PERKIN 1

Substitution of α-azido ethers with Grignard reagents and its use in combinatorial chemistry

Mukulesh Baruah and Mikael Bols *

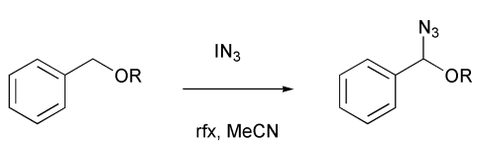
Department of Chemistry, University of Aarhus, Langelandsgade 140 Aarhus C, DK-8000, Denmark. E-mail: mb@kemi.aau.dk

Received (in Cambridge, UK) 14th November 2001, Accepted 7th January 2002
First published as an Advance Article on the web 22nd January 2002

α-Azidobenzyl ethers were reacted with alkyl or arylGrignard reagents in toluene to produce α-alkylbenzyl or diarylmethyl ethers in 82–94% yield. α-Azidobenzyl ethers were also reacted with multicomponent Grignard reagents to produce libraries of α-alkylbenzyl ethers.

Introduction

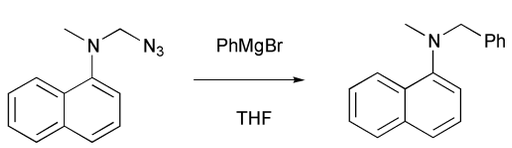
Recently we reported that benzyl ethers (**1**) react with IN_3 in refluxing acetonitrile to give the corresponding α-azido ether **2** (Scheme 1).[1] This radical reaction is high-yielding, efficient and



1 **2**

Scheme 1 Radical azidonation of benzyl ether.

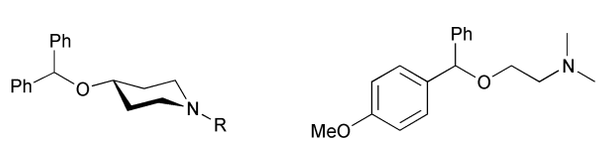
simple to carry out and has the advantage that the monosubstituted azido ether is selectively obtained probably because the azide destabilises a radical cation intermediate. A related reaction has been reported by Magnus *et al.*, who were able to directly azidonate in the α-position of amines using $TMSN_3$–$PhI(OAc)_2$ to obtain compounds like **3**.[2] They also reported that reaction between **3** and phenylmagnesium bromide gave the adduct **4** Scheme 2. A similar substitution reaction could



3 **4**

Scheme 2 Substitution of α-azidoamine with phenylmagnesium bromide.

potentially be useful on α-azidobenzyl ethers like **2**, since this would lead to diaryl or alkylaryl ethers, which are quite abundant among bioactive compounds. Thus antihistamines diphenylpyraline (**5**), ebastine (**6**) and medrylamine (**7**) are examples of such compounds (Fig. 1). Combinatorial approaches to such



5 R = Me
6 R = $CH_2CH_2NMe_2$ **7**

Fig. 1 The antihistamines diphenylpyraline (**5**), ebastine (**6**) and medrylamine (**7**).

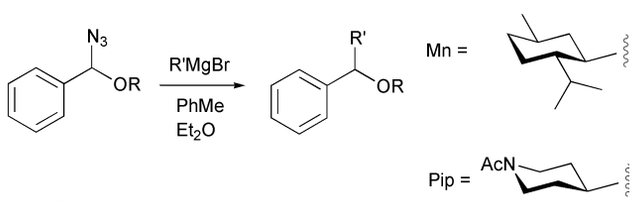
Table 1 The results from the reaction shown in Scheme 3

Substrate	Product	R	R′	Time/min	Yield (%)
2a	**8a**	Me	Me	20	90
2a	**8b**	Me	Ph	20	89
2a	**8c**	Me	Pr	30	88
2a	**8d**	Me	Allyl	90	85
2b	**8e**	Et	Me	20	89
2b	**8f**	Et	Ph	20	87
2b	**8g**	Et	Pr	30	87
2b	**8h**	Et	All	90	85
2c	**8i**	Mn	Me	30	82
2c	**8j**	Mn	Pr	50	82
2d	**8k**	Pip	Me	10	94
2d	**8l**	Pip	Pr	10	90
2d	**8m**	Pip	n-C_6H_{13}	10	90

structures could also be useful. In this paper we report our findings regarding the reaction between Grignard reagents and α-azidobenzyl ethers, and also report the synthesis of libraries of diphenylpyraline analogues using multicomponent Grignard reagents.

Results and discussion

Initially reaction of methylmagnesium bromide with α-azidobenzyl methyl ether was attempted (**2a**, Scheme 3 and Table 1) in

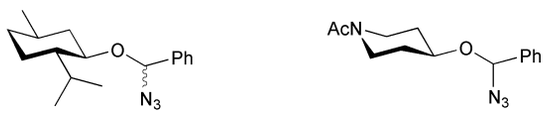


2 **8**

Scheme 3 Substitution of α-azido ethers with alkyl or arylmagnesium bromide. Reaction and substituent details are given in Table 1.

THF similar to the reaction described by Magnus *et al* (Scheme 2), but no reaction was observed at all. Obviously the azido ether **2a** is much less reactive than the azidoamine **3** which is also witnessed by a much greater stability of **2a**. However a review of the literature revealed that the reactivity of the Grignard reagent might be increased if toluene was used as solvent.[3,4] Indeed when the Grignard reagent in ether was added to the azido ether **2a** in toluene an excellent yield of 1-phenylethyl methyl ether (**8a**) was obtained (Scheme 3, Table 1) after 20 min at room temperature.

The reaction was now attempted on the series of azido ethers **2a**–**2d** of which **2a** and **2b** were previously known,[1] while **2c** and **2d** were new. These were made by treatment of the corresponding benzyl ethers, made by benzylation (NaH–BnBr) of menthol and known *N*-acetyl-4-oxypiperidine[5] (**1d**), with IN_3 in refluxing acetonitrile, which gave the azido ethers **2c** and **2d** in 82% and 55% yield, respectively (Fig. 2).

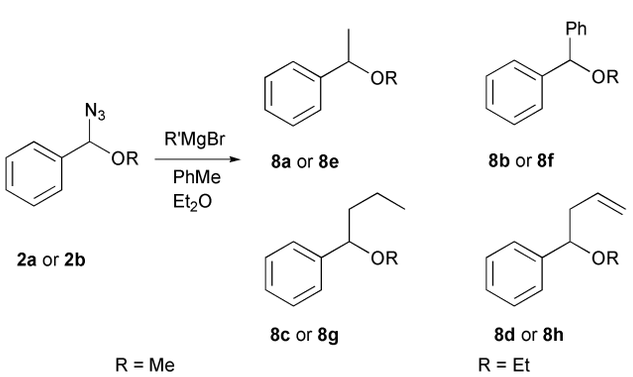


2c (82%) **2d** (55%)

Fig. 2 The azido ethers **2c** and **2d**. In parentheses is given the yield of the azide obtained from reaction of the corresponding benzyl ether with IN_3.

Reaction between azido ethers **2a**–**2d** and MeMgI, PrMgBr, PhMgBr or CH_2=$CHCH_2MgBr$ in toluene–ether at 25 °C gave the adducts **8a**–**8m** in 82–94% yield (Table 1). The reaction appears to have a broad scope with respect to the Grignard reagent. The reactions were monitored by TLC and interestingly some variation in reaction times were observed. Particularly the allyl Grignard reagent was considerably more sluggish towards the azido ethers, which is surprising because CH_2=$CHCH_2MgBr$ reacts with acetone much faster than both MeMgI and PrMgBr.[6]

We have recently found that it is possible to prepare multicomponent Grignard reagents and add them to aldehydes, esters and ketones to create uniform libraries of secondary and tertiary alcohols.[7] We now investigated whether similar chemistry would be feasible here; if so libraries of analogues of the drugs **5**–**7** could essentially be made in one step. Since the reactions between individual Grignard reagents and α-azido ethers had revealed a considerable difference in rate of reaction between allylmagnesium bromide and the other Grignard reagents it was clear that such experiments would fail and no allyl product would be formed unless precautions were made to ensure formation of allyl product. This was done by slow addition of the multicomponent Grignard reagent to the azide solution. Thus a 4 component Grignard reagent was made by reaction of a mixture of MeI, PhBr, $CH_3CH_2CH_2Br$ and CH_2=$CHCH_2Br$ with excess magnesium and added over 2 h to a solution of **2a** (Scheme 4). This gave the products **8a**–**8d** in an essentially uniform mixture. The ratio was 3 : 4 : 3 : 4, which could be seen from ^{1}H NMR since the absorptions of substituents in **8a**–**8d** are widely different. The reaction was also carried out with **2b** giving a 1 : 1 : 1 : 1 ratio of **8e**–**8h**.

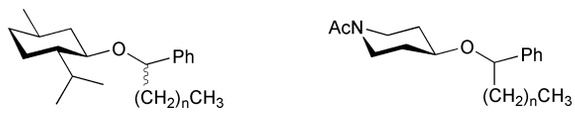


Product	8a	8b	8c	8d
Ratio (%)	21	28	24	27

Product	8e	8f	8g	8h
Ratio (%)	25	25	25	25

Scheme 4 Solution-phase combinatorial reactions between the 4 Grignard reagents MeMgI, PhMgBr, $CH_3CH_2CH_2MgBr$ and CH_2=$CHCH_2MgBr$, and the azides **2a** or **2b**.

We also carried out a similar reaction with an 8 component Grignard reagent consisting of MeMgI and $CH_3(CH_2)_nMgBr$ with *n* being from 1 to 7. The reagent was prepared from an equimolar mixture of the corresponding halides and excess Mg, and then in two separate experiments reacted with the azides **2c** and **2d** (Fig. 2). While, in both cases, NMR of the product mixture was consistent with the presence of the 8 possible products (Fig. 3), it could not ensure their presence due to the



8i n = 0
8n n = 1
8j n = 2
8o n = 3
8p n = 4
8q n = 5
8r n = 6
8s n = 7

8k n = 0
8t n = 1
8l n = 2
8u n = 3
8v n = 4
8m n = 5
8x n = 6
8y n = 7

Fig. 3 The possible products from the reaction of an 8 component Grignard reagent, consisting of $CH_3(CH_2)_nMgX$ (*n* = 0–7), with azides **2c** and **2d**, respectively.

number of very similar compounds. However mass spectroscopy of the two libraries gave signals corresponding to the products **8i**, **8j** and **8n**–**8s** being obtained from **2c**, and products **8k**–**8m** and **8t**–**8y** being obtained from **2d**. The mass spectrum of the library obtained from **2d** is shown in Fig. 4. While the

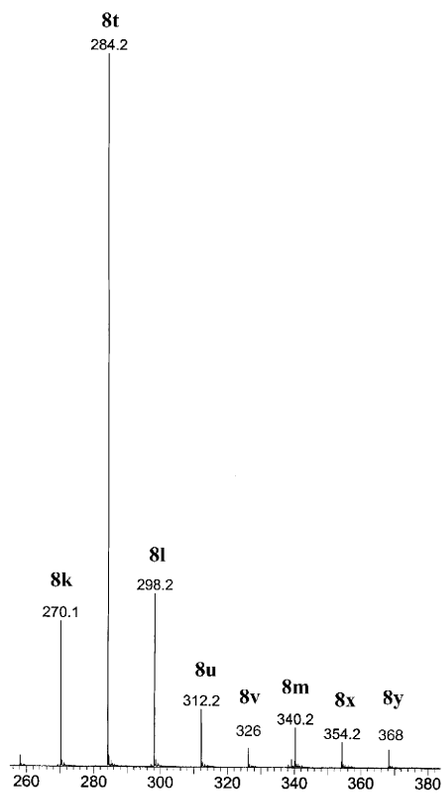


Fig. 4 Electrospray mass-spectrum of the products obtained from reaction of **2d** with an 8 component Grignard reagent. The spectrum shows the presence of **8k**–**8m** and **8t**–**8y**.

intensity of the peaks appears to suggest that some of the compounds **8k**–**8m** and **8t**–**8y** are present in larger amounts the peak intensity cannot be taken as significant. HPLC of the product mixture suggested that the products were present in roughly equal amounts (Fig. 5).

In summary we have shown that the azido group in α-azidobenzyl ethers can be substituted with Grignard reagents

when toluene is the solvent. The reaction is efficient and can be applied to aromatic, allylic and aliphatic Grignard reagents.

Experimental

α-Azidobenzyl (−)-menthyl ether (2c)

A solution of ICl (1.01 g, 6 mmol) in CH_3CN (50 mL) was cooled down to −10 °C to which NaN_3 (1.07 g, 14 mmol) was added with continuous stirring. After 15 minutes, the cooling bath was removed and benzyl (−)-menthyl ether (492 mg, 2 mmol) was added. The mixture was heated to 80 °C for 1 h or until disappearance of the starting material was observed (monitored by TLC). Then the mixture was cooled to room temperature, CH_2Cl_2 (200 mL) was added, and the mixture was washed with 5% $Na_2S_2O_3$ solution (150 mL). The dried (Na_2SO_4) organic layer was evaporated and the residue was purified by flash chromatography on silica (pentane–ethyl acetate 20 : 1) to give the pure azide **2c** (470 mg) in 82% yield. ^{1}H NMR (200 MHz; $CDCl_3$): δ 0.79 (d, 3H, *J* 6.3 Hz), 0.98 (d, 6H, *J* 6.9 Hz), 1.0 (m, 2H), 1.2 (m, 1H), 1.4 (m, 2H), 1.65 (m, 2H), 2.1 (m, 1H), 2.2 (m, 1H), 3.65 (dt, 1H), 5.45 (s, 1H), 7.4 (m, 5H); MS(ES): *m*/*z*: 310.1877 (calcd. for $C_{17}H_{25}N_3O$ + Na: 310.1895).

1-Acetyl-4-benzyloxypiperidine (1d)

To a suspension of NaH (240 mg,10 mmol) in dry DMF (10 mL) was slowly added (over 10 minutes) a solution of the 1-acetyl-4-oxypiperidine[5] (1.14 g, 8 mmol) in DMF (5 mL) at r.t. Stirring was continued for 30 minutes at the same temperature. Then benzyl bromide (1.36 g, 8 mmol) was slowly added, and the reaction mixture was stirred for 16 h. After completion of the reaction, DMF was evaporated *in vacuo*, and 10 mL of water was added. Then the product was extracted with CH_2Cl_2 (2 × 75 mL). The dried (Na_2SO_4) organic layer was concentrated and purified by flash chromatography on silica (ethyl acetate) to give pure **1d** (1.2 g, 60%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.42–1.62 (m, 2H), 1.63–1.91 (m, 2H), 2.0 (s, 3H), 3.1–3.28 (m, 2H), 3.45–3.65 (m, 2H), 3.79–3.88 (m, 1H), 4.45 (s, 2H), 7.2–7.4 (m, 5H, Ar); MS(ES): *m*/*z*: 256.1 ([M + Na]$^+$).

1-*N*-Acetyl-4-(α-azidobenzyloxy)piperidine (2d)

A solution of ICl (1.01 g, 6 mmol) in CH_3CN (50 mL) was cooled to −10 °C to which NaN_3 (1.07 g, 14 mmol) was added with continuous stirring. After 15 minutes, the cooling bath was removed and the substrate (350 mg, 1.5 mmol) was added. The mixture was heated to 80 °C for 40 minutes or until disappearance of the starting material was observed (TLC). Then the mixture was cooled to room temperature, CH_2Cl_2 (200 mL) was added, and the mixture was washed with 5% $Na_2S_2O_3$ solution (150 mL). The dried (Na_2SO_4) and evaporated organic layer was purified by flash chromatography on silica (ethyl acetate) to give pure azide **2d** (226 mg) in 55% yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.45–1.65 (m, 2H), 1.66–1.88 (m, 2H), 2.08, (s, 3H), 3.18–3.45 (m, 2H), 3.46–3.84 (m, 2H), 3.89–4.09 (m, 1H), 5.41 (s, 1H), 7.30–7.42 (m, 5H); MS(ES): *m*/*z*: 297.1331, calcd. for $C_{14}H_{18}N_4O_2$ + Na: 297.1327.

Substitution of azide by Grignard reagents

The reactions were carried out by dissolving 0.5 mmol of the azide **2** in 5 mL of dry toluene. A freshly prepared ether solution (0.4 mL) of the desired Grignard reagents (2 equivalents) was slowly added with continuous stirring at room temperature. After stirring for 10–20 minutes (monitored by TLC) the reactions were quenched by adding 1 mL saturated solution of NH_4Cl and 1 mL of water. Then the product was extracted with diethyl ether (2 × 10 mL), dried over Na_2SO_4 and evaporated *in vacuo* to obtain **8** in 82–94% yields. The products **8a**,[8] **8b**,[9] **8c**,[10] **8d**,[11] **8e**,[12] **8f**,[9] **8h**[13] and **8i**[14] were known compounds, and characterised by comparison of NMR spectra. Compounds **8g**, **8k**, **8l** and **8m** had the following data.

1-Ethoxy-1-phenylbutane (8g). ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.9 (t, 3H), 1.1 (t, 3H), 1.2–1.7 (m, 4H), 3.25 (m, 2H), 4.1 (dd, 1H), 7.1–7.3 (m, 5H).

1-*N*-Acetyl-4-(α-methylbenzyloxy)piperidine (8k). ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.20–1.27 (d, 3H, *J* 6.7 Hz), 1.20–1.85 (m, 4H), 2.0 (s, 3H), 3.0–3.2 (m, 2H), 3.25–3.64 (m, 2H), 3.8–4.0 (m, 1H), 4.4–4.6 (q, 1H), 7.1–7.3 (m, Ar); MS (ES, positive mode): 270.1469, calcd. for $C_{15}H_{21}NO_2$ + Na: 270.1469.

1-*N*-Acetyl-4-(α-propylbenzyloxy)piperidine (8l). MS (ES, positive mode): 298.1775, calcd. for $C_{17}H_{25}NO_2$ + Na: 298.1782.

1-*N*-Acetyl-4-(α-hexylbenzyloxy)piperidine (8m). ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.6–0.8 (t, 3H, *J* 6.6 Hz), 1.0–1.3 (m, 8H), 1.4–1.85 (m, 6H), 2.0 (s, 3H), 3.0–3.2 (m, 2H), 3.4–3.6 (m, 2H), 3.7–3.9 (m, 1H), 4.2–4.4 (q, 1H), 7.1–7.3 (m, aromatic); MS (ES, positive mode): *m*/*z*: 340.2257, calcd. for $C_{20}H_{31}NO_2$ + Na: 340.2252.

Reaction of α-azido compounds with multicomponent Grignard reagents

Preparation of a multicomponent Grignard reagent. Mg turnings (600 mg) were suspended in diethyl ether (12 mL) in a three necked round-bottomed flask fitted with a reflux condenser in the middle. All four halides *i.e.* PhBr (1.5 g, 1 mL); CH_3I (1.3 g, 0.5 mL); $CH_3CH_2CH_2Br$ (1.3 g, 1 mL) and allyl bromide (1.2 g, 0.9 mL) were mixed together and added slowly by continuous stirring. When the reflux started the flask was cooled in an ice–water bath, and the mixture was stirred for another 1.5 h. Then the solution was directly taken out by syringe and used.

4-Member libraries. 163 mg (1 mmol) of the α-azidobenzyl methyl ether (**2a**), or 177 mg (1 mmol) of the α-azidobenzyl ethyl ether (**2b**), was dissolved in 10 mL of dry toluene and 1 mL of the mixture of Grignard reagents was added slowly (*ca* 2 h) with constant stirring. After completion of the addition of reagents the reaction mixture was worked up in the way described above. The composition of the library was confirmed by comparing the ^{1}H NMR spectrum with the spectra of the individual compounds.

8-Member libraries. An 8 component Grignard reagent was prepared as previously described[7] by adding a mole equivalent mixture of alkyl halides (CH_3I, CH_2CH_2Br, $CH_3(CH_2)_2Br$, $CH_3(CH_2)_3Br$, $CH_3(CH_2)_4Br$, $CH_3(CH_2)_5Br$, $CH_3(CH_2)_6Br$, $CH_3(CH_2)_7Br$, 30 mmol total) to the suspension of Mg metal (2 equivalents, 60 mmol) in diethyl ether (20 mL).

1 mL (1.5 mmol) of this freshly prepared Grignard reagent was slowly added through a syringe to the solution of α-azidobenzyl (−)-menthyl ether (**2c**, 287 mg, 1 mmol), or 1-*N*-acetyl-4-(α-azidobenzyloxy)piperidine (**2d**, 274 mg, 1 mmol), in dry toluene (10 mL). The reaction mixture was stirred for 30 minutes at room temperature. Then aqueous NH_4Cl (1 mL) was added and the product was extracted by diethyl ether. The dried (Na_2SO_4), and concentrated organic phase contained the library of 8 compounds.

Library from **2c**: MS (ES, positive mode): *m*/*z*: 283.2036 (calcd. for **8i** + Na 283.2037); 297.2183 (calcd. for **8n** + Na: 297.2194); 311.2370 (calcd. for **8j** + Na: 311.2350); 325.2564 (calcd. for **8o** + Na: 325.2507); 339.2656 (calcd. for **8p** + Na: 339.2663); 353.2847 (calcd. for **8q**: 353.2820); 367.2990 (calcd. for **8r**: 367.2976); 381.3111 (calcd. for **8s**: 381.3133).

Library from **2d**: MS (ES, positive mode), *m*/*z*: 270.1464 (calcd. for **8k** + Na: 270.1469), 284.1716 (calcd. for **8t** + Na:

284.1626), 298.1844 (calcd. for **8l** + Na: 298.1782), 312.2030 (calcd. for **8u** + Na: 312.1939), 326.2077 (calcd. for **8v** + Na: 326.2095), 340.2257 (calcd. for **8m** + Na: 340.2252), 354.2507 (calcd. for **8x** + Na: 354.2408), 368.2577 (calcd. for **8y** + Na: 368.2565).

Acknowledgements

We thank the Danish National Science Research Council (SNF) and the Lundbeck foundation for financial support.

References

1 C. Viuf and M. Bols, *Angew. Chem., Int. Ed.*, 2001, 623–625.
2 P. Magnus, J. Lacour and W. Weber, *Synthesis*, 1998, 547–551.
3 H. Ishikawa, S. Ikeda and T. Mukaiyama, *Chem. Lett.*, 1975, 1051–1054.
4 H. Ishikawa and T. Mukaiyama, *Chem. Lett.*, 1975, 305–306.
5 R. S. Atkinson, E. Barker and M. J. Sutcliffe, *Chem. Commun.*, 1996, **9**, 1051–1052.
6 T. Holm, *Acta Chem. Scand. Ser. B*, 1983, **37**, 567–584.
7 X. Liang and M. Bols, *J. Chem. Soc., Perkin Trans. 1*, 2002, DOI: 10.1039/b109952n.
8 H. C. Brown and M.-H. Rei, *J. Am. Chem. Soc.*, 1969, **91**, 5646–5647.
9 K. G. Rutherford, O. A. Mamer, J. M. Prokipcak and R. A. Jobin, *Can. J. Chem.*, 1966, **44**, 2337–9.
10 Y. L. Chow and B. Marciniak, *J. Org. Chem.*, 1983, **48**, 2910–2914.
11 P. H. Dussault, I. Q. Lee, H.-J. Lee, R. J. Lee, Q. J. Niu, J. A. Schultz and U. R. Zope, *J. Org. Chem.*, 2000, **65**, 8407–8414.
12 A. McKillop and M. E. Ford, *Tetrahedron*, 1974, **30**, 2467–2475.
13 R. Imwinkelried and D. Seebach, *Angew. Chem.*, 1985, **97**, 781–2.
14 G. Dauphin, A. Kergomard and A. Scarset, *Bull. Soc. Chim. Fr.*, 1973, **3**, 1104–1108.