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Reactions of Primary Amines and Alcohols with 4-Toluoyl Azide

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Summary. Primary amines **2** [R: *n*-butyl (**2a**), cyclohexyl (**2b**), 3-pentyl (**2c**)] react with 4-toluoyl azide **1** in non-nucleophilic solvents in a clear second order reaction, which is strongly dependent on the size of the amine **2** and the solvent polarity (k_2 [Acetonitril; 25 °C]: 15.51 (**2a**), 0.83 (**2b**) and 0.19 (**2c**) l/mol · min; $\Delta H^{\#} = 22.1$ kJ/mol, $\Delta S^{\#} = -170.5$ J/mol · K [**2b** in Acetonitril]). Drastic changes occur in the presence of nucleophilic solvents. With nucleophilic amines **2** added to these in the solutions a concurrent reaction with alcohols **4** [R: methyl (**4a**), ethyl (**4b**), *n*-butyl (**4c**)] yielding 4-toluoyl ester **5** is observed. This is especially dominating with the "smallest" alcohol methanol (**4a**) and/or effectively promoted by "bulky" amines (**2b**, **2c**; up to 99% **5a**). Compared with the pure alcoholysis a huge acceleration of the ester formation, proportional to the cencentration of the nucleophilic amine **2**, is observed. The reaction mechanism is discussed with special emphasis on steric effects in the competition of nucleophiles for the aroyl azide **1**.

Keywords. Aroyl azide; 4-Toluoyl azide; Alcoholysis; Aminolysis; "Nucleophilic catalysis"; Kinetics; Steric effects.

Reaktionen primärer Amine und Alkohole mit 4-Toluoylazid

Zusammenfassung. Primäre Amine reagieren in nicht-nucleophilen Lösungsmitteln mit 4-Toluoylazid in einer einheitlichen Reaktion 2. Ordnung, die durch die Größe des Amins und die Lösungsmittel-Polarität beeinflußt wird. Das ändert sich in Gegenwart von Alkoholen, wo auch die Bildung von 4-Toluylsäureestern beobachtet wird. Diese Konkurrenzreaktion wird durch den „kleinsten" Alkohol (Methanol) und/oder die relativ größeren Amine (Cylohexylamin bzw. 3-Pentylamin) besonders stark begünstigt. Verglichen mit der einfachen Alkoholyse von 4-Toluoylazid wird eine enorme Beschleunigung der Esterbildung, proportional zur Konzentration des nucleophilen Amins, beobachtet. Der Reaktionsmechanismus wird mit besonderer Berücksichtigung sterischer Effekte bei der Konkurrenz von Nucleophilen um das Aroylazid diskutiert.

Introduction

Activation of amino acids by preparation of acyl azides is common in peptide synthesis [1]. In analogy, the carbonyl azide method for enzyme immobilisation makes use of polymeric acyl azides [2]. Mostly, azide derivatives of aliphatic

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carboxylic acids are applied. Aromatic carbonyl azides (aroyl azides) possess a much higher thermal stability and additionally give the chance of an effective photochemical induction of coupling reactions [3]. In the course of a project to prepare aroyl azides polymers – formally derived from 4-vinyl-benzoyl azide – for enzyme immobilisation we have been interested in the reactivity of aroyl azides towards N-nucleophiles under various conditions.

Besides the experience from applications mentioned above, in the – to our knowledge – only mechanistic work published, it had been found that the reaction of 2-naphthoyl azide with various amines, even in alcohols as solvent, in every case in a clear second order reaction yields 2-naphthoyl amides [4].

In this paper we present results with 4-toluoyl azids as model compound, especially the reaction in the presence of three selected amines in various solvents. The mechanism for the nucleophilic substitution of aroyl azides will be discussed with special emphasis on steric effects.

Experimental

4-Toluoyl azide **1** was synthesised, in analogy to [5], from 4-toluoyl chloride (Merck, Darmstadt, Germany) by reaction with sodium azide in acetone/water at 0 °C. The amines **2a–c**, alcohols **4a–c** and other solvents were products of Merck (Darmstadt, Germany) of "Uvasol^{R}" or "p.a." quality. The amides **3a–c** and esters **5a–c** were easily obtained by aminolysis resp. alcoholysis of 4-toluoyl chloride [6]. All products gave satisfactory C, H and N analyses, UV-, IR- and MS-spectra and were homogeneous according to HLPC analysis.

All product analyses were performed using a HPLC system (LC6A; Shimadzu, Kyoto, Japan) with a RP column (ET 250/8/4; 5 µm, C_{18}; Macherey-Nagel, Düren, Germany). The following chromatographic conditions were applied: methanol/water mixtures (90/10, 70/30 resp. 60/40; *v/v*), 1 ml/min, 35 °C. In every case the chromatographic resolution of two compounds for quantitative analysis was better than 1.25. All reactions and all HPLC runs (for calibration and product analysis) have been repeated at least three times. Accuracy and reproducibility were better than ± 3%. Checking the product composition with azide (**1**) conversion gave no changing yields within this limit.

The conversion of **1** ($c_0 = 2 \cdot 10^{-5} \cdots 1 \cdot 10^{-3}$ mol/l) under the various conditions was monitored UV-spectroscopically ($d = 1.00$ cm; spectrometer PU 8735, Philips Analytical, Cambridge, UK; stirring with CUV-O-STIR, model 333, Hellma GmbH, Müllheim, Germany). The temperature control for the kinetic measurements ($T = 25.0 \pm 0.1$ °C for the simple rate constant measurements; six temperatures in the range $15 \leqslant T \leqslant 35$ °C, max. ± 0.1 K, for the determination of activation parameters) was realised with a thermostatable cuvette holder and an external thermostat. At least 30 absorbance values (E_t^λ) at various wavelengths [$\lambda = 260 \cdots 280$ nm; $\lambda_{max}(\mathbf{1}) = 260.2$ nm, $\varepsilon_{max} = 21090$ l/mol cm (MeOH)] at different degrees of conversion (up to about 80%, constant time intervals depending on reaction rates 0.05 ··· 5 minutes) were registrated with the help of the data recording facilities of the spectrometer. The absorbance changes of the solutions during the course of the reactions are only determined by the azide **1** and the product **3** resp. **5** but not by the amines **2** or alcohols **4** and the product HN_3. A non-linear regression of the absorbance (E_t^λ) vs. time (t) curves based on the equation

$$E_t^\lambda = E_0^\lambda \cdot e^{-k_1' t} + + E_\infty^\lambda \cdot (1 - e^{-k_1' t})$$

yielded k_t' (together with E_0^λ and E_∞^λ; computer program: Statgraphics, Statistical Graphics Corp., Rockville, USA) In typical cases the regression coefficient was $r > 0.99$.

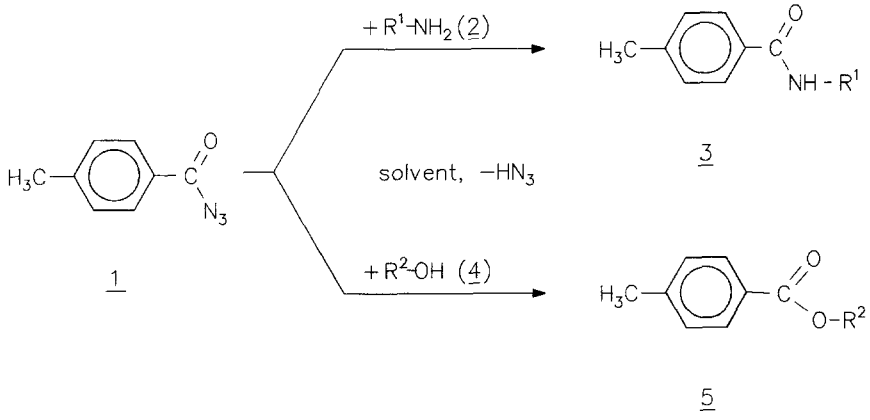
The linear regression of k_1' versus the concentrations of amine yielded k_2 ($r > 0.998$). The activation parameters were derived from an Arrhenius plot of ln k_2 versus $1/T$ ($r \geqslant 0.98$).

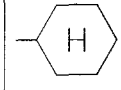
Results

At temperatures below 40 °C 4-toluoyl azide **1** is quite stable, the rate constant for the Curtius rearrangement is appr. $2.1 \cdot 10^{-5}\,min^{-1}$ ($\tau_1 = 550$ h, 25 °C, dioxane, derived from $E_A = 120.2$ kJ/mol). This enabled us to study the nucleophilic reactions of **1** without a disturbing side reaction.

Product Studies

The only reaction product of 4-toluoyl azide **1** with cyclohexyl amine **2b** in non-nucleophilic solvents (such as cyclohexane, dioxane, tetrahydrofuran and acetonitrile) at room temperature is 4-toluoyl cyclohexyl amide **3b** (see Scheme 1).



compound	R^1
2a, 3a	$-(CH_2)_3CH_3$
2b, 3b	
2c, 3c	$-CH(CH_2CH_3)_2$

compound	R^2
4a, 5a	$-CH_3$
4b, 5b	$-CH_2CH_3$
4c, 5c	$-(CH_2)_3CH_3$

Scheme 1

In alcohols the reaction is not uniform. In the extreme case, with methanol (**4a**), the major product is the methyl ester **5a**. The results of variations of the concentrations of azide **1** and of amine **2b** in methanol are shown in Fig. 1. Clearly, also at comparatively high amine concentrations (1 mol/l), it is not possible to achieve quantitative yields of amide **3b** (max. 60%).

The dependence of amide formation on the kind of alcoholic solvent is illustrated with the data in Table 1. It is clearly visible that the nature of the alcohol (namely the size as illustrated with the steric substituent parameters) more than its excess relative to the amine **2** influences the product yields. Especially, the result of the competition experiment between methanol **4a** and ethanol **4b** which yields a **5a** : **5b** ratio of 92 : 1 is remarkable.

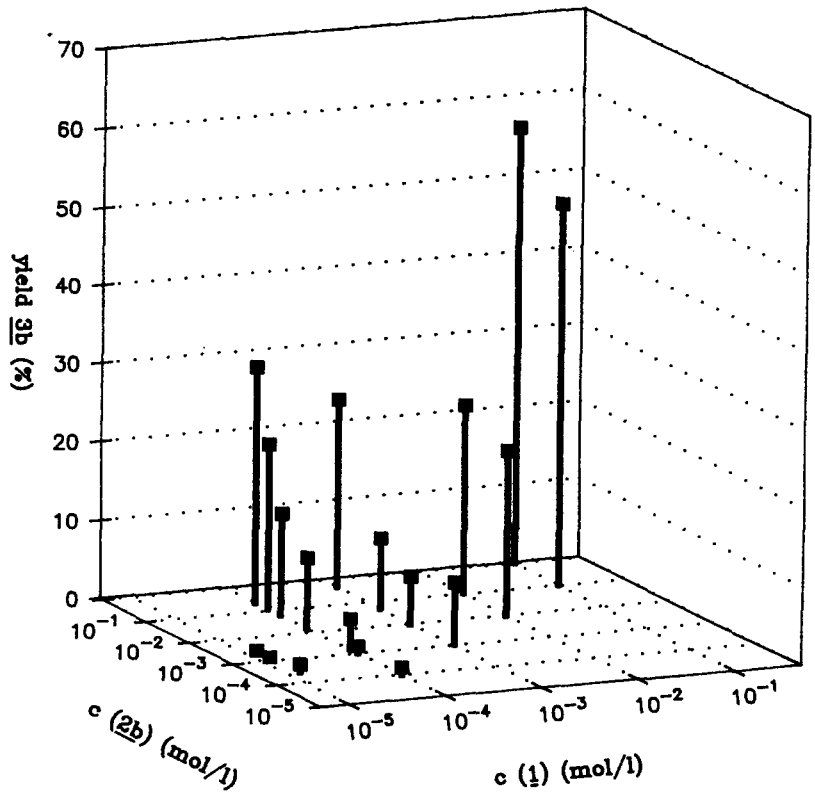


Fig. 1. Yield of 4-toluoyl cyclohexyl amide **3b** depending on the concentrations of 4-toluoyl azide **1** and cyclohexyl amine **2b** in methanol (**4a**) (the only second product is 4-toluoyl methyl ester **5a**)

The reaction with amines depends also on their steric requirements, as shown in Table 2. In every case an at least 10 fold excess of amine **2** relatively to **1** has been applied. It is possible to change the major reaction path from amide formation [93% **3a**; with the "small" **2a**, at high azide concentrations, with consequently comparatively low methanol : azide excess (264 : 1)] to ester production. In presence of **2b** and

Table 1. Cyclohexyl amide (**3b**) yields after reaction of 4-toluoyl azide **1** with cyclohexyl amine **2b** in different alcohols

Solvent[a]	E_s[b]	Ω_s[c]	Yield (**3b**) (%)
Methanol (**4a**)	0.00	0.288	1
Ethanol (**4b**)	−0.07	0.334	64
n-Butanol (**4c**)	−0.39	0.341	87
Mixture **4a**/**4b** (1 : 1 molar)			7[d]

[a] Constant concentrations: $c(\mathbf{1}) = 10^{-4}$ mol/l, $c(\mathbf{2b}) = 10^{-3}$ mol/l

[b] From [7]

[c] From [8]

[d] Yields of the corresponding esters: 92% (**5a**), 1% (**5b**)!

Table 2. Yields of 4-toluoyl amides **3** after reaction of 4-toluoyl azide **1** with different amines **2** in methanol

Amine	E_s[a]	Ω_s[b]	Yield **3** (%)[c]	Yield **3** (%)[d]
2a	−0.39	0.341	93	44
2b	−0.79	0.381	60	6
2c	−1.98	0.392	41	2

[a] From [7]
[b] From [8]
[c] $c(\mathbf{1}) = 10^{-1}$ mol/l, $c(\mathbf{2}) = 1$ mol/l
[d] $c(\mathbf{1}) = 10^{-3}$ mol/l, $c(\mathbf{2}) = 10^{-2}$ mol/l

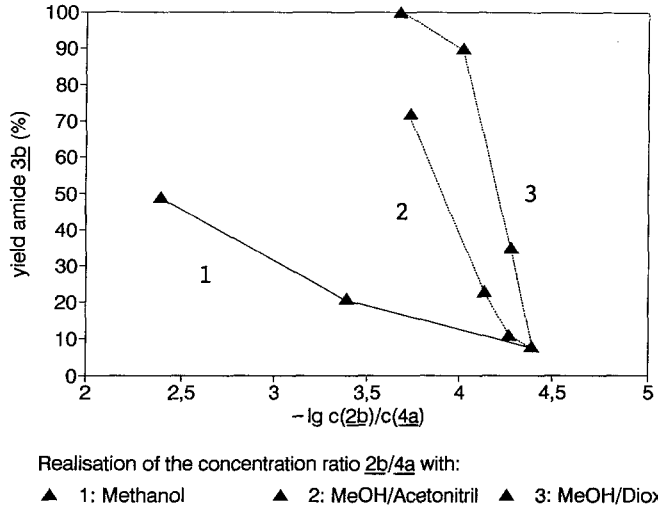


Fig. 2. Solution composition dependence of the 4-toluoyl cyclohexyl amide **3b** yield after reaction of 4-toluoyl azide **1** with cyclohexyl amine **2b** (molar ratio 1:1) in methanolic solutions (Curve **1**: concentration change of **1** and **2b** in pure methanol; curves **2**, **3**: solution of **1** and **2b** in solvent mixtures of varied compositions; 3/1, 1/1, 1/3; *v/v*)

2c, resp., and if the excess of methanol is high enough (**4a** : **1** ratio 26400 : 1) the major product is the ester **5a** (94% resp. 98%). By "assistance" of the very bulky amine **2c**, even with a methanol excess of only 264 : 1 (relative to **1**) resp. 26.4 : 1 (relative to **2c**), the ester yield is surprisingly high (59%).

In Ref. [4] ethanol and the even more bulkier 2-methyl-2-butanol had been used as solvent for the aroyl azide. The only observed exception from > 90% yield of substituted naphth-2-yl amide was the reaction with *t*-butyl amine in ethanol (< 50% yield). In agreement with these results in our investigation also only 2% of ester **5b** is produced from **1** and **2b** (1 : 1) in ethanol **4b** [$c(\mathbf{1}) = 10^{-1}$ mol/l, ethanol (**4b**) : **1** ratio 171 : 1]. Compatible with the hypothesis of a sterical control, 4-toluoyl azide **1** and **2b** in methanol **4a** under the same conditions [$c(\mathbf{1}) = c(\mathbf{2b}) = 10^{-1}$ mol/l, methanol (**4a**) : **1** ratio only 134 : 1] yield 51% of ester **5a**.

Together with the results of the manipulation of the methanol excess by changing the amine concentration (data from Fig. 1), the results of a variation of the methanol (**3a**) concentration by dilution with "inert" solvents are shown in Fig. 2. A descriptive explanation is that the same methanol:amine ratio in a more polar solution yields preferentially ester, in an apolar medium the commonly expected amide.

Kinetics

The reaction rate of **1** with **2b** seems to increase with the polarity of the solvent (see Table 3). The activation parameters (Table 4) are in the same order of magnitude as the values for the reaction of 2-naphthoyl azide with cyclohexyl amine in ethanol ($\Delta H^{\#} = 21.4$ kJ/mol, $\Delta S^{\#} = -207$ J/mol K; [4]). The reaction rate for the amide (**3**) formation becomes much smaller with increasing size of the amine **2** (Table 3).

A high acceleration of the reaction is characteristic for the ester formation from **1** in the presence of amine **2b**. E.g., with $1.4 \cdot 10^{-5}$ molar solutions of **1** in methanol and variation of the cyclohexyl amine (**2b**) concentration between $4 \cdot 10^{-4}$ and $1.4 \cdot 10^{-2}$ mol/l (yield of **5a** > 95%) the observed k_1 is linearely dependent on amine concentration ($r > 0.998$). A k_2 of 14.4 l/mol min (25 °C) can be calculated. It is remarkable that the formation rate of an ester depends strongly on the concentration of a nucleophilic primary amine.

The additional influence of the amine structure on the accelerated formation of the ester **5a** is illustrated by a comparison of "pseudo-first-order reaction" rate constants for the "amine promoted esterification": 0.13, 0.10 resp. 0.06 min^{-1} in the

Table 3. Rate constants for the reactions of 4-toluoyl azide **1** with cyclohexyl amine **2b** in various solvents and with *n*-butyl (**2a**) resp. 3-pentyl amine (**2c**) in acetonitrile (25.0 °C)

Solvent[a]	E_T[b]	k_2 (**2b**) (1/mol min)[c]	k_2(**2a**) (1/mol min)[d]	k_2(**2c**) (1/mol min)[d]
Cyclohexane	31.2	0.036		
Dioxane	36.0	0.138		
Tetrahydrofuran	37.4	0.202		
Acetonitrile	46.0	0.831	15.51	0.19

[a] Concentration of **1**: $c(\mathbf{1}) = 10^{-4}$ mol/l

[b] From [9]

[c] Concentration variation for **2b**: $c(\mathbf{2b}) = 1 \cdot 10^{-2} \cdots 10^{-1}$ mol/l; linear regression of k_1' vs. $c(\mathbf{2b})$: $r > 0.998$

[d] Concentration variation: $c(\mathbf{2}) = 1 \cdot 10^{-2} \cdots 1$ mol/l; linear regression of k_1' vs. $c(\mathbf{2})$: $r > 0.998$

Table 4. Activation parameters for the reaction of 4-toluoyl azide **1** with cyclohexyl amine **2b** in two solvents[a]

Solvent	$\Delta H^{\#}$ (kJ/mol)	$\Delta S^{\#}$ (J/mol K)
Dioxane	26.3 ± 3.8	-186.4 ± 35.2
Acetonitrile	22.1 ± 2.5	-170.5 ± 19.4

[a] $c(\mathbf{1}) = 10^{-4}$ mol/l, $c(\mathbf{2b}) = 1.4 \cdot 10^{-2} \cdots 5.8 \cdot 10^{-1}$ mol/l; 15 °C $\leqslant T \leqslant$ 35 °C; Arrhenius plot ln k_2 vs. $1/T$: $r > 0.98$

presence of **2a**, **2b** resp. **2c** [$c(\mathbf{1}) = 1.5 \cdot 10^{-5}$ mol/l, $c(\mathbf{2}) = 3.10^{-3}$ mol/l in methanol; > 95% yield of **5a**]. For comparison, the rate of the alcoholysis of **1** in pure methanol under the same conditions is $7.6 \cdot 10^{-5}$ min^{-1} (25 °C)!

Discussion

The product and the kinetic studies demonstrate that the clear second order reaction of a nucleophilic amine **2** with the aroyl azide **1**, which is strongly dependent on the size of the nucleophilic amine and the polarity of the solution, changes its course in the presence of alcohols:

- ester (**5**) formation as concurrent reaction with alcohols **4** is especially effective with the "smallest" methanol;
- the dependence of ester formation efficiency on the size of the present amine causes especially high yields with "bulky" amines;
- the rate of the alcoholysis is proportional to the concentration of the (nucleophilic) amine and is highly accelerated compared with the simple alcoholysis.

All kinetic data for the "pure" *aminolysis* including the activation parameters, especially the highly negative entropy, and the solvent polarity dependence are in agreement with an "ordered", polar intermediate state (IS). There is no experimental evidence for additional catalytic effects of the amine. This is in agreement with a similar case reported by Jencks et al. [10], who found that because of sterical hindrance a base catalysis in the course of the aminolysis of phenyl acetate is only detectable with very small amines (methyl or ethyl amine).

From the kinetic experiments under identical conditions one may estimate characteristic half life times τ_1 for the aroyl azide **1** under various reaction conditions:

- for methanolysis τ_1(**4a**) ~ 160 h,
- for aminolysis τ_1(**2b**, acetonitrile) ~ 35 min.

Considering the solvent polarity dependence of the aminolysis rate (Table 3) τ_1 for a hypothetical "pure" aminolysis (with **2b**) in methanol as solvent should be approximately 10 min.

For the "amine accelerated" *esterification* of **1** we find τ_1(**4a**/**2b**) ~ 7 min. All arguments, the half life times (nearly the same τ_1 for the "pure aminolysis" in methanol and the "amine accelerated" methanolysis), the analogous solvent polarity dependence and the interrelated sterical substituent effects support the hypothesis of a common intermediate state for both reactions consisting of aroyl azide **1** and amine **2**. Its reaction with alcohol **4** yielding the ester **5** is favoured in the presence of a large amine **2** (relative slow conversion IS to **3**; see Table 2), but only if the size of the alcohol is small and its excess high enough. A destabilisation of IS, e.g. in apolar solvents, decreases the chances for an attack of the alcohol. In this case the formation of **5** is also suppressed (see Fig. 2).

With this approach the large acceleration of the "amine promoted" ester formation as compared with the simple alcoholysis can easily be understood. The role of the amine is formally in analogy to that of tertiary amines in "nucleophilic catalysis", e.g. the alcoholysis of carbonyl halides.

Additional experimental evidence for this hypothesis is derived from the slow formation of methyl ester **5a** (84% yield, besides amide **3b**), from the ethyl ester **5b** in methanol (**4a**) in the presence of cyclohexyl amine (amine **2b**: ester **5b** ratio 10:1)! Starting with the methyl ester **5a** under identical conditions the solvent methanol **4a** – again the smaller nucleophile – possibly only "reproduces" (via. IS) the educt. No conversion to amide **3b** can be observed.

Especially when looking at the huge differences between methanol and ethanol, it seems that the Ω_s values, derived from molecular force field calculations [8], are better suited to describe the steric influences on the course of these reactions than the commonly used Taft parameters E_s.

The special structure of the carboxylic acid derivative **1** (consisting of a donor substituted aryl-group and azide as leaving group) with the consequence of a moderate reactivity may be an important condition for the observed unexpected sensitivity and selectivity of the substitution reactions depending on the involved nucleophile(s) and the conditions. The reactivity in the presence of water and of buffered solutions and the consequences of the results of these model reactions for the enzyme immobilisation onto aroyl azide polymers are under investigation.

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