Experiments related to the synthesis and analysis of a hydrazine library †

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Substitutions under competition conditions are performed with a triprotected hydrazine reagent **A** as nucleophile and various halides as electrophiles and the product distribution determined by HPLC. Subsequently, after partial deprotection, stepwise substitution on the other nitrogen is studied similarly in order to define the scope of such reagents for the synthesis of libraries comprising multisubstituted hydrazines. In the course of this work a large number of partially protected hydrazine derivatives are prepared and characterized spectroscopically and chromatographically. The results indicate that *n*-alkyl and benzyl halides are of comparable reactivity under the conditions used, whereas others deviate too much in this respect as a result of which product mixtures severely distorted from equimolar ones are formed. In the course of this work, hydrazine libraries containing up to nine components are characterized quantitatively.

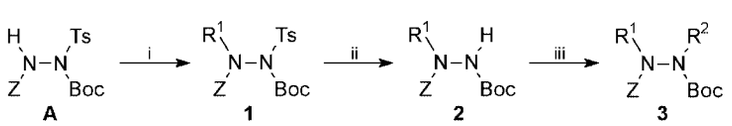
Introduction

Hydrazine derivatives are of considerable technical and commercial importance in agriculture and as pharmaceuticals.[1] Although many procedures are currently available for the preparation of such compounds,[2] until recently a simple procedure for *stepwise* synthesis of multisubstituted hydrazines was missing. For this purpose triprotected reagents can be applied.[3] They undergo substitution under relatively mild conditions and, due to the presence of the protecting groups, normally the reactions can be driven to completeness without formation of side products. In the case of additional clean and complete cleavage of the auxiliary groups, further important requirements for the successful application of these reagents are fulfilled. In the present paper an attempt has been made to exploit these favorable properties for the preparation of a small library of tetrasubstituted derivatives based on the inexpensive, most easily accessible reagent **A** (Scheme 1) of this type[4] with major emphasis on careful identification and quantitation of the individual library components and detection of side products. The synthesis of such a library has to our knowledge not previously been reported.[5]

Reagent **A** features the three well known amino-protecting groups tosyl (Ts), *tert*-butoxycarbonyl (Boc) and benzyloxycarbonyl (Z),[6] of which the first two are present on the same nitrogen atom, together forming a base-stable, strongly electron-withdrawing sulfonylcarbamate moiety. As a consequence alkylation of **A** becomes highly facilitated. From the product **1** the tosyl group can be cleaved by reduction with magnesium powder in anhydrous methanol to give **2** without detectable side reactions.[7,8] This product can again be alkylated, although not quite under the same mild conditions as before, when no heating is required. The twice alkylated product **3** contains only Boc and Z groups, for the handling of which overwhelming experience is available in the field of peptide synthesis.[9] In principle they can be selectively cleaved in arbitrary order.

Compounds such as **4** undergo acylation to produce **5** (Scheme 2).[10] Removal of the last protecting group furnishes **6** which can be acylated a second time to give the fully substituted hydrazine derivatives **7**.[11] Briefly, the outlined chemistry forms the basis of the synthetic work described below, aiming at exploring its scope for the preparation of a small, focused hydrazine library in solution.[12] In parallel work a fairly large number of reference compounds were prepared (for details, see Supplementary Information) in order to allow all library components to be identified by HPLC and subsequently quantitatively determined.

† Synthetic procedures for additional novel reference substances with spectral and chromatographic data, including 2 tables and typical ^{1}H and ^{13}C spectra, are available as supplementary data. For direct electronic access see http://www.rsc.org/suppdata/p1/b0/b000139m/. See Instructions for Authors, available *via* the RSC web page (http://www.rsc.org/authors).



1-3: R^1=Me **(a)**, Pr^i **(b)**, Bn **(c)**, $EtOCOCH_2$ **(d)**, Et **(e)**, Pr **(f)**;
3: R^2=$EtOCOCH_2$ **(xa)**, 4-$ClC_6H_4CH_2$ **(xb)**, 4-$BrC_6H_4CH_2$ **(xc)**
(**x** = **a–c** as defined by R^1)

Scheme 1 Initial steps in the synthesis of a hydrazine library. *Reagents and conditions*: i, R^1X, PTC, RT or R^1OH, DEAD, TPP; ii, Mg/MeOH; iii, R^2X, PTC, 50 °C.

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Table 1 Competition experiments with triprotected hydrazine reagent **A**[a]

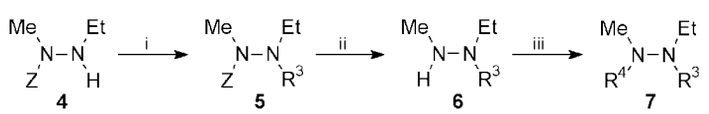
Entry	Relative incorporation (%)[b] MeI	(%)[c]	Pr^iI	BnX	$EtOCOCH_2X$	EtI	PrI	**A** recovered (%)	Comments
1	100	31.2		206^{Br}		14		<0.1	Fig. 1
2	100	8.4		203^{Br}	888^{Br}			<0.1	
3	100	70.1	0.6			24		12.4	
4	100	60.7				29	16	12.3	
5	100	35.1		31^{Cl}	154^{Cl}			<0.1	
6	100	25.5		141^{Br}	152^{Cl}			<0.1	
7	100	75.5	4			28		1.2	comparison[d]

[a] Experiments conducted at room temperature with one mol equiv. each of three representative halides (including MeI) at a time. [b] Based on separation and determination by HPLC. [c] Relative amount of **1a** present in the chromatogram. [d] Experiments performed with alcohols instead of halides under Mitsunobu conditions.

Table 2 Reaction of **2** with various halides[a]

Entry	Hydrazine	Relative incorporation (%)[b] $EtOCOCH_2Br$	$4\text{-}ClC_6H_4CH_2Cl$	$4\text{-}BrC_6H_4CH_2Br$	Comments
1	**2a**	343	72		2 × 2 system
	2c	304	100		
2	**2a**	242/399	42/69		alternative
	2b	173/285	100/165		2 × 2 system
3	**2a**	409	71		3 × 2 system
	2b	275	165		
	2c	351	100		
4	**2a**	490	106	99	3 × 3 system
	2b	229	155	166	Fig. 2
	2c	472	100	121	
5	**2a**	112	86		for comparison
	2c	80	100		with entry 1[c]

[a] Experiments conducted at 50 ± 3 °C. Equimolar mixture with two or three halides (except in entry 5); 3 mol equiv. in total based on total amount of **2**. [b] Based on separation and determination by HPLC. [c] Relative amounts of $4\text{-}ClC_6H_4CH_2Cl$: $EtOCOCH_2Br$ = 3 : 1; 3 mol equiv. in total based on total amount of **2**.



5-7: R^3=4-FC_6H_4CO **(a)**, 1-$C_{10}H_7CO$ **(b)**; **7:** R^4=BzNHCO **(xa)**, TsNHCO **(xb)**
(**x** = **a** or **b** as defined by R^3)

Scheme 2 Further steps in the synthesis of a hydrazine minilibrary. *Reagents*: i, R^3X; ii, H_2/Pd; iii, R^4NCO.

Results and discussion

Design of the experiments

Novel reference compound **1b** was preferably prepared by the Mitsunobu reaction between **A** and propan-2-ol. This procedure gave a higher yield of purer product than the corresponding alkylation with isopropyl iodide under phase-transfer catalysis (PTC) conditions which had previously been used to make **1a** and **1c**.[4]

In the combinatorial experiments, the first alkylation step was accomplished by reaction of **A** with 3 mole equivalents (in total) of the appropriate mixture of halides in dry acetonitrile under PTC conditions, essentially according to a previously described protocol.[4] The crude reaction mixture was centrifuged and the clear supernatant was then suitable for chromatographic analysis for individual components **1a**–**c** (Table 1). Removal of the tosyl group in monoalkylated compounds **1** was smoothly achieved with magnesium in dry methanol by analogy with the published procedure for authentic **2a** and **2c**.[4,7]

The syntheses of reference compounds **3** were generally performed in high yields (>90%) with few exceptions (Table β, Supplementary information). A detailed procedure for one representative example (**3ba**) is presented in the Experimental section. These alkylations under PTC conditions appeared to be significantly more sluggish and required elevated temperature (50 °C) overnight to go to completion. In combinatorial experiments appropriate mixtures of halides, 3 mole equivalents in total, were employed and after complete reaction the crude mixtures were subjected to chromatographic separation (Table 2). A key experiment was the preparation of the 9-component library of compounds **3**.

Acylation of **4** with 1-naphthoyl chloride in dry pyridine according to the procedure for **5a** afforded **5b** in excellent yield.[11] Subsequent removal of the Z group provided **6b** by analogy with the preparation of **6a**.[11] The deprotected hydrazine derivatives **6a** and **6b** were then allowed to react with benzoyl or tosyl isocyanate in dry dichloromethane to furnish the three novel urea derivatives **7aa**, **7ba** and **7bb** in satisfactory yields. For details on these compounds (except **7ba**), see Supplementary information.

In the combinatorial approach, the reaction of **4** with a mixture of 4-fluorobenzoyl and 1-naphthoyl chloride (1.5 mole equivalents each) under the same conditions gave a crude mixture which was analyzed as such by HPLC (Table 3). Competitive reactions of **6a** and **6b** as well as a mixture thereof with a mixture of benzoyl and tosyl isocyanate (in total 3 mole equivalents) under synthetic conditions afforded a crude mixture which could be analyzed by chromatography (Table 3).

Table 3 Acylation experiments with dialkylated hydrazines **4** and **6**[a]

Entry	Relative incorporation (%)[b]				
	Hydrazine	4-FC_6H_4CO	1-$C_{10}H_7CO$	BzNHCO	TsNHCO
1	**4**	130	100		
2	**6a**			83	128
	6b			100	108

[a] Experiments conducted at room temperature with 2 × 1.5 mol equiv. of acylating reagent at a time. [b] Based on separation and determination by HPLC.

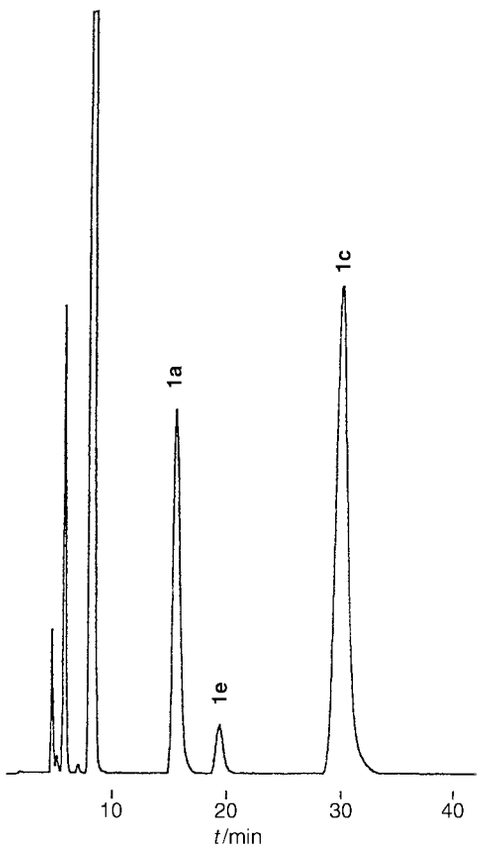


Fig. 1 Separation of the reaction mixture described in Table 1, entry 1 (3 components). Column: Waters Spherisorb C8, 3 μm (100 × 4.6 mm). Mobile phase: MeCN–0.05 M acetate, pH 4.35 (60:40). Detector set at 277 nm. Elution time in min.

Results

Some results from alkylation experiments involving reagent **A** and three halides at a time under competition conditions are given in Table 1. The data are based on chromatographic separation and quantitative determination of all species formed in these reactions and comparison with authentic reference substances. One representative chromatogram is shown in Fig. 1. The halides, most of them of alkyl and benzyl types, were chosen as examples of those used in the preparation of simple derivatives of amines and similar compounds. At the same time they should to some extent reflect the variation in reactivity within this functional class.

Similar experiments related to alkylation on the other nitrogen after removal of the tosyl group were also conducted and the corresponding data are presented in Table 2. As shown in Fig. 2 which refers to entry 4 in this Table, satisfactory separation of all the species formed could still be obtained for this 9-component mixture. On the other hand, it should be pointed out in this context that several additional substitution experiments have been carried out but difficulties in the chromatographic separation of all the species formed in these cases discouraged us from pursuing these substitutions further.

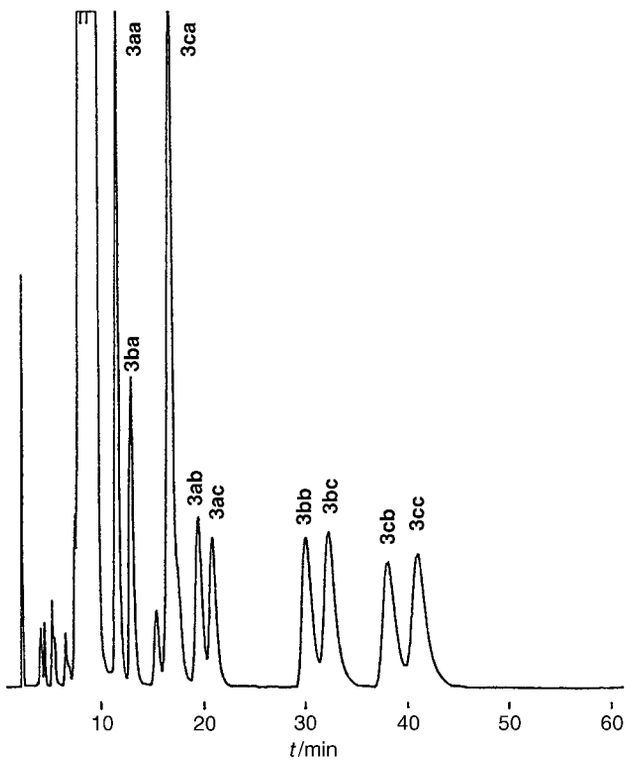


Fig. 2 Separation of the reaction mixture described in Table 2, entry 4 (9 components). Column: Waters Spherisorb C8, 3 μm (100 × 4.6 mm). Mobile phase: MeCN–0.05 M acetate, pH 4.35 (60:40). Detector set at 258 nm. Elution time in min.

A few experiments related to acylation of 1,2-dialkylated hydrazines were also performed (Table 3). Such acylations of hydrazines were originally carried out by reaction with anhydrides,[10,13,14] acid chlorides[10] and isocyanates[11] to give hydrazides and ureas. Examples illustrating formation of both of these products are given but since acylations presented few problems in comparison with alkylations, these experiments were intentionally kept at a minimum. The rather hydrophilic nature of the ureas required a slight modification of the chromatographic conditions.

In order to identify the products formed in the competition experiments as well as to determine their relative amounts, a large number of reference compounds were prepared. This work is described in detail in the Supplementary information. The same refers to the basic chromatographic work, *i.e.* as related to the retention times and relative absorptions of the reference compounds.

Discussion

Table 1 summarizes results from substitution experiments with reagent **A** as nucleophile under competition conditions. In all cases except entry 7, which deals with data obtained with the corresponding alcohols according to Mitsunobu, MeI is present as a reference. As seen from entries 1, 3 and 4, aliphatic homologs are significantly less reactive than MeI. As an example, the

data indicate that the Me/Et/Pr derivatives are formed in the approximate proportions 6:2:1. The modest reactivity of alkyl halides is also reflected in the fact that some **A** is still present in the reaction mixture after 24 h. On the other hand (entries 1 and 2), BnBr and, particularly, bromoacetate are superior to MeI under the conditions used, as a result of which bromoacetate gives nearly 10 times more product than does MeI. As expected, the corresponding chloro derivatives behaves similarly, although they react more slowly (entries 5 and 6). As a result no significant amount of **A** was detectable after 24 h in these cases. Of all alkylating reagents investigated in this context isopropyl iodide exhibits the lowest reactivity and therefore the ratio of Me/Pr^i derivative formed is very high (>100 in entry 3). The low reactivity of isopropyl iodide was noticed also in the preparation of the authentic substance **1b** as well as in our earlier work and therefore a special procedure was devised for the introduction of secondary R^1 groups.[15] In the last entry the corresponding alcohols were allowed to compete similarly in the Mitsunobu reaction.[16] Previous applications of this alkylation method have demonstrated that secondary alcohols react with relative ease in a wide range of reactions with miscellaneous nucleophiles. More surprisingly, in selected cases the secondary hydroxy function appears to react in clear preference to a primary one.[17] Indeed, significantly more Pr^i derivative seemed to form in the Mitsunobu than in the Pr^iI experiment.

As judged from the amounts of the products in the first alkylation step, an approximate order of reactivity of the reagents used could be estimated. Ethyl bromoacetate and benzyl bromide appear to be the most efficient electrophiles in this study, followed in decreasing order of reactivity by Me > Et > Pr ⩾ Pr^i (iodides used). These findings are also in full agreement with early seminal work on similar displacement reactions as summarized in a classical monograph.[18]

The high reactivity of $EtOCOCH_2Br$ compared with the other halides used in these substitution reactions is also reflected in the experiments of Table 2, as a result of which in entry 1 3–4 times more **3aa** and **3ca** than **3ab** and **3cb** was formed. As expected these ratios could be reduced considerably by increasing the relative amount of 4-$ClC_6H_4CH_2Cl$ (entry 5) in which case a nearly equimolar mixture could be obtained. Entries 2–4 record additional experiments, involving an additional nucleophile, **2b**, believed to be somewhat sterically hindered in comparison with the other two. The results with respect to the relative reactivity of $EtOCOCH_2Br$ are conclusive. On the other hand, partly as a result of the design of these experiments, relatively high values for the reactivity of 4-$ClC_6H_4CH_2Cl$ and in entry 4 also for 4-$BrC_6H_4CH_2Br$ with **2b** are shown in these experiments. Both steric and electronic factors may be operating but it seems that further data are required before their relative contributions can be evaluated.

The decision to include hydrophilic carbamoyl groups as substituents R^4 in **7** required R^3 to be rather hydrophobic in order to allow chromatographic separation of the ensuing product mixtures. With reference to the structural similarity between the two aromatic acyl chlorides used in the first acylation step (Table 3, entry 1), no major difference in their reactivities was either expected or detected. The results from the experiment with the two isocyanates seem to be interpretable in terms of a slightly higher reactivity of the tosyl derivative.

Conclusions

In experiments with a triprotected hydrazine derivative **A** as nucleophile and more than one halide simultaneously present, the well known variation in reactivity between different halides is reflected in a more-or-less distorted product distribution. As an example, in an experiment with methyl, ethyl and propyl iodide, the corresponding products were obtained in the proportions 6:2:1. Similar experiments have provided dialkylhydrazine libraries with up to nine components remarkably free from by-products. Based on these experiments it is concluded that the higher the requirements with respect to equimolarity of the desired product mixtures, the more important it is that the reagents used exhibit closely similar reactivities.

Experimental

General experimental details

See Supplementary Information.

1-Benzyloxycarbonyl-2-(*tert*-butoxycarbonyl)-1-isopropyl-2-tosylhydrazine 1b

Recrystallized **A** (2.10 g, 5.00 mmol) and dry propan-2-ol (360 mg, 6.00 mmol) were dissolved in dry THF (15 cm^3) and cooled to −15 °C under argon. Recrystallized, dried Ph_3P (1.57 g, 6.00 mmol) was then added in one portion with thorough mixing and the resulting clear solution was treated dropwise with a solution of diethyl azodicarboxylate (DEAD) (1.13 g, 6.50 mmol) in dry THF (4 cm^3), with rapid stirring during 30 min until a pale yellow color persisted. The reaction mixture was then allowed to assume ambient temperature over a period of 2 h, whereafter the stirring was continued overnight at room temperature. The solvent was removed at reduced pressure and the semisolid residue was applied to a silica column with Et_2O–light petroleum (bp 40–65 °C) 1:2 as eluent. Slow elution furnished a chromatographically (B) pure, essentially colorless oil (2.30 g, 99%). HPLC indicated 99% purity; ^1H NMR (400 MHz; $CDCl_3$; major/minor conformer) δ 1.28/1.29 (2 s, 9 H), 1.43/1.40 (2 d, J 6.6 Hz, 6 H), 2.33/2.43 (2 s, 3 H), 4.34 (perturbed m, $J \approx 6$ Hz, 1 H), 4.91, 5.21/5.24, 5.28 (2 ABq, J 12.3 Hz, 2 H), 7.03–7.09 and 7.21–7.39 (complex signal, 7 H), 7.81/8.06 (2 d, J 8.4 Hz, 2 H); ^{13}C NMR δ_C 19.13/19.88, 20.89/21.38, 21.62/21.70, 27.72, 54.09/54.00, 67.94/68.42, 85.15, 127.89, 128.07, 128.16, 128.25, 128.31, 128.57, 128.74, 128.88, 129.83, 130.07, 135.26, 135.34, 135.61, 135.84, 144.69, 150.19/150.24, 154.23/155.22.

1-Benzyloxycarbonyl-2-(*tert*-butoxycarbonyl)-1-isopropylhydrazine 2b

Obtained by Mg-mediated detosylation of **1b** by analogy with the published procedure.[7] The yield of crude, chromatographically pure (A) product suitable for further work was 96% in a 4.4 mmol run. Column chromatography on silica in Et_2O–light petroleum (bp 40–65 °C) 1:2 followed by crystallization from light petroleum gave fluffy crystals, mp 72–72.5 °C; ^1H NMR (400 MHz; $CDCl_3$; major/minor conformer) δ 1.14 (d, J 6.2 Hz, 6 H), 1.42/≈1.36 (2 br, 9 H), 4.46 (br, 1 H), 5.15 (br s, 2 H), 6.17/5.99 (2 br, 1 H), 7.30–7.35 (complex signal, 5 H); ^{13}C NMR δ_C 19.68, 28.07/27.96, 49.33/49.93, 67.79/67.53, 81.13/81.61, 127.91, 128.07, 128.43, 136.14, 155.53/155.92 (Found: C, 62.1; H, 7.8; N, 9.1. Calc. for $C_{16}H_{24}N_2O_4$: C, 62.32; H, 7.85; N, 9.08%).

Typical procedure for mild PTC alkylation of 1-alkyl-2-Boc-1-Z-hydrazines

Preparation of 1-benzyloxycarbonyl-2-(*tert*-butoxycarbonyl)-2-ethoxycarbonylmethyl-1-isopropylhydrazine 3ba. To a stirred slurry of crystalline **2b** (308 mg, 1.00 mmol), finely ground, dry K_2CO_3 (0.55 g, 4.0 mmol), and tetrabutylammonium hydrogen sulfate (TBAHS) (70 mg, 0.20 mmol) in dry MeCN (4 cm^3) under argon was added neat ethyl bromoacetate (0.140 cm^3, 1.25 mmol) over a period of ≈10 min before the flask was transferred to an oil-bath at 50 ± 2 °C with stirring. The reaction was monitored by TLC (B) and after 24 h essentially all **2b** had been consumed. Most of the solvent was stripped off at reduced pressure and the semisolid residue was partitioned between Et_2O (80 cm^3) and 1 M aq. $KHSO_4$ (40 cm^3). The organic extract was washed in turn with 1 M aq. $KHSO_4$, 1 M aq. $NaHCO_3$ and brine (3 × 20 cm^3 each) and dried ($MgSO_4$).

Removal of the solvent furnished a colorless oil (375 mg, 95%). Traces of impurities were conveniently removed by chromatography on silica using system B as eluent. The resulting essentially colorless oil gave one spot on TLC (B). Spectral data are given in Table β (Supplementary Information) which includes such data also for the other eight analogs.

1-Benzoylcarbamoyl-2-ethyl-1-methyl-2-(1-naphthoyl)hydrazine 7ba

Crude **5b** was hydrogenolyzed in methanol as described for **5a**[11] and crude, essentially pure (A) **6b** was obtained in 89% yield in a 2 mmol run as a colorless oil which slowly solidified on storage. With BzNCO instead of TsNCO otherwise as described,[11] **7ba** was obtained as a white, essentially pure (C, D) powder in 93% yield in a 0.5 mmol run; mp 114–115 °C [from Et_2O–light petroleum (1:1); 20 cm^3 g^{-1} at −20 °C]; ^{1}H NMR (400 MHz; $CDCl_3$; major/minor conformer) δ 1.20/1.35 (2 br s, 3 H), 2.95, 3.45 and 3.95 (3 br, together 5 H), 7.39–7.57 and 7.85–7.94 (complex, together 12 H), 8.86 (br s, ≈1 H); ^{13}C NMR (100.4 MHz; $CDCl_3$; major/minor conformer) δ_C 13.20, ≈37.2/≈35.9, ≈45.5/≈43.6, 123.52, 124.37, 124.79, 126.65, 127.35, 127.82, 128.43, 128.57, 128.65, 129.47, 130.14, 132.27, 132.70, 133.14, 133.45, ≈153.0, 166.16, ≈170.2 (Found: C, 70.5; H, 5.6; N, 11.2. Calc. for $C_{22}H_{21}N_3O_3$: C, 70.38; H, 5.64; N, 11.19%).

Preparation and analysis of a 9-component library 3 by combinatorial alkylation (representative example; entry 4, Table 2)

Substrates **2a**–**c** (67 μmol each) were dissolved in dry MeCN (1.5 cm^3) under argon and a mixture of $BrCH_2CO_2Et$, 4-$ClC_6H_4CH_2Cl$ and 4-$BrC_6H_4CH_2Br$ (200 μmol each) in MeCN (0.5 cm^3) was then added with thorough mixing. The clear solution was then treated with finely ground, dried K_2CO_3 (800 μmol), followed by TBAHS (40 μmol), whereafter the thick slurry was stirred vigorously at 50 ± 3 °C for 22 h with exclusion of moisture. The solid material was allowed to settle for about 10 min before the sample was centrifuged, whereupon 25 mm^3 of the clear supernatant was diluted to 2.0 cm^3 with MeCN. An aliquot (10 mm^3) of this solution was applied to a Spherisorb C8 column (3 μm, 100 × 4.6 mm) with 0.05 M acetate buffer, pH 4.35/MeCN (40:60) as the mobile phase (for further details see Supplementary Information). The product peaks were detected at 258 nm and the integrated peak areas were corrected using data compiled in Table α (Supplementary Information). The product ratios in some selected competitive alkylation experiments are given in Tables 1 and 2.

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