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Author

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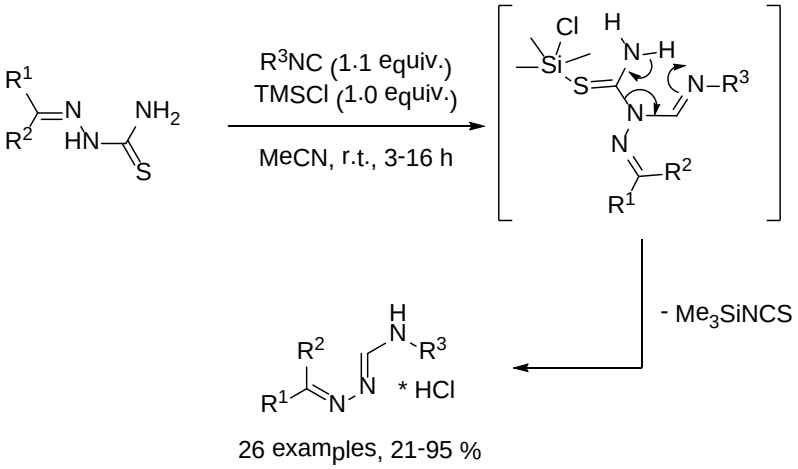

Synthesis of N^1,N^3-disubstituted formamidrazones via the TMSCl-promoted reaction of isocyanides with thiosemicarbazones

Pakornwit Sarnpitak,[a] Sergey Tsirulnikov,[b] Mikhail Krasavin*[a]

[a] *Eskitis Institute for Cell and Molecular Therapies, Griffith University, Nathan, Queensland 4111, Australia*

[b] *Science and Education Center "Innovative Research", Yaroslavl State Pedagogical University, Yaroslavl 150000, Russia*

*Corresponding author, e-mail: m.krasavin@griffith.edu.au, phone: +61 7 3735 6041, fax: +61 7 3735 6001.

Abstract: A hitherto undescribed TMSCl-promoted reaction of thiosemicarbazones was found to give rare N^1,N^3-disubstituted formamidrazones in fair to excellent yields. The scope of this new reaction was investigated and a plausible mechanism proposed.

Keywords: isocyanide-based multicomponent reactions, isocyanide insertion, Lewis acid catalysis, chlorotrimethylsilane, formamidrazones.

The reaction of an isocyanide with an imine component **1** is key in the Ugi reaction,[1] a prominent four-component reaction that leads to facile formation of dipeptoid adducts. Oximes **2**[2] and hydrazones **3**[3] have been successfully utilized as surrogate replacements for the imine component and have provided access to structurally novel, peptidomimetic Ugi-type products (Scheme 1). Combining an oxime[2] or a hydrazone[4] motif with an isocyanide-intercepting carboxylate functionality in the same reaction component has been shown to lead to ring-forming reactions with isocyanides, a strategy exploited extensively for the Ugi reaction itself.[5]

The use of semicarbazones as components for the Ugi reaction has been exemplified in the remarkable synthesis of 1,2,4-triazin-1-yl substituted alaninamides by Marcaccini and co-workers.[6] However, no account of a thiosemicarbazone reacting with an isocyanide existed in the literature. Intrigued by this void, and encouraged by the theoretical possibility of the

thiocarbamoyl motif to act, in the absence of a carboxylic acid component, as an internal isocyanide-intercepting nucleophile, we have investigated this reaction (Scheme 2).

The use of an acid catalyst/promoter for an isocyanide-based multicomponent reaction (IMCR) is important. Previously, we used equimolar amounts of chlorotrimethylsilane (TMSCl) to successfully promote various IMCRs.[7] This reagent was also chosen for this study. When treated with TMSCl and *tert*-butyl isocyanide in dry acetonitrile (the solvent previously found by us[8] to provide optimum results in TMSCl-promoted IMCRs), the model substrate **4** (prepared from *p*-anisaldehyde and thiosemicarbazide) underwent, after 3 hours at room temperature, full conversion into a new product that precipitated from the reaction mixture and was isolated by filtration. Contrary to our expectations of heterocycle formation (*vide supra*), ^{1}H and ^{13}C NMR spectroscopic data were consistent with the structure of 1-(*tert*-butyl)-4-(4-methoxybenzylidene)formamidrazone **5a** hydrochloride salt (Scheme 3). Single-crystal X-ray analysis[9] further confirmed this assignment (Figure 1).

Formamidrazones similar to **5a** have rarely appeared in the literature. They were prepared for the first time in 1968 via the two-step condensation of benzaldehyde hydrazone with triethyl orthoformate and various aliphatic amines;[10] formamidrazones have been implicated as valuable synthons for heterocycle synthesis.[11] The formamidrazone linkage has also been shown to be central to the design of antitubercular compounds.[12] Encouraged by the technically simple and high-yielding preparative access to **5a** depicted in Scheme 3 and by the absence of its analogs in existing commercially available screening collections,[13] we investigated the scope of this reaction with a range of thiosemicarbazones and isocyanides (Table 1).[14] While in some cases the product formamidrazone hydrochlorides precipitated from the acetonitrile solution and were isolated conveniently by filtration, the majority of the reactions the products were isolated in the free base form, following aqueous work-up of the reaction mixture with sat. aq. $NaHCO_3$, EtOAc extraction and column chromatography. Free-base formamidrazones (except for **5b**, **5k-l**, **5s** and **5u** derived from an aromatic isocyanide) existed as tautomeric mixtures that complicated their NMR spectroscopic characterization. However, they could be "locked" in a single tautomeric form when converted back into hydrochloride salts for easier characterization.[15] The yields of the precipitated hydrochloride salts were excellent while reactions requiring aqueous workup and chromatographic purification provided the free-base products in yields varying from moderate to good. Thiosemicarbazones of aromatic aldehydes and ketones generally provided better yields compared to their aliphatic counterparts (**5q**, **5x-z**).

The observed reaction was essentially a condensation of the hydrazone motif of **4** with the isocyanide, accompanied by a formal loss of isothiocyanic acid (HNCS). This result can be justified by the known ability of isocyanides to undergo facile insertion into N-H bonds (reported under $ZnCl_2$,[16] CuCl[17] or Cu_2O[18] catalysis). Moreover, such isocyanide reactivity has already been exploited for the preparation of formamidrazones from hydrazines and isocyanides.[19] Our mechanistic interpretation is presented in Scheme 4. *Tert*-butyl isocyanide is expected to insert into the N-H bond of the Lewis acid activated thisemicarbazone.[20] The basic amidine nitrogen thus installed can subsequently trigger the elimination of HNCS. The TMSCl present in the reaction mixture in an equimolar amount is then able to scavenge the HNCS whereby an equivalent of HCl is generated leading to the formamidrazone hydrochloride products.[21] The scavenging of HNCS by an equimolar amount of TMSCl and product hydrochloride formation may essentially drive the reaction forward. For instance, using only 0.2 equiv. of TMSCl in MeCN led to proportionally lower conversions and product yields (as determined by ^{1}H NMR spectroscopy). Similarly, inefficient (albeit not negligible) conversions were achieved using other Lewis acid promoters (0.2 equiv.): $Yb(OTf)_3$, $InCl_3$, $Sc(OTf)_3$, $Zn(OTf)_2$ as well as concentrated HCl. This attests to the unique character of TMSCl as a promoter in this reaction. Reactions in acetonitrile provided the best results,[22] but acceptable product yields could be achieved in dichloromethane and THF while running the reactions in methanol led to markedly poorer results (possibly due to its protic character and interference with HNCS scavenging).

According to our mechanistic interpretation, similar reactivity should be expected of semicarbazones (with respective loss of isocyanic acid). Although the product **5a** was indeed isolated as a free base (following basic work-up and extraction) from the reaction of the semicarbazone analog of **4**, the yield (27%) and abundance of unwanted side-products were far less appealing. The reasons for the less efficient reactivity of semicarbazones toward isocyanides, compared to that of thiosemicarbazones, are not clear at present.

The mechanism presented in Scheme 4 also implies that TMSCl-promoted insertion of an isocyanide into an H_2NCSN-H bond, with subsequent loss of isothiocyanic acid may be general in nature. We reacted *t*-BuNC with unsubstituted thiourea and thiosemicarbazide in the presence of 1 equiv. of TMSCl. The hydrochlorides of monosubstituted amidine **6** and formamidrazone **7** were isolated from the respective reactions by filtration, although the yield of the former was of little practical value (Scheme 5). Interestingly, an attempted alternative synthesis of the free-base compound **5a** from monosubstituted formamidrazone **7** (MeCN, *p*-

anisaldehyde, Et_3N, r.t., 2 h) led to the conversion of the latter into a complex product mixture containing only a small amount of the target material (according to TLC analysis).

In summary, a new TMSCl-promoted reaction of isocyanides with thiosemicarbazones was shown to provide diversely substituted formamidrazones in fair to excellent yields for a range of substrates. Preliminary mechanistic interpretation suggests that the generality of this reaction extends beyond thiosemicarbazones and will be further investigated. The potential applications of N^1,N^3-disubstututed formamidrazones **5** in heterocycle synthesis are currently being investigated in our laboratories. The results of these studies will be reported in due course.

Acknowledgements

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References and notes

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9. Crystallographic data (excluding structure factors) for structure **5a** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 894123. Copies of the data can be obtained free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].
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13. Compounds synthesized in this work have been deposited with the Queensland Compound Library (Griffith University) and are available for collaborative discovery projects.
14. General procedure for the preparation of formamidrazones **5a-z**: A magnetically stirred suspension (solution) of an aldehyde or ketone thiosemicarbazone (1 mmol) in dry MeCN (15 mL) was treated with TMSCl (1 mmol) and stirred for 10 min. Next the isocyanide (1.1 mmol) was added, the reaction flask was purged with argon and the mixture was stirred at r. t. until the reaction was complete (3-16 h, as judged by the disappearance of the starting material according to TLC analysis). Solid products precipitated from the reaction mixtures (**5a**, **5e**, **5n-p**, **5t**, **5w**) were filtered off, washed with Et_2O, and air-dried to provide analytically pure formamidrazone hydrochlorides. In all other cases the mixture was diluted with EtOAc (50 mL), washed with sat. aq. $NaHCO_3$, dried over anhydrous $MgSO_4$, filtered and concentrated to provide the crude product. The latter was purified by column chromatography on silica using an appropriate gradient of EtOAc in hexanes or MeOH in CH_2Cl_2 to provide analytically pure free base formamidrazones.
15. Characterization data for representative formamidrazone hydrochlorides: **5a**·HCl - White solid, mp = 162-164°C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.25 (br s, 1H, HCl), 9.51 (d,

J = 13.5 Hz, 1H, amidine CH), 8.49 (s, 1H, Ar-CH=N), 8.19 (d, *J* = 13.5 Hz, *t*-BuNH), 7.92 (d, *J* = 8.0 Hz, 2H, 4-MeOC_6H_4), 7.05 (d, *J* = 8.0 Hz, 2H, 4-MeOC_6H_4), 3.84 (s, 3H, OMe), 1.42 (s, 9H, *t*-Bu); ^{13}C NMR (125 MHz, DMSO-d_6) δ 161.6, 152.9, 146.8, 129.9, 124.5, 113.8, 54.9, 54.5, 28.2. HRMS *m/z* (M+H+) calcd for $C_{13}H_{20}N_3O$ 234.1601, found 234.1595. **5e**·HCl - Grey solid, mp = 173-175 °C (decomp.) ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.40 (br s, 1H, HCl), 9.72 (dd, *J* = 13.0, 7.5 Hz, 1H, amidine CH), 8.43 (s, 1H, Ar-CH=N), 8.19 (d, *J* = 13.0 Hz, 1H, *c*-HexNH), 7.90 (d, *J* = 8.5 Hz, 2H, 4-MeOC_6H_4), 7.06 (d, *J* = 8.5 Hz, 2H, 4-MeOC_6H_4), 3.84 (s, 3H, OMe), 3.49-3.55 (m, 1H, *c*-Hexyl CH-NH), 1.88-1.92 (m, 2H), 1.76-1.81 (m, 2H), 1.61—1.65 (m, 1H), 1.52 (ddd, *J* = 24.5, 12.5, 2.5 Hz, 2H), 1.23-1.32 (m, 2H), 1.08-1.15 (m, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 161.1, 157.0, 154.5, 149.4, 129.2, 114.0, 55.7, 55.3, 54.3, 31.6, 30.6. HRMS *m/z* (M+H^+) calcd for $C_{15}H_{22}N_3O$ 260.1757, found 260.1746. **5h**·HCl - Beige hygroscopic solid, mp = 116-120 °C (broad); ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.64 (br s, 1H, HCl), 9.65 (d, *J* = 13.5 Hz, 1H, amidine CH), 8.57 (s, 1H, 2-furyl-CH=N), 8.20 (d, *J* = 13.5 Hz, 1H, *t*-BuNH), 7.99 (s, 1H, 2-furyl), 7.25 (d, *J* = 3.2 Hz, 1H, 2-furyl), 6.74 (m, 1H, 2-furyl), 1.39 (s, 9H, *t*-Bu); ^{13}C NMR (125 MHz, DMSO-d_6) δ 147.2, 146.9, 146.5, 142.4, 117.6, 112.3, 54.7, 28.1. HRMS *m/z* (M+H^+) calcd for $C_{10}H_{16}N_3O$ 194.1288, found 194.1280. **5n**·HCl - White solid, mp = 144-146 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.62 (br s, 1H, HCl), 9.57 (d, *J* = 13.8 Hz, 1H, amidine CH), 8.58 (s, 1H, Ar-CH=N), 8.23 (d, *J* = 13.8 Hz, 1H, *t*-BuNH), 7.71 (d, *J* = 7.9 Hz, 1H, Ar), 7.69 (s, 1H, Ar), 7.26 (d, *J* = 7.9 Hz, 1H, Ar), 2.29 (s, 6H), 1.42 (s, 9H, *t*-Bu); ^{13}C NMR (125 MHz, DMSO-d_6) δ 153.5, 147.1, 140.3, 136.4, 129.6, 129.4, 129.0, 125.6, 54.7, 28.2, 19.0, 18.7. HRMS *m/z* (M+H^+) calcd for $C_{14}H_{22}N_3$ 232.1808, found 232.1806. **5o**·HCl - Beige solid, mp = 157-159 °C (decomp.). ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.79 (br s, 1H, HCl), 9.78 (d, *J* = 13.7 Hz, 1H, amidine CH), 8.64 (s, 1H, Ar-CH=N), 8.28 (d, *J* = 13.7 Hz, 1H, *t*-BuNH), 8.15 (s, 1H, Ar), 7.89 (d, *J* = 7.6 Hz, 1H, Ar), 7.60 (m, 1H, Ar), 7.54 (t, *J* = 7.8 Hz, 1H, Ar), 1.44 (s, 9H, *t*-Bu); ^{13}C NMR (125 MHz, DMSO-d_6) δ 151.8, 147.7, 134.2, 133.2, 130.8, 130.2, 127.3, 126.7, 54.9, 28.2; HRMS *m/z* (M+H^+) calcd for $C_{12}H_{17}ClN_3$ 238.1106, found 238.1105.

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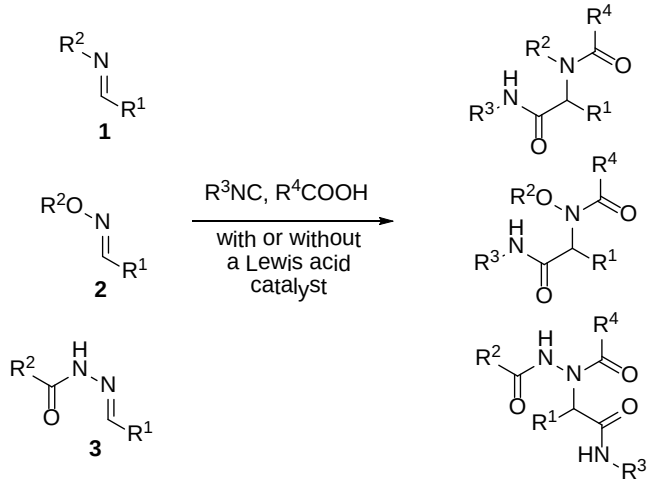
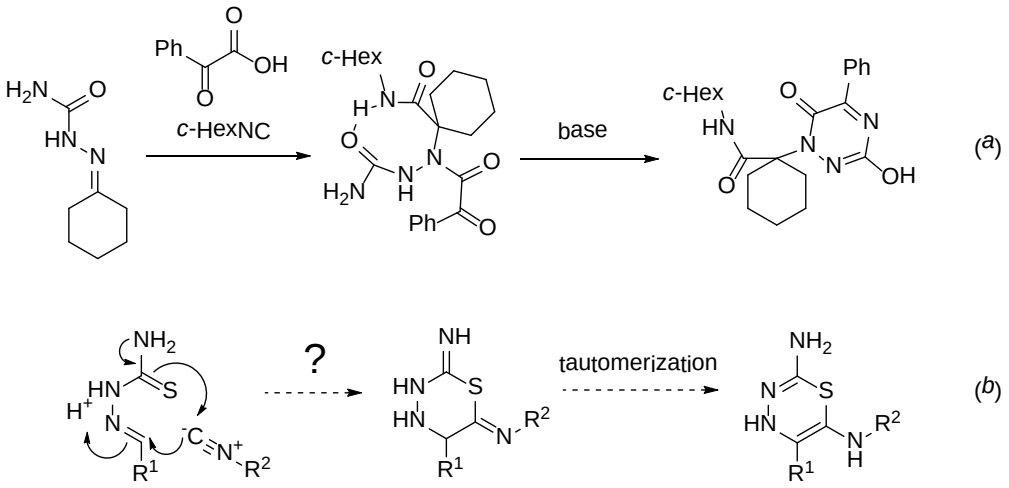
20. ^{1}H NMR monitoring of the reaction depicted in Scheme 3 (in CD_3CN) revealed that the signals corresponding to the starting thiosemicarbazone **4** broadened on addition of TMSCl (indicating some degree of interaction between these reagents), but remained unchanged for at least 1 h, until *t*-BuNC was added.
21. On completion of the reaction, the ^{1}H NMR (500 MHz, CD_3CN) spectral signal the corresponding to TMS group experienced a slight downfield shift (0.37 → 0.46 ppm) that was consistent with the conversion of TMSCl into the thioisocyanatotrimethylsilane implicated in the proposed mechanism.
22. Acetonitrile is able to form a complex with TMSCl (see, for example: Olsson, L.; Ottosson, C.-H.; Cremer, D. *J. Am. Chem. Soc.* **1995**, *117*, 7460-7479), which may attenuate the Lewis acidity of the latter.

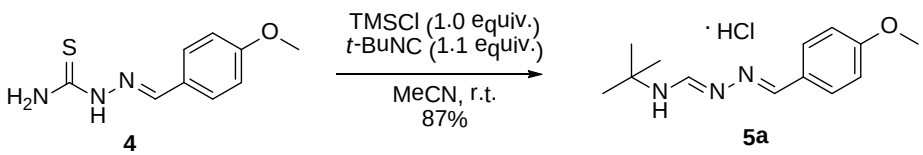
Scheme 1. Imine, oxime and hydrazine components in the Ugi reaction.



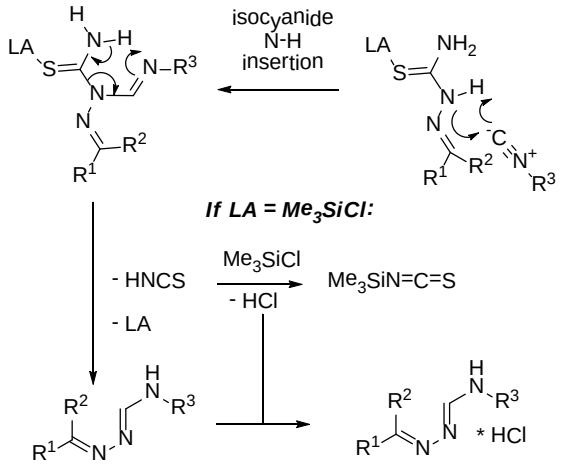
Scheme 2. An example of using semicarbazones[6] (*a*) and the potential bifunctional character of thiosemicarbazones (*b*) in reactions with isocyanides.



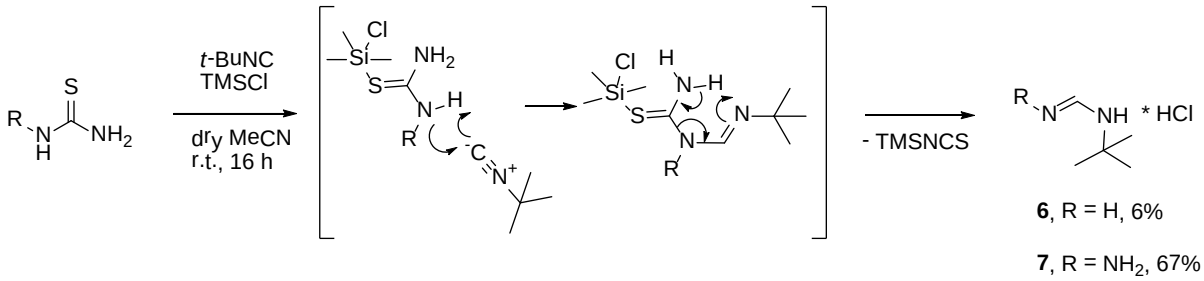
Scheme 3. Model TMSCl-promoted reaction of a thiosemicarbazone with an isocyanide.



Scheme 4. Mechanistic interpretation of the reaction toward formamidrazones **5a-z**.



Scheme 5. Reactions of thiourea and thiosemicarbazone with *t*-BuNC promoted by TMSCl.



6, R = H, 6%

7, R = NH_2, 67%

Figure 1. Single-crystal X-ray structure of compound **5a** (ORTEP plot representing the atoms as thermal ellipsoids at 50% probability level).

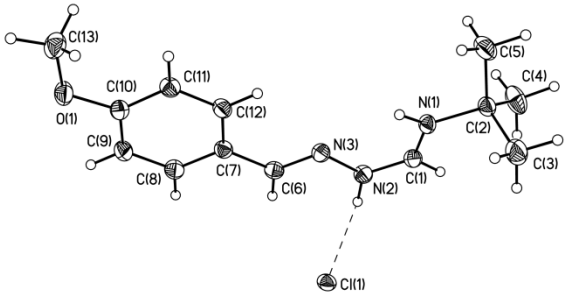
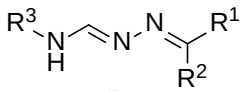
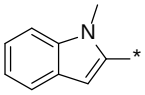
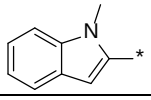
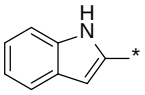
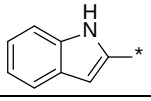
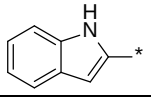


Table 1. Formamidrazones **5a-z** synthesized in this work.[a]



5a-z

Product	R^1	R^2	R^3	Yield, %	Isolated as (A) free base or (B) HCl salt
5a	4-$MeOC_6H_4$	H	*t*-Bu	87	B
5b	2-$CF_3C_6H_4$	H	4-$MeOC_6H_4$	51	A
5c	2-$CF_3C_6H_4$	H	MeO_2CCH_2	46	A
5d	2-$CF_3C_6H_4$	H	Bn	67	A
5e	4-$MeOC_6H_4$	H	cyclohexyl	94	B
5f	2-$O_2NC_6H_4$	H	$(CH_3)_3CH_2(CH_3)_2C$	63	A
5g	2-$O_2NC_6H_4$	H	cyclohexyl	70	A
5h		H	*t*-Bu	62	A
5i		H	cyclohexyl	68	A
5j		H	MeO_2CCH_2	58	A
5k	4-MeC_6H_4	H	4-$MeOC_6H_4$	33	A
5l	4-$MeOC_6H_4$	H	4-$MeOC_6H_4$	40	A
5m	2-BrC_6H_4	H	Bn	69	A
5n	3,4-diMeC_6H_3	H	*t*-Bu	88	B
5o	3-ClC_6H_4	H	*t*-Bu	90	B
5p		H	cyclohexyl	90	B
5q	$(CH_3)_2CHCH_2$	H	Bn	42	A
5r	Ph	Me	*t*-Bu		A
5s	Ph	Me	4-$MeOC_6H_4$		A
5t		H	*t*-Bu	88	B
5u		H	4-$MeOC_6H_4$	29	A
5v	2-BrC_6H_4	H	MeO_2CCH_2		A
5w	2-BrC_6H_4	H	cyclohexyl	95	B
5x	-$(CH_2)_5$-		*t*-Bu	50	A
5y	Me	Me	*t*-Bu	21	A
5z	$(CH_3)_2CHCH_2$	H	cyclohexyl	41	A