_2 (10.0 mmol) was added and stirred at rt for 8 h to afford corresponding isothiocyanate (Cbz-phg-ψ[CH_2NCS], 2a) in 91% yield after column purification. Excess of CS_2 was used to make sure the reaction does not suffer from formation of corresponding symmetrical carbodiimides, and THF was a chosen solvent as it was found that various N^{β}-protected amino alkyl azides were neatly soluble in it. Concerned over the prolong reaction durations, we repeated the experimentation under reflux condition. It was found that 1a completely reacted with PPh_3 to form iminophosphorane within 30 min. Continuing the reflux after addition of CS_2 was found to be highly effective as the corresponding isothiocyanate formation was completed in an hour and afforded 90% yield. Therefore, reflux condition was preferred for further preparation of N^{β}-protected alkyl isothiocyanates. Though reactions in dichloromethane (DCM) and 1,4-dioxane were tested and found productive as that of THF, low boiling point of DCM deterred us from its further use in reflux condition, and high boiling point of 1,4-dioxane, on the other hand, brings inconvenience during its removal from reaction mixture, especially at large-scale synthesis. Various N^{β}-protected alkyl azides were smoothly converted to corresponding isothiocyanates to give good yield of products (Scheme 2, Entries 2a-k). Fmoc, Boc and Cbz protecting groups showed absolute compatability with the present strategy as the reaction is of neutral condition and sterically hindered proline showed facile formation of isothiocyanate from corresponding azide (Scheme 2, entry 2g). And also, compound 2e was obtained from large-scale synthesis (2.7g, 11.5 mmol of azide) and found to be equally productive as small-scale. Purification of isothiocyanates was easy as they were relatively non-polar compared to triphenylphosphine disulfide, whose presence inflicts difficulties in column purifications. To demonstrate proficiency of the protocol, few N^{β}-protected alkyl azides with side chain protections were studied and good yields of products were obtained without affecting the side chain protection. Tertiary butyl and benzyl group in the side chain was not at all affected (Table 1, Entries 2l-o).



Scheme 2 Synthesis of N^{β}-protected amino alkyl isothiocyanates from N^{β}-protected amino alkyl azides

It is important to note that reaction was not subsided by the presence of side chain as bulky as in compound 2p. The compatibility of these compounds towards present strategy was reflected in the isolated yields (Table 1, Entries 2l-p). During this, hitherto unreported compounds were also few of the prepared compounds (Scheme 2, entry g and Table 1, entries 2l-p) and all final compounds were completely characterized by IR, mass, melting point, optical rotation, ^{1}H and ^{13}C NMR studies. The synthesized compounds were subjected to RP-HPLC analysis and good purity was observed.

Table 1 Few side chain protected N^{β}-protected amino alkyl isothiocyanates



The synthesis of N^{β}-protected alkyl isothiocyanates from corresponding azides were of neutral condition, nonetheless, racemization studies were carried out to confirm the legitimacy of the protocol. During this, compound 2a was coupled with (*R*)-1-phenylethylamine and (*S*)-1-phenylethylamine separately to obtain compounds 3a and 3a*

(Fig. 3). RP-HPLC analyses showed retention time (t_R) 14.28 min for 3a while t_R of 3a* was 12.67 min.

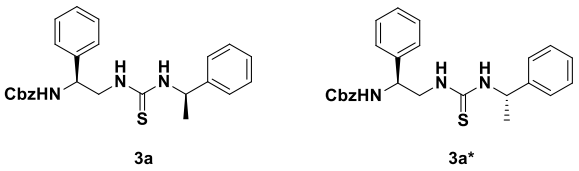


Fig. 3 Epimeric thiourea derivatives

And, equimolar mixture of 3a and 3a* showed retention times 14.86 min and 12.79 min, respectively. Further, ^{1}H NMR spectra of 3a and 3a* showed a doublet at δ 1.46 and 1.42 respectively, which correspond to the methyl protons of each of the epimers. These analyses provided an unequivocal evidence of racemization free synthesis of title compounds.

Conclusions

Staudinger/aza-Wittig reaction was employed as an ad hoc approach to obtain N^{β}-protected alkyl isothiocyanates from their corresponding azides. The protocol is an improved and unified version of our previous protocol to achieve the same. It shall be the preferred choice considering the fact how easily precursor azides are accessible and also, most importantly, nullifying the need of amines to obtain isothiocyanates makes the protocol step-economical and cost-effective. Neutral reaction condition benefits to achieve racemization free synthesis of title compounds bearing acid and base sensitive moieties.

Experimental Section

General experimental details

All chemicals were used as obtained from Sigma Aldrich Company, USA. All the solvents were dried and purified using recommended procedures in the literature whenever necessary. High resolution mass spectra were recorded on a Micromass Q-TOF spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AV NMR 400 MHz and 100 MHz spectrometers, respectively. The RP-HPLC analysis of epimers was carried out using the Agilent instrument (method: gradient 0.1% TFA water-acetonitrile (0-100%) in 30 min; VWD at λ = 254 nm; flow rate: 1.0 mL/min; column: Agilent Eclipse, XDB-C18, pore size-5 µm, diameter x length = 4.6 x 150 nm). Optical rotations of the compounds were recorded at 25°C and melting points were determined in an open capillary and are uncorrected. TLC experiments were performed using MERCK TLC aluminum sheets (silicagel 60 F254) and chromatograms were visualized by exposing in an iodine chamber or to a UV-lamp or $KMnO_4$ stain. Column chromatography was performed on silica gel (100–200 mesh) using ethylacetate and hexane (obtained from Merck, and distilled and dried prior to use) mixtures as the eluent.

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General procedure for the synthesis of N^{β}-protected amino alkyl azides from N^{α}-protected amino acid

To a solution of N^{α}-protected amino acid (1.0 equiv.) in THF at -15°C was added *N*-methylmorpholine (NMM, 1.0 equiv.) and ethylchloroformate (ECF, 1.0 equiv.) and stirred at same temperature for 15 min. The inorganic salts were filtered off and the filtrate was treated with moist $NaBH_4$ (2.0 equiv.) for 30 min. Excess water was added and stirred for 15 min. THF was removed by vacuum evaporation and then resulting solution was extracted with EtOAc and washed with 10% Na_2CO_3, 10% citric acid, brine and dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The resulting compound without prior purification was used in next step.

In the next step, the solution of N^{β}-protected aminol (1.0 equiv.) in CH_2Cl_2 was added to a stirred mixture of PPh_3 (3.0 equiv.), Imidazole (5.0 equiv.) and Iodine (3.0 equiv.) in dry CH_2Cl_2. After 6 h, the reaction mixture was evaporated and the crude was subjected to a flash chromatography using 10% ethyl acetate in hexane as eluent to afford corresponding N^{β}-protected amino alkyl iodides.

Then, to the solution of N^{β}-protected amino alkyl iodides (1.0 equiv.) in DMF was added sodium azide (1.5 equiv.) and stirred for 6 h at rt. Corresponding amino alkyl azides **1** were obtained in good yields and purity after aqueous workup.

General procedure for the synthesis of N^{β}-protected alkyl isothiocyanates from N^{β}-protected alkyl azides (2a-p)

To a stirred solution of N^{β}-protected alkyl azide (1.0 equiv.) in dry THF was added PPh_3 (1.1 equiv.) and refluxed for 30 min. After the consumption of azide (by TLC) CS_2 (10.0 equiv.) was added and refluxed for another hour. The solvent was evaporated under reduced pressure and the obtained residue was subjected to column chromatography to isolate corresponding isothiocyanate in good yield.

General procedure to prepare thiourea derivatives (3a and 3a*)

To a stirred solution of 2a (1.0 equiv.) in THF was added (*R*)-1-phenylethylamine (or (*S*)-1-phenylethyamine, 1.1 equiv.) and stirred for 2 h at rt. The solvent was vacuum evaporated and diluted with EtOAc, washed with 5% citric acid (2 x 10 mL), water (2 x 10 ml) and brine (10 mL), and dried over Na_2SO_4. The worked-up compound solution was vacuum evaporated to obtain 3a (or 3a*) in good yield and purity.

Cbz-phg-ψ[CH$_2$NCS] (2a). White solid (90% yield); m.p. 131-133 °C; $[\alpha]^{25}_D$ (c 1.0, $CHCl_3$) +12.0; IR (ν_{max} cm^{-1}): 2200, 2096, 1686; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25-7.41 (m, 10H), 5.33 (d, *J* = 8Hz, 1H), 5.13 (dd, *J* = 20 Hz, 12 Hz, 2H), 4.96-5.02 (br m, 1H), 3.82-3.92 (br m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.5, 137.5, 135.9, 133.7, 129.1, 128.6, 128.5, 128.2, 128.1, 126.4, 67.3, 54.9, 49.7; HRMS (ESI):*m/z* calcd for $C_{17}H_{16}N_2O_2SNa$ $[M+Na]^+$ 335.0830, found: 335.0832.

Cbz-Ala-ψ[CH$_2$NCS] (2b). White solid (92% yield); m.p. 112-114 °C; $[\alpha]^{25}_D$ (c 1.0, $CHCl_3$) -97.3; IR (ν_{max} cm^{-1}): 2204, 2092, 1686;

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^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26-7.37 (m, 5H), 5.07-5.15 (m, 2H), 4.83 (br s, 1H), 3.97 (br m, 1H), 3.72 (d, *J* = 12 Hz, 1H), 3.56 (dd, *J* = 12 Hz, 4 Hz, 1H), 1.27 (d, *J* = 8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.4, 136.1, 132.8, 128.6, 128.3, 128.1, 67.0, 50.1, 46.9, 17.9; HRMS (ESI): *m/z* calcd for $C_{12}H_{14}N_2O_2SNa$ [M+ Na]$^+$ 273.0674, found: 273.0677.

Cbz-Phe-ψ[CH$_2$NCS] (2c). White solid (86% yield); m.p. 126-128 °C; $[\alpha]^{25}_D$ (c 1.0, $CHCl_3$) -22.6; IR (ν_{max} cm^{-1}): 2206, 2104, 1697; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18-7.36 (m, 10H), 5.10 (s, 2H), 4.93 (d, *J* = 8 Hz, 1H), 4.09 (br m, 1H), 3.68 (dd, *J* = 12 Hz, 4 Hz, 1H), 3.50 (dd, *J* = 16 Hz, 4 Hz, 1H), 2.95 (dd, *J* = 12 Hz, 8 Hz, 1H), 2.84 (dd, *J* = 16 Hz, 8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.4, 138.2, 136.0, 133.3, 129.1, 128.9, 128.6, 128.3, 128.1, 127.7, 67.1, 52.1, 47.3, 37.8; HRMS (ESI): *m/z* calcd for $C_{18}H_{18}N_2O_2SNa$ [M+Na]$^+$ 349.0987, found: 349.0986.

Cbz-Gly-ψ[CH$_2$NCS] (2d). Oily liquid (90% yield) IR (ν_{max} cm^{-1}): 2195, 2101, 1696; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26-7.37 (m, 5H); 5.21 (s, 1H), 5.12 (s, 2H), 3.65 (t, *J* = 8 Hz, 2H), 3.41-3.46 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.2, 136.1, 132.8, 128.6, 128.3, 128.2, 67.1, 45.3, 41.0; HRMS (ESI): *m/z* calcd for $C_{11}H_{12}N_2O_2SNa$ [M+Na]$^+$ 259.0517, found: 259.0518.

Cbz-β-ala-ψ[CH$_2$NCS] (2e). White solid (89% yield); m.p. 55-57 °C; IR (ν_{max} cm^{-1}): 2184, 2099, 1692; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26-7.39 (m, 5H), 5.10 (s, 2H), 4.90 (br s, 1H), 3.59 (t, *J* = 8 Hz, 2H), 3.30-3.34 (m, 2H), 1.90-1.93 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.4, 136.3, 132.3, 128.5, 128.2, 128.1, 66.9, 42.6, 38.2, 30.2; HRMS (ESI): *m/z* calcd for $C_{12}H_{14}N_2O_2SNa$ [M+ Na]$^+$ 273.0674, found: 273.0677.

Cbz-Leu-ψ[CH$_2$NCS] (2f). White solid (91% yield); m.p. 106-108 °C; ; $[\alpha]^{25}_D$(c 1.0, $CHCl_3$) -112.0; IR (ν_{max} cm^{-1}): 2172, 2103, 1694; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.37 (m, 5H), 5.11 (s, 2H), 4.79 (d, *J* = 4 Hz, 1H), 3.88-3.94 (m, 1H), 3.74 (dd, *J* = 16 Hz, 4 Hz, 1H), 3.55 (dd, *J* = 16 Hz, 4 Hz, 1H), 1.62-1.72 (m, 1H), 1.37-1.46 (m, 2H), 0.94 (d, *J* = 8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.6, 136.1, 132.6, 128.5, 128.2, 128.1, 67.0, 49.2, 40.9, 24.7, 22.8, 22.0; HRMS (ESI): m/z calcd for $C_{15}H_{20}N_2O_2SNa$ [M+ Na]$^+$ 315.1143, found: 315.1141.

Boc-Pro-ψ[CH$_2$NCS] (2g). Oily liquid (85% yield); $[\alpha]^{25}_D$ (c 1.0, $CHCl_3$) -99.4; IR (ν_{max} cm^{-1}): 2189, 2081, 1687; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.85-3.96 (br m, 2H), 3.60-3.64(m, 1H), 3.37-3.48 (br m, 2H), 2.06-2.13 (m, 1H), 1.83-1.92 (m, 3H), 1.47 (s, 9H),; ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.1, 131.5, 79.9, 56.4, 47.9, 47.1, 28.4, 23.7; HRMS (ESI): *m/z* calcd for $C_{11}H_{18}N_2O_2SNa$ [M+Na]$^+$ 265.0987, found: 265.0983.

Boc-Phe-ψ[CH$_2$NCS] (2h). White solid (87% yield); m.p. 106-108 °C; $[\alpha]^{25}_D$ (c 1.0, $CHCl_3$) -39.3; IR (ν_{max} cm^{-1}): 2203, 2113, 1685; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20-7.35 (m, 5H), 4.67 (br s, 1H), 4.02 (br s, 1H), 3.65 (br d, *J* = 12 Hz, 1H), 3.48 (dd, *J* = 12 Hz, 8 Hz, 1H), 2.92 (br m, 1H), 2.81 (dd, *J* = 12 Hz, 8 Hz, 1H), 1.44 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.9, 136.3, 132.8, 129.1, 128.8, 127.0, 80.1, 51.5, 47.6, 37.9, 28.3; HRMS (ESI): *m/z* calcd for $C_{15}H_{20}N_2O_2SNa$ [M+Na]$^+$ 315.1143, found: 315.1141.

Boc-Phg-ψ[CH$_2$NCS] (2i). White solid (88% yield); m.p. 90-92 °C; $[\alpha]^{25}_D$ (c 1.0, $CHCl_3$) +11.0; IR (ν_{max} cm^{-1}): 2209, 2093, 1681; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26-7.40 (m, 5H), 5.05 (d, *J* = 12 Hz, 1H), 4.93 (br s, 1H), 3.82-3.92 (m, 2H), 1.46 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.9, 138.0, 133.3, 129.0, 128.5, 126.5, 80.5, 55.6, 49.8, 28.3; HRMS (ESI): *m/z* calcd for $C_{14}H_{18}N_2O_2SNa$ [M+Na]$^+$ 301.0987, found: 301.0988.

Fmoc-Phe-ψ[CH$_2$NCS] (2j). White solid (89% yield); m.p. 187-189 °C; $[\alpha]^{25}_D$ (c 1.0, $CHCl_3$) -18.1; (ν_{max} cm^{-1}): 2164, 2097, 1687; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8 Hz, 2H), 7.54 (t, *J* = 8 Hz, 2H), 7.29-7.41 (m, 9H), 4.87 (d, *J* = 8 Hz, 1H), 4.39 (d, *J* = 8 Hz, 2H), 4.19 (t, *J* = 8 Hz, 1H), 4.04 (br s, 1H), 3.44 (br d, *J* = 8 Hz, 1H), 3.34 (br d, *J* = 8 Hz, 1H), 2.79-2.84 (br m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.6, 143.7, 141.3, 136.8, 129.2, 129.0, 128.9, 128.7, 127.7, 127.0, 126.8, 124.9, 119.9, 66.7, 53.1, 51.8, 47.2, 38.0; HRMS (ESI): *m/z* calcd for $C_{25}H_{22}N_2O_2SNa$ [M+ Na]$^+$437.1300, found: 437.1303.

Fmoc-Val-ψ[CH$_2$NCS] (2k). White solid (83% yield); m.p. 164-166 °C; $[\alpha]^{25}_D$ (c 1.0, $CHCl_3$) -74.0; IR (ν_{max} cm^{-1}): 2196, 2011, 1684; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8 Hz, 2H), 7.60 (d, *J* = 8 Hz, 2H), 7.40 (t, *J* = 8 Hz, 2H), 7.33 (t, *J* = 8 Hz, 2H), 4.83 (d, J = 8 Hz, 1H), 4.46 (d, *J* = 8 Hz, 2H), 4.24 (t, *J* = 8 Hz, 1H), 3.69-3.75 (m, 2H), 3.55-3.61 (m, 1H), 1.80-1.89 (m, 1H), 0.97 (t, *J* = 8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.9, 143.7, 141.3, 132.5, 127.7, 127.1, 127.0, 125.0, 124.9, 120.0, 66.7, 56.5, 47.3, 29.4, 19.3, 18.6; HRMS (ESI): *m/z* calcd for $C_{21}H_{22}N_2O_2SNa$ [M + Na]$^+$389.1300, found: 389.1301.

Boc-Phe(OBzl)-ψ[CH$_2$NCS] (2l). White solid (85% yield); m.p. 79-81 °C; $[\alpha]^{25}_D$ (c 1.0, $CHCl_3$) +19.6; IR (ν_{max} cm^{-1}): 2202, 2089, 1691; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.43 (m, 5H), 7.12 (d, *J* = 8 Hz, 2H), 6.93 (d, *J* = 8 Hz, 2H), 5.05 (s, 2H), 4.65 (br s, 1H), 3.96 (br s, 1H), 3.63 (d, *J* = 12 Hz, 1H), 3.47 (dd, *J* = 12 Hz, 8 Hz, 1H), 2.86 (d, *J* = 8 Hz, 1H), 2.74 (dd, *J* = 12 Hz, 8 Hz, 1H), 1.44 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.9, 154.9, 136.9, 132.7, 130.1, 128.5, 127.9, 127.4, 115.2, 80.1, 70.0, 51.6, 47.5, 37.0, 28.3; HRMS (ESI): *m/z* calcd for $C_{22}H_{26}N_2O_3SNa$ [M+Na]$^+$421.1562, found: 421.1566.

Fmoc-Phe(O^{t}Bu)-ψ[CH$_2$NCS] (2m). Gummy solid (79% yield); $[\alpha]^{25}_D$ (c 1.0, $CHCl_3$) +6.2; IR (ν_{max} cm^{-1}): 2186, 2096, 1701; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.83-7.76 (m, 12H), 4.91 (s, 1H), 4.42 (d, *J* = 8 Hz, 2H), 4.22 (t, *J* = 8 Hz, 1H), 4.02-4.10 (br m, 1H), 3.67 (br d, *J* = 12 Hz, 1H), 3.48 (br d, *J* = 12 Hz, 1H), 2.74-2.88 (br m, 2H), 1.33 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.4, 154.5, 143.6, 141.3, 133.2, 129.5, 128.5, 127.7, 127.1, 124.9, 124.4, 120.0, 78.5, 66.8, 52.1, 47.4, 47.2, 37.0, 28.8; HRMS (ESI): *m/z* calcd for $C_{29}H_{30}N_2O_3SNa$ [M+Na]$^+$509.1875, found: 509.1873.

Fmoc-Ser(^{t}Bu)-ψ[CH$_2$NCS] (2n). White solid (81% yield); m.p. 86-88 °C; $[\alpha]^{25}_D$ (c 1.0, $CHCl_3$) -14.3; IR: (ν_{max} cm^{-1}): 2119, 2074, 1691; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8 Hz, 2H), 7.59 (d, *J* = 8 Hz, 2H), 7.41 (t, *J* = 8 Hz, 2H), 7.32 (t, *J* = 8 Hz, 2H), 5.15 (d, *J* = 8 Hz, 1H), 4.41 (d, *J* = 8 Hz, 2H), 4.24 (t, *J* = 8 Hz, 1H), 3.99 (br s, 1H), 3.65 (br s, 2H), 3.54 (d, *J* = 8 Hz, 1H), 3.41-3.44 (m, 1H), 1.20 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.7, 143.8, 141.3, 132.2, 127.7, 127.1, 125.0, 124.9, 120.0, 73.6, 66.9, 59.9, 50.7, 47.2, 45.4, 27.4; HRMS (ESI): *m/z* calcd for $C_{23}H_{26}N_2O_3SNa$ [M+Na]$^+$ 433.1562, found: 433.1560.

Fmoc-Thr(^{t}Bu)-ψ[CH$_2$NCS] (2o). Oily liquid (81% yield); $[\alpha]^{25}_D$ (c 1.0, $CHCl_3$) +9.7; IR (ν_{max} cm^{-1}): 2194, 2092, 1719; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 4 Hz, 2H), 7.60 (d, *J* = 8 Hz, 2H), 7.30-7.40 (m, 4H), 5.14 (d, *J* = 8 Hz, 1H), 4.44 (d, *J* = 8 Hz, 2H), 4.25

(t, *J* = 8 Hz, 1H), 3.87 (br d, *J* = 4 Hz, 1H), 3.70-3.80 (br m, 1H), 3.54-3.58 (m, 2H), 1.22 (t, *J* = 16 Hz, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.1, 143.8, 141.3, 131.8, 127.7, 127.0, 125.0, 124.9, 119.9, 74.2, 66.9, 64.9, 55.9, 47.2, 45.7, 28.7, 20.3; HRMS (ESI): *m/z* calcd for $C_{24}H_{28}N_2O_3SNa$ $[M+Na]^+$ 447.1718, found: 447.1715.

Fmoc-Cys(Trt)-ψ[CH$_2$NCS] (2p). Oily liquid (83% yield); $[\alpha]^{25}_D$ (c 1.0, $CHCl_3$) -13.9; IR (ν_{max} cm^{-1}): 2193, 2091, 1701; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (t , *J* = 8 Hz, 2H), 7.56 (d, *J* = 8 Hz, 2H), 7.20-7.41 (m, 19H), 4.59 (br s, 1H), 4.40 (d, *J* = 8 Hz, 2H), 4.19 (t, *J* = 8 Hz, 1H), 3.52 (br s, 3H), 2.46 (br s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.3, 144.1, 143.6, 141.3, 133.1, 129.4, 128.1, 128.0, 127.7, 127.0, 124.9, 120.0, 67.4, 66.7, 50.2, 47.7, 47.1, 33.2; HRMS (ESI): *m/z* calcd for $C_{38}H_{32}N_2O_2S_2Na$ $[M+Na]^+$ 635.1803, found: 635.1807.

Cbz-phg-ψ[CH$_2$NHCSNH]-(*R*)-(+)-1-phenylethylamine (3a). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17-7.34 (m, 15H), 6.60 (br s, 1H), 6.10 (br s, 1H), 5.66 (br s, 1H), 5.06 (dd, *J* = 16 Hz, 8 Hz, 2H), 4.72-4.76 (br m, 2H), 4.0-4.08 (br m, 1H), 3.69 (br d, *J* = 8 Hz, 1H), 1.46 (d, *J* = 8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.6, 156.5, 141.9, 139.0, 136.2, 129.0, 128.5, 128.2 (2C), 128.1, 127.8, 126.4, 125.7, 67.0, 60.3, 56.0, 53.8, 29.7.

Cbz-phg-ψ[CH$_2$NHCSNH]-(*S*)-(-)-1-phenylethylamine (3a*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19-7.27 (m, 15H), 6.57 (br s, 1H), 6.04 (br s, 1H), 5.72 (br s, 1H), 4.97 (s, 2H), 4.63 (br s, 2H), 3.82-3.86 (br m, 1H), 3.71-3.77 (br m, 1H), 1.42 (d, *J* = 4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.5, 156.7, 142.0, 138.8, 136.2, 129.0, 128.5, 128.1, 127.9, 127.8, 126.4, 125.8, 66.8, 55.2, 53.5, 50.4, 23.6.

Conflicts of interest

Authors declare no conflict of interest.

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Graphical Abstract

Staudinger/aza-Wittig reaction to access N^{β}-protected amino alkyl isothiocyanates

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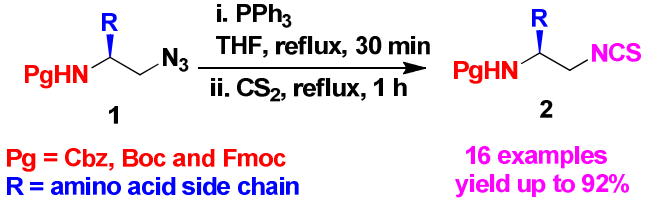

General strategy of Staudinger/aza-Wittig reaction has been effectively employed as an ad hoc approach to access N^{β}-protected alkyl isothiocyanates from N^{β}-protected alkyl azides.