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Bromo–nitro substitution on a tertiary α carbon—a previously uncharacterized facet of the Kornblum substitution†

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Sodium nitrite in dimethylformamide substitutes nitro for bromine alpha to an amide carbonyl in high yield at a tertiary site. Hammett plots show a strongly positive ρ value (+0.67), indicating a negatively-charged transition state, in contrast to the typical S_N1/S_N2 mechanism domain for Kornblum substitutions.

Introduction

The Kornblum substitution is the replacement of a halogen on an organic compound by a nitro group by using sodium nitrite ($NaNO_2$) as a nitrite source and DMF as a solvent. The reaction proceeds in high yields at room temperature and does not require anhydrous conditions. It was discovered and widely characterized by Nathan Kornblum (Fig. 1) at Purdue University, Indiana in the 1950s.[1–3]

In 1991 Noboru Ono published a textbook that summarized the key methods for the preparation of nitro compounds[4] followed by an updated version in 2001 (ref. 5) (while writing this book, Ono collaborated with Kornblum, who was late in his career and died shortly after). Ono named the substitution "the Kornblum reaction" in both the 1991 and 2001 versions.[4,5] However, in 2002 the term "Kornblum reaction" was used by Mamedov *et al.* to refer to the Kornblum oxidation,[6] which is a different reaction that was also elucidated by Kornblum. Yet a third reaction has also been named after Kornblum, namely the Kornblum–DeLaMare rearrangement.[7] We propose that the X–NO_2 substitution that was characterized by Kornblum be described as the 'Kornblum substitution'. We here discuss and further characterize the Kornblum substitution.

The Kornblum substitution was summarized by Ono and others as occurring on primary and secondary halogeno compounds, but not tertiary where a HX elimination product is consistently observed[4,5,8,9] (Fig. 2). Kornblum's original observations[2] support this view.

However, we have found that the Kornblum substitution does proceed on a tertiary centre that is alpha to an anilide carbonyl group. We have hence used the Kornblum substitution to prepare an α-nitroisobutyranilide (**2**) in order to perform an alternative synthesis of the hydantoin anti-baldness compound RU58841, a process that we published in 2014.[10] The reaction was simple and performed in high yield with low cost materials (Fig. 3).

We had discovered that it was possible to do a Kornblum substitution on the α-bromoisobutyranilide (**1**) when we observed that the product of **1** treated with $NaNO_2$ in DMF appeared as an M-89 signal on a GC-MS. We found that an aryl isocyanate (Ar–NCO) was forming with the loss of 2-nitropropane under the high temperature conditions of the GC-MS injector port, but that at room temperature the α-bromoisobutyranilide (**1**) readily formed the α-nitroisobutyranilide (**2**), which could be crystallized by the addition of water.

We note that among Kornblum's original writings on the topic, in one paper Kornblum described the substitution as occurring on primary and secondary carbons alpha to a carbonyl.[11] He subsequently placed a patent on this process for the preparation of α-nitroesters from α-haloesters which included an example of a tertiary nitro compound – the preparation of ethyl α-nitroisobutyrate (**4**) from ethyl α-bromoisobutyrate (**3**)[12] (Fig. 4).

The example in this patent of a tertiary halo–nitro substitution alpha to a carbonyl seems to have remained unnoticed; in 1971 Sayo *et al.* used a longer four-step synthesis to achieve a

Fig. 1 Nathan Kornblum.

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‡ The following content is taken, in part, from the PhD thesis of the primary author, Matthew Leonard.

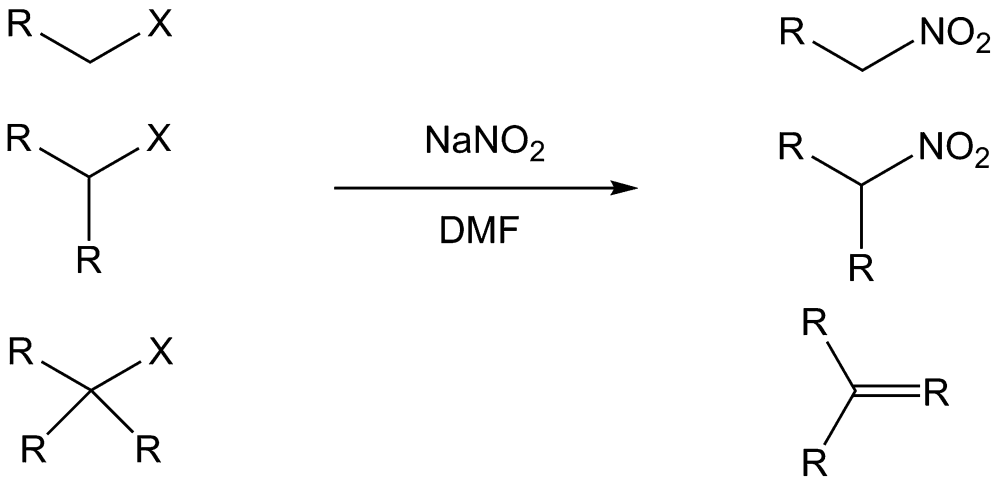


Fig. 2 The Kornblum substitution.

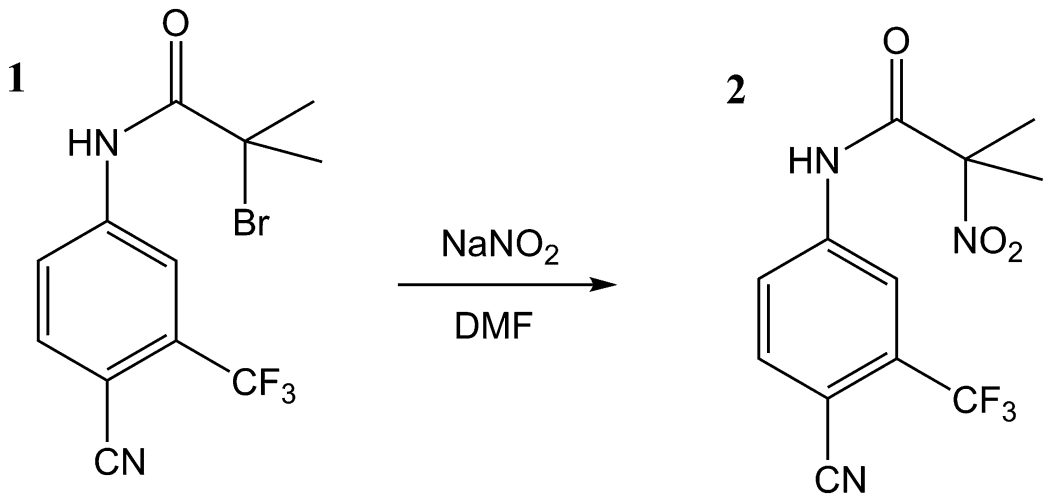


Fig. 3 An α-nitroisobutyranilide from an α-bromoisobutyranilide.

library of α-nitroisobutyranilides,[13] which could have been done in two steps if they had used the pathway shown in Fig. 3.

The Kornblum substitution was subsequently performed on a tertiary alpha carbon twice more by other workers, neither of whom commented on the novelty of the substitution's occurring at a tertiary halo carbon. In 1957 Kissinger and Ungnade[14] stated that they followed Kornblum's method from his 1956 paper[2] to prepare ethyl α-nitroisobutyrate (**4**) from ethyl α-bromoisobutyrate (**3**); in 1977 Gelbard and Colonna[15] carried out the Kornblum substitution on tertiary halo ethyl esters in order to characterize the effectiveness of a new type of nitrite resin. These three reports have gone generally unnoticed by the organic synthesis community; later publications in the 1990s and 2000s still regarded the Kornblum substitution as not

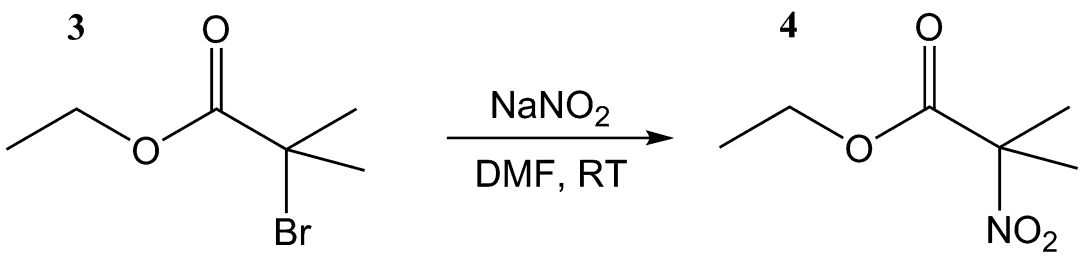


Fig. 4 Preparation of ethyl α-nitroisobutyrate from Kornblum's 1957 patent.[12]

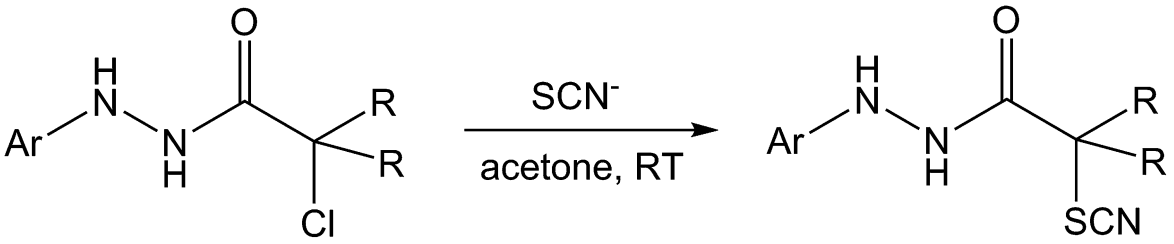


Fig. 5 Chloro–thiocyanate substitution as observed by Glushkov *et al.*[22]

proceeding on a tertiary centre.[16–18] Kornblum spoke entirely in terms of S_N2 and S_N1 mechanisms, and the general belief is that a bromo–nitro substitution will not proceed at such sites due to steric hindrance on the tertiary carbon, which impedes an S_N2 pathway.[19] It does encourage S_N1, but the nitrite ion is an ambident nucleophile,[20] and S_N1 substitution by nitrite is known usually to involve nucleophilic attack by the harder oxygen atom (acting under charge control[21]), giving an alkyl nitrite product (R–O–N=O).[8] S_N2, on the other hand, sees nucleophilic attack occur from the softer nitrogen atom (under orbital control) to furnish an alkyl nitro compound (R–NO_2).[8] The concept that an S_N1 or an S_N2 process will control the product of an attack by an ambident nucleophile has been called "Kornblum's rule".[20]

A 1997 paper by Glushkov and co-workers[22] shows evidence that Kornblum's rule does not apply to tertiary halo carbons with an alpha carbonyl. The authors expected that Kornblum's rule would see thiocyanate ions (SCN^-) attacking the carbocation from a tertiary halo compound in an S_N1 manner to form an isothiocyanate (R–NCS), but instead from their substrates they observed thiocyanate products (R′–SCN) (Fig. 5), which are the expected result of an S_N2 substitution (attack by the more polarizable atom on the ambident nucleophile).

Glushkov *et al.* postulated that the destabilizing effect of an alpha carbonyl prevented the formation of a carbocation and caused their substitution to occur by an S_N2 process.[22] Their language, like many others', suggests that they consider S_N1 and S_N2 to be the only two options.

It has been frequently noted that nucleophilic substitution reactions alpha to a carbonyl show atypical properties.[23,24] They are, in particular, unusually fast,[25–31] though how much so depends on the nucleophile and other circumstances.[32–40] Various mechanistic reasons have been proposed for this. Some authors argue that addition takes place initially at the carbonyl, followed by either a 1,2-shift of the nucleophile to the alpha position,[41–47] or, alternatively, formation of an epoxide that reacts with further nucleophile at the alpha position.[40,48–55] Other authors reject this and contend that the reacting nucleophile makes an ordinary S_N2-like attack at the carbon bearing the leaving group, but is assisted by interaction with carbonyl π^* antibonding orbitals that temporarily accept electron density (often described as conjugation with the p orbitals or the π system, or as an enolate-like transition state),[34,37,38,56–65] or alternatively by purely electrostatic effects.[23,66–69] More recently a halfway position between these two extremes has been urged: that the attacking nucleophile bridges the carbonyl and the alpha carbon (and, by the principle of microscopic reversibility, the leaving group must also bridge both positions).[70] This mechanism has been supported by recent computational studies,[71–73] some of which suggest that there is a bifurcation in the potential energy surface after the transition state, a situation in which conventional transition state theory breaks down and molecular dynamics may become important.[74–77] It has also been suggested that substitution is by S_N1 reaction, and that this is accelerated by neighbouring group participation by the carbonyl, creating a 2*H*-oxirenium cation,[78] or by prior enolisation on the other side, creating an allylic system;[79] other suggestions include *via* a carbene produced from an enolate,[67] and through nucleophilic attack at the halogen.[32,41,67] Evidence for each mechanism, and against other mechanisms, has been found by different workers in different reactions, and many writers give evidence that different mechanisms dominate in different circumstances.[23,32,55,73]

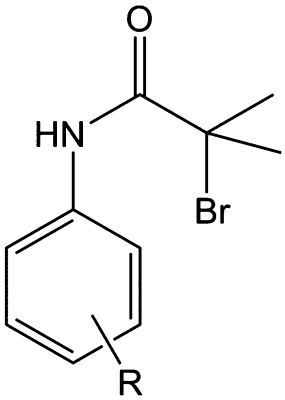
In most papers Kornblum generally described the substitution as S_N2, but in one paper he described it as more S_N2 than S_N1 in nature, but with properties of both.[80] As the substitution's proceeding on a tertiary centre is at odds with Kornblum's stated S_N2 mechanism, we suspected that a different mechanism was operative. We have therefore prepared a library of α-nitroisobutyranilides to show *prima facie* trends of the rate of Br–NO_2 substitution, and to prepare Hammett plots from the rate data to indicate any charge in the transition state that would hint at the mechanism.

Results and discussion

In order to prepare a library of α-bromoisobutyranilides, anilines of varied substitution were selected with both greater and lesser electron withdrawing capacity than R = phenyl and also aniline itself (Table 1). The library of α-bromoisobutyranilides were then each exposed to a 10 : 1 molar ratio of sodium nitrite to reactant compound using DMF as solvent at ambient temperature. The rate of conversion was monitored by taking hourly aliquots for GC-MS analysis. It was observed that the more electron-withdrawn the compound, the faster the bromo–nitro substitution took place.

As well as α-bromoisobutyranilides, which have an aryl group beyond the amide nitrogen, two compounds with an alkyl group in place of the aryl, *n*-butyl and benzyl, were also prepared, and found to undergo bromo–nitro substitution but

Table 1 α-Bromoisobutyranilides monitored for their rate of Br–NO_2 substitution



Bromo compound	Nitro compound	R-Substituents
1	**2**	*p*-Cyano-*m*-trifluoromethyl
5	**6**	H
7	**8**	*p*-Methyl
9	**10**	*o*-Carboethoxy
11	**12**	*o*-Nitro
13	**14**	*m*-Nitro
15	**16**	*p*-Nitro
17	**18**	*o*-Bromo
19	**20**	*o*-Chloro
21	**22**	*m*-Chloro
23	**24**	*p*-Chloro
25	**26**	*o*-Methoxy
27	**28**	*m*-Methoxy
29	**30**	*p*-Methoxy
31	**32**	Benzyl in place of phenyl
33	**34**	*n*-Butyl in place of phenyl
35	**36**	2,4-Dinitro

at a much reduced rate compared with the aryl compounds. An additional α-bromoisobutyranilide with 2,4-dinitro substitution (**35**) was not characterized due to extreme difficulty of isolation but its rate of Br–NO_2 substitution to give **36** could be easily monitored. It is therefore included in the graph to show the additional increase in rate when the compound's R group had the electron withdrawing capacity of two nitro groups and, as expected, it proceeds much faster than the mono-nitros and the CN/CF_3 substituted compounds (**1**).

Some general trends in the bromo–nitro substitution were immediately apparent before any calculations were applied to the data. The first principle that overrides all others is that the reaction goes faster when the R group is more electron withdrawing, no matter how the R group is configured. Changes such as switching between *ortho*, *meta* and *para* substituted groups have a comparatively small effect on rate.

An overview of the rate data is shown in Fig. 6. The % substrate is plotted logarithmically: most compounds showed close to pseudo-first order behaviour. The sodium nitrite was present in ten-fold excess; it has limited solubility in DMF and excess solid was present. The solution was rapidly stirred, keeping the nitrite concentration constantly near saturation. Approximate straight lines of best fit are shown.

It was observed that reactions of *ortho* substituted α-bromoisobutyranilides proceeded faster than the equivalent *meta* or *para* isomers for the three substituents, methoxy, chloro and nitro, for which we had data. It may be that a substituent on the aryl ring closer to the site of halo–nitro substitution facilitates the substitution through some form of steric acceleration. This is shown in Fig. 7–9.

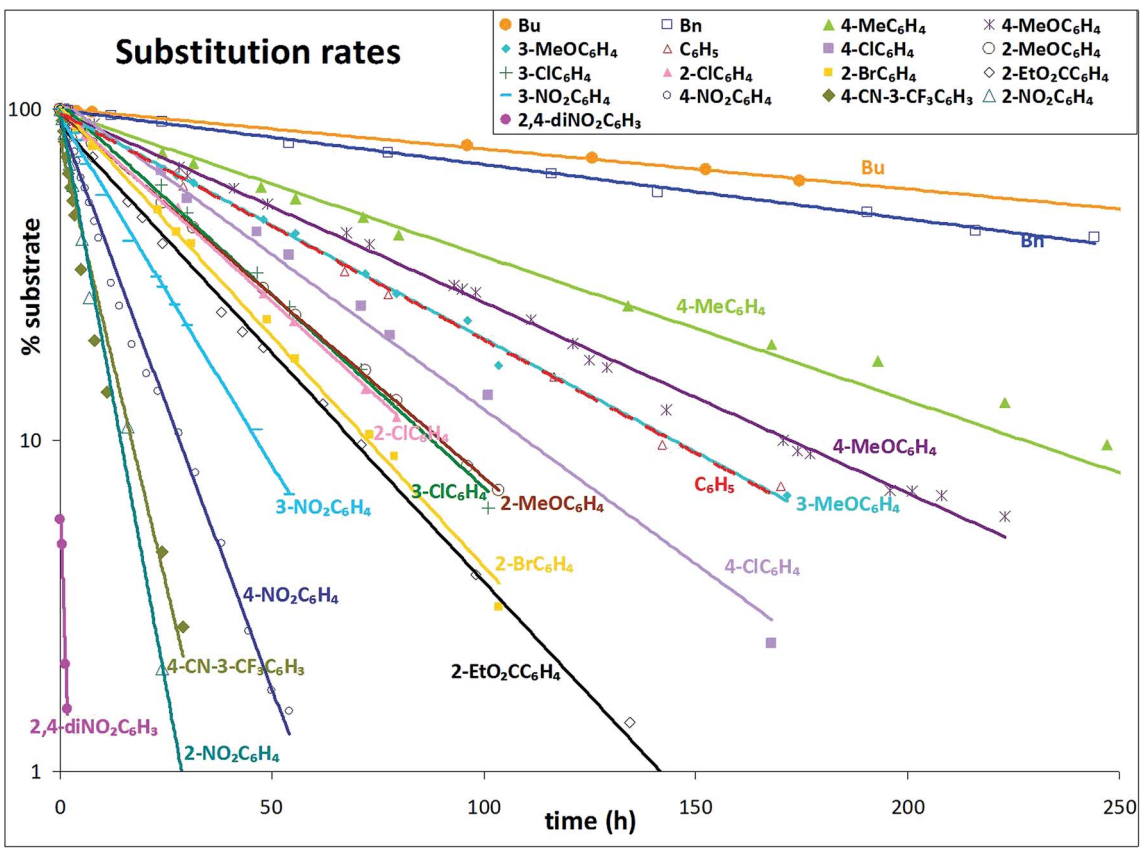


Fig. 6 Substitution rate for tertiary α-bromoisobutyranilides.

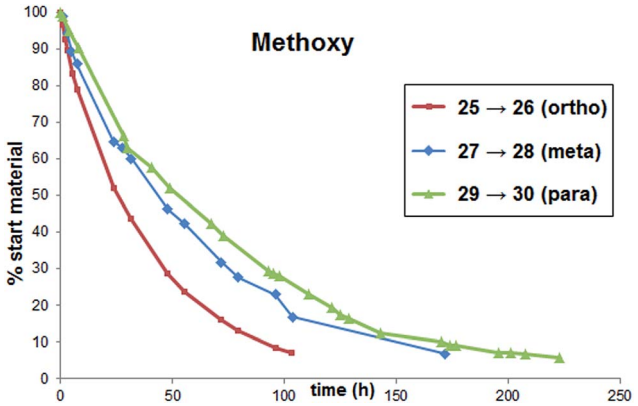


Fig. 7 Substitution rate for methoxy substituted α-bromoisobutyranilides.

The rate varied much less between the three chloro substituted compounds than it did for the nitro and methoxy compounds. The difference could be steric, or perhaps due to nitro and methoxy's capability for hydrogen bonding; both can bend with free rotation and contain free electron pairs.

However, one exception to the first principle of increased rate with more electron-withdrawing R groups is that bromo in the *ortho* position gives significantly faster reaction than chloro in the *ortho* position. As bromo and chloro are quite similar except for size, it appears that in this case we are observing steric facilitation of the nearby substitution by the larger bromo group managing to outweigh the normally stronger effect of rate increasing with electronegativity.

This contrasts with reported observations that *ortho* substituted phenacyl bromides are less reactive in nucleophilic substitution by pyridine or *t*-butylamine.[41,42,65]

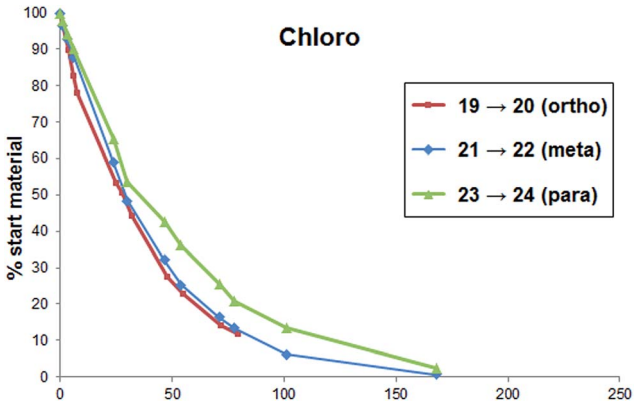


Fig. 8 Substitution rate for chloro substituted α-bromoisobutyranilides.

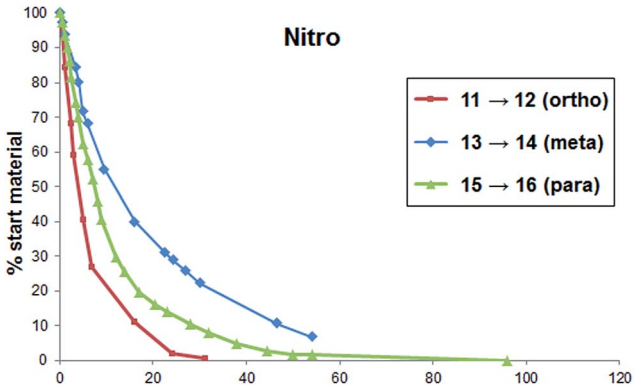


Fig. 9 Substitution rate for nitro substituted α-bromoisobutyranilides.

Br–NO_2 substitution at low nitrite concentration

Our reaction conditions used saturated sodium nitrite in DMF. To investigate the dependence of the rate on nitrite concentration, we sought to increase the solubility of nitrite ions in DMF by using a co-solvent. Kornblum reported that the addition of 8% urea to the DMF dissolved far more $NaNO_2$ which further increased the rate of substitution.[11] When we tried the reaction this way we observed a slight reduction in rate, and saw no increase in solubility. We are puzzled by Kornblum's use of urea. He may have intended it to react with free nitrous acid[81] (which he discussed as responsible for the degradation of the desired nitro products), but there may have been reaction with some nitrite.

Therefore we instead used a low concentration experiment to compare the substitution rate of **1** → **2** in a saturated solution of $NaNO_2$ in DMF with rates observed in solutions that contained only 75% and 50% the concentration of a saturated $NaNO_2$ solution. The reaction rate was lowered under these conditions (Fig. 10).

This change in rate is evidence against an S_N1 mechanism as the rate-limiting step of an S_N1 reaction would be the formation of a cationic intermediate, independent of the presence of nitrite ions. This clearly cannot be an exclusive S_N1 process and we can declare that the nitrite must be taking part in the rate-limiting step.

Hammett plots

First-order plots of ln(%substrate) against time were prepared for the reactions of the compound library. The slope of these is $-k'$, where k' is the pseudo-first-order rate constant. As has been mentioned, a dilution experiment showed that the reaction rate depends also on nitrite concentration, so these reactions are

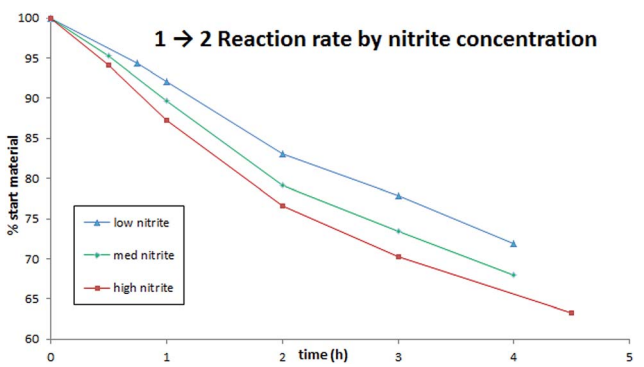


Fig. 10 Effect of nitrite concentration on **1** → **2** reaction rate.

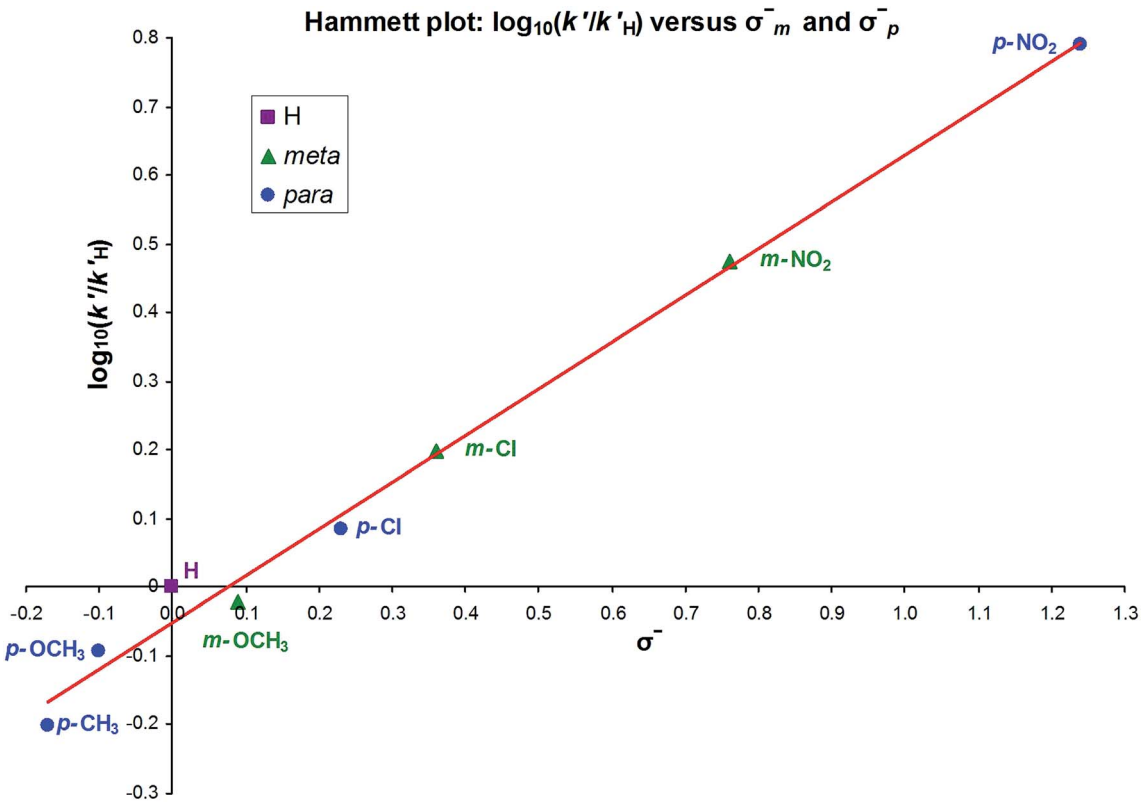


Fig. 11 Hammett plot.

only pseudo first order due to the nitrite concentration's remaining effectively constant throughout the reaction. The nitrite concentration was the same in each experiment: ~5 mmol of the α-bromoisobutyranilide reactant (1–2 g) with $NaNO_2$ (4.00 g, 44.9 mmol) in 40 mL of DMF.

Data and plots for individual compounds are shown in the ESI,† with linear regression analysis. The linearity of these first order plots is reasonably good, except for the fastest reactions, especially **1** → **2**. In many cases, however, there was some noticeable deviation from linearity or accuracy at the longer time scales and using the earlier portion of the data (never fewer than nine data points) gave more accurate linearity and improved the R^2 value considerably (these are shown in the ESI†). As well as the usual decline of analytical accuracy at lower concentrations, a small amount of the formed nitro product may degrade by further reaction with nitrite ions *via* a nitroso intermediate to produce the alkyl nitrite by-product (a process described by Kornblum[82]).

The k' values obtained from these graphs for the *meta* and *para* substituted anilides were used to construct Hammett plots. The *meta* examples, when plotted (as $\log_{10} k'/k'_H$) against ordinary σ_{meta} values[83] (which are based on K_a values for benzoic acids), gave a reasonable fit ($R^2 = 0.97$) and showed a positive ρ value of 0.70, indicating that the transition state develops a negative charge relative to the starting species in the rate-determining step.

The *para* substituted compounds are more complex to consider because 'through conjugation' is possible, where a canonical form can be drawn that puts the charge right at the *para* position and potentially on the substituent itself. A Hammett plot against ordinary σ values (from benzoic acid K_a values) gave a fit that was not terribly good ($R^2 = 0.92$). A plot using σ^+ values[84] (based on benzylic S_N1 solvolysis, with a positive charge next to the ring), which have strong through-conjugation effects with electron-donating substituents gave a much worse fit ($R^2 = 0.76$). We then tried σ^- values,§ originally based on phenol K_a values, so a negative charge next to the ring and strong through-conjugation effects with electron-withdrawing substituents: this gave the best fit of all ($R^2 = 0.99$) and a ρ of +0.67: in the phenol acidity standard ρ is 2.01.

This result implies that not only does this reaction have a negative charge on the transition state, but that charge can readily conjugate onto the ring.

A combined Hammett plot of both *meta* and *para* substituted compounds, using σ_{meta}^- and σ_{para}^- values,¶ gave $R^2 = 0.992$ and a ρ value of 0.68 (Fig. 11).

The positive ρ implies a mechanism in which the nucleophile attacks first, before the leaving group leaves. One might think that the large ρ and the correlation with σ^- implies the

§ We have normally used the preferred σ_p^- values of Hansch, Leo and colleagues.[85,86] However there is disagreement concerning the best value of σ_p^- for methoxy. Hansch *et al.* prefer −0.26, which is essentially σ_p (−0.27); but this and similar values are only obtained when the anilinium acidity is used as the basis of measurement. When using aqueous phenols, *p*-methoxyphenol's acidity requires a σ_p^- in the range −0.10 to −0.135,[87–92] and these values give the best fit to our data.

¶ We used Chuchani and Frohlich's values of σ_m^- and σ_p^- for methoxy[92] and Zeng's values of σ_m^- for chloro and nitro.[93] The remaining σ_p^- values are from Hansch, Leo and colleagues.[85,86]

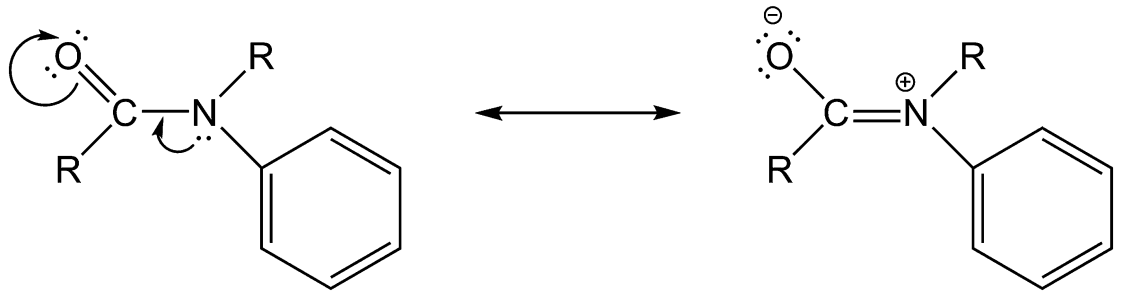


Fig. 12 Planar and conjugated anilide π system.

negative charge that forms must be on the nitrogen, but this isn't necessarily so. In anilides there is strong π character in the nitrogen–carbonyl bond and therefore the whole group has a π system that is planar with and conjugated with the aromatic ring's π system (Fig. 12).

Therefore the negative charge that forms could be on the amide carbonyl, or on the position α to the carbonyl, as even there it will be conjugated with the ring (*cf.* hydrolysis of cinnamic esters, which has $\rho = 1.27$.).

If the mechanism started with deprotonation of the amide NH, where would it go next? One can only imagine forming an α-lactam, which would surely break open at the carbonyl. In any case, that mechanism wouldn't be available when the starting compound was an α-bromoester, and we know they also react.[1,12] Hence it appears that it must start with at least partial addition at the carbonyl, or formation of an enolate. This provides several possibilities, each of which has several sub-possibilities:

(1) In the rate-determining step nitrite adds to the carbonyl as nitro, forming a negative oxygen. The carbonyl re-forms pushing the nitro to do a 1,2-shift onto the adjacent atom (like a semipinacol rearrangement), displacing the halogen (which may leave first to give either a carbocation or an epoxide). [*cf.* (ref. 41–47)] (Fig. 13).

(2) In the rate-determining step nitrite adds to the carbonyl as nitrite, forming a negative oxygen. The carbonyl re-forms, pushing the nitrite nitrogen onto the adjacent atom in a four-centre reaction and displacing the halogen (which may leave first to give either a carbocation or an epoxide) (Fig. 14).

(3) The negative oxygen formed in possibilities 1 or 2 could form an epoxide by displacing the adjacent bromide (which may leave first), then more nitrite could add at the other side of the epoxide. The carbonyl re-forms, pushing off the first nitrite. [*cf.* (ref. 40 and 48–55)] (Fig. 15).

(4) The nitrite nucleophile bridges the carbonyl and the alpha carbon. Some electron density temporarily resides in the carbonyl π* antibonding orbital. The nucleophile finally displaces bromide in an S_N2-like attack. [*cf.* (ref. 70–73)] (Fig. 16).

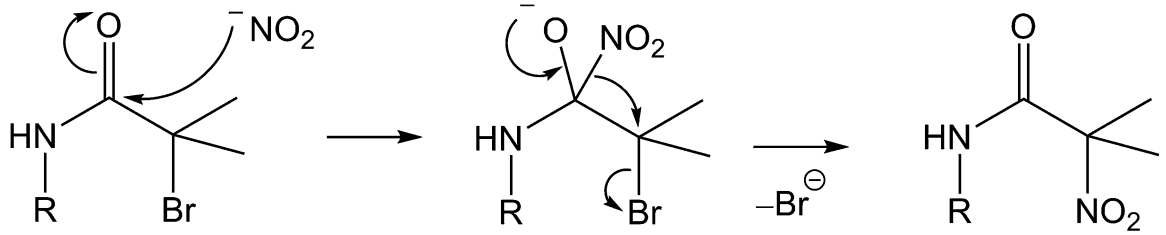


Fig. 13 Possible mechanism number one.

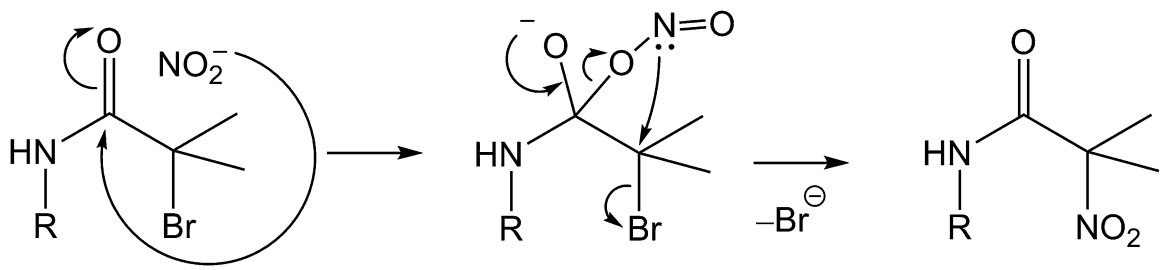


Fig. 14 Possible mechanism number two.

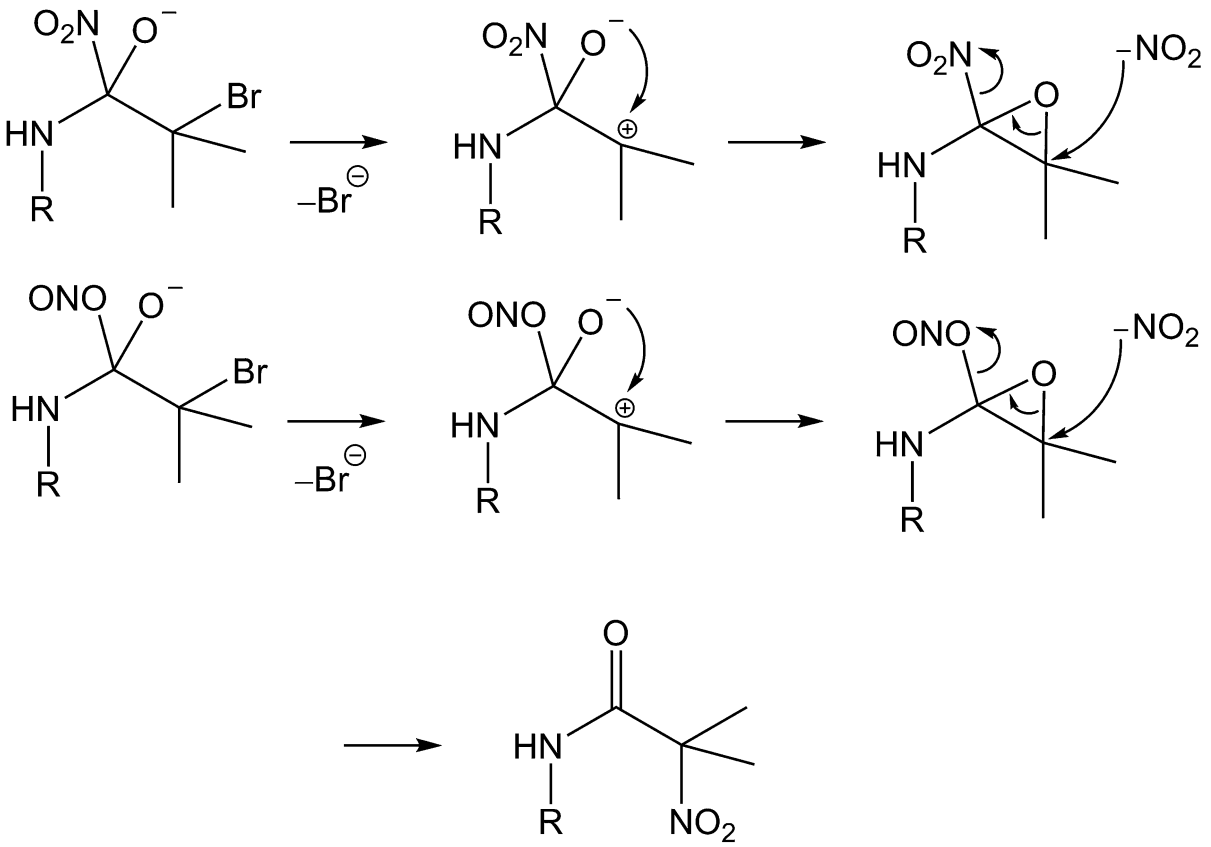


Fig. 15 Possible mechanism number three.

(5) The rate-determining step is nucleophilic attack by nitrite (through nitrogen) at the bromine, with enolate as leaving group and forming nitryl bromide. The enolate formed could then react with the nitryl bromide to form the nitro product.

None of these options can be ruled out completely. The plausibility of mechanism 4 is supported by the molecular computations on reactions of (non-tertiary) α-halo carbonyls with nucleophiles,[71–73] and by an observation of stereospecific substitution with second-order kinetics at a tertiary centre

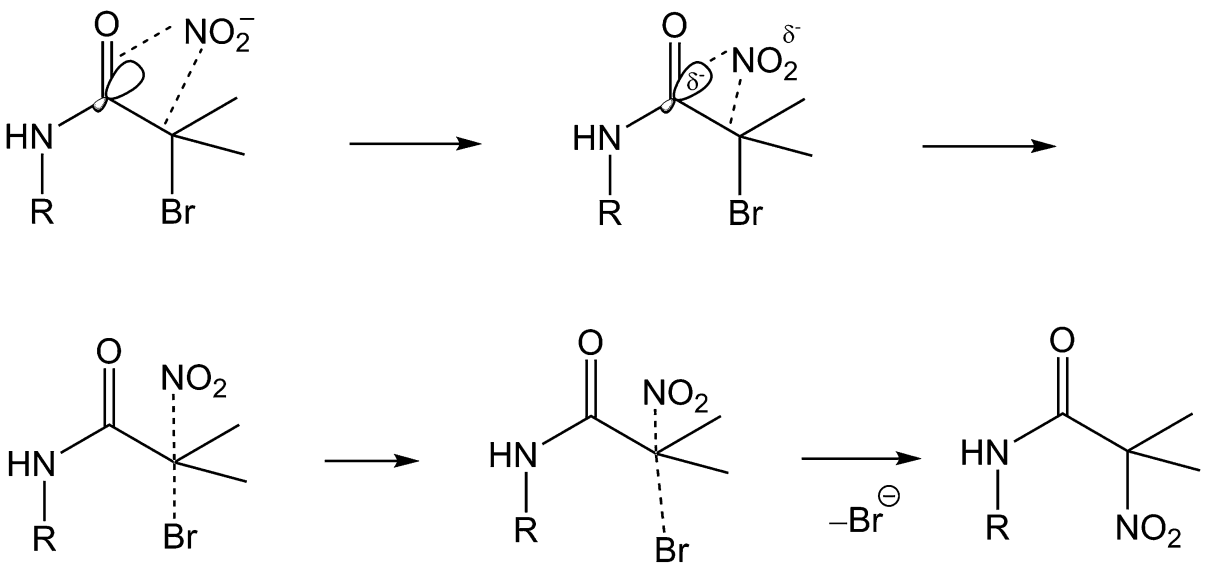


Fig. 16 Possible mechanism number four.

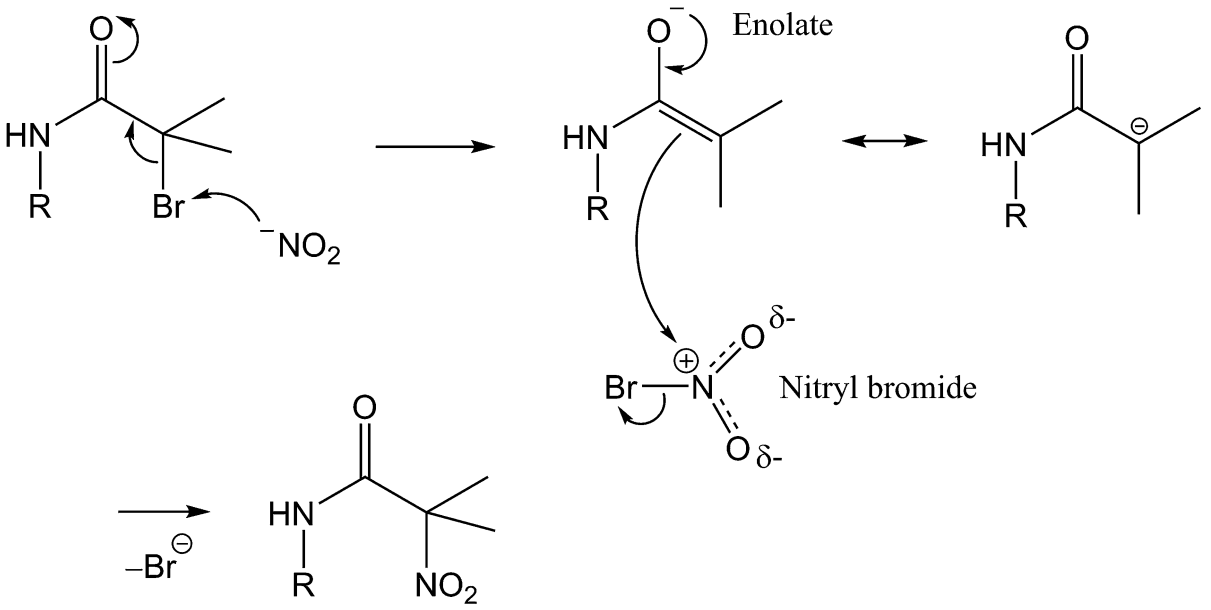


Fig. 17 Possible mechanism number five.

alpha to a carbonyl.[94] The report from Edwards and Grieco for a long time remained an isolated witness, but is now joined by recent evidence of definite stereoinversion in tertiary α-chloroesters reacted with azide, thiols and fluoride.[95,96] The bridging lowers the energy of the transition state, and, by delivering the nucleophile to the right position, may overcome the steric problems of tertiary S_N2. The ρ value is similar to the values (*ca.* 1.05) obtained from reaction of phenacyl chlorides with carboxylate, which were interpreted as supporting a bridging mechanism,[70] though the same paper references other substitutions of phenacyl halides in which the ρ value was much less.

However mechanism 5 is the only mechanism of these in which a full negative charge is directly part of the π system, supporting maximum through-resonance. Although nucleophilic attack on halogen as a means to substitution was considered by some early researchers[32,41,67] it rarely appears in modern papers, though it is very similar to what happens in the specific reduction of α-halo carbonyls by soft nucleophiles.[97] For example, it is commonly accepted that the α-halogenation of carbonyl compounds proceeds by the reaction of enol or enolate with molecular bromine, displacing bromide anion [*cf.* (ref. 98 and 99)]. This reaction is known to be reversible, so the principle of microscopic reversibility requires that the reduction of α-bromo carbonyl compounds by reaction with bromide occur by attack by bromide at the bromine, as has been pointed out by Altschul and Bartlett[100] and Newman.[101] Nitryl bromide is known to form and last for up to 30 min under some conditions.[102]

Br–NO_2 substitution in the absence of O_2

It has been suggested to us that as the reactions were carried out under air this substitution may be proceeding by means of a radical mechanism involving elemental oxygen (O_2). A later experiment ruled out this proposal as the reaction proceeded at the same rate in the absence of oxygen.

Conclusions

The Kornblum substitution has been robust from its inception and the few rules that govern it are widely known; mainly that it proceeds with primary or secondary but not tertiary carbons. We have re-addressed these rules for the examples shown here where the substitution is seen to proceed on tertiary halocarbons that are α to a carbonyl (Fig. 17), albeit probably by a different mechanism to the standard Kornblum substitution (Fig. 18).

Many earlier researchers discussed substitution mechanisms in terms of a comparison between S_N1 and S_N2, a dichotomy that implied that these are the only two possibilities,[103,104] and Kornblum himself wrote this way when discussing the reaction presented above.[1,22,105] However, this type of Kornblum substitution does not behave like the usual S_N1 or S_N2 and it adds to the growing repertoire of substitutions that do not fit into the simple S_N1/S_N2 model that earlier researchers had leaned upon.[106]

Further, the reaction represents a good way to prepare alpha-nitro ketones, esters and amides which are versatile building blocks in organic synthesis as the nitro group may be reduced to an amino group. The preparation of our library of α-nitroisobutyranilides using the Kornblum substitution represents a far more convenient route to these compounds than what has been reported previously.[13] Ono quoted the Kornblum substitution as high yielding for primary and secondary alkyl halides (50–70%), but low yielding (0–5%) for tertiary alkyl halides.[4,5] We may now add to this that the Kornblum substitution is very high yielding (70–99%) for tertiary alkyl halides alpha to an anilide carbonyl.

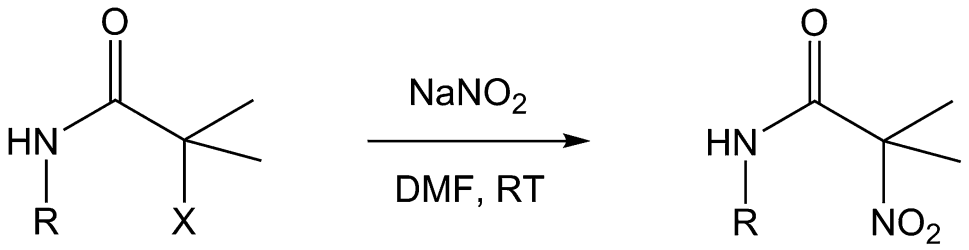


Fig. 18 Kornblum substitution on a tertiary α-carbon.

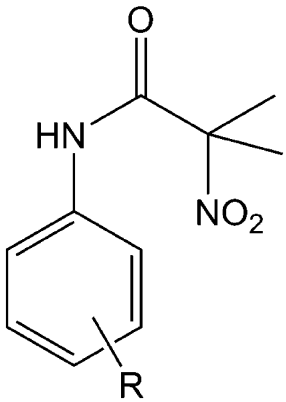
Experimental section

General

IR spectra were measured from 4000–650 cm^{-1} using a Varian 1000 FTIR spectrometer with a diamond Attenuated Total Reflectance (ATR) attachment. Reaction rate was monitored using a Varian CP-3800 gas chromatograph equipped with an SGE Analytical Science BPX5 column (column width 0.25 mm, film width 0.25 μm) which was adjoined to a Varian Saturn 2200 GC/MS/MS. Accurate mass spectra were measured using a Waters GCT Premier HR-TOFMS equipped with an Agilent 7890 GC column. NMR spectra were obtained using a Bruker Avance 300 MHz spectrometer. Chemical shifts in ^{1}H NMR spectra are relative to chloroform at 7.24 ppm; in ^{13}C NMR spectra are relative to the central peak of deuterochloroform at 77.5 ppm.

Rather than using IUPAC names, we have named the compounds as α-bromoisobutyranilides and α-nitroisobutyranilides in order to match the names given to them by Sayo *et al.*[13] who have earlier reported the synthesis of some of the compounds in this category. Seven of the α-nitroisobutyranilides prepared by Sayo *et al.* have been prepared by our new method. Table 2 compares our measured melting points to those of Sayo *et al.*

Table 2 Comparison of α-nitroisobutyranilide melting points



Compound	R=	M.p. (°C)	Sayo *et al.*[13]
6	H	104–107	104–105
8	*p*-Me	115–118	115–116
14	*m*-NO_2	135–136	135–136
16	*p*-NO_2	138–140	137.5–139
22	*m*-Cl	125–128	134.5–136
24	*p*-Cl	124–127	121–122.5
30	*p*-OMe	69–71	73–74

Acylation reactions

The library of reactant compounds was prepared by reacting anilines (or in two cases, benzylamine and *n*-butylamine) with α-bromoisobutyryl bromide. All reactions were carried out at room temperature using ~21.5 mmol (1.5–4 g) of the reactant amine, dissolved in 1,2-dichloroethane (35 mL). Oven-dried K_2CO_3 (3.00 g, 21.7 mmol) was added, then a 5% molar excess of α-bromoisobutyryl bromide was added last, dropwise. The flask was sealed and the reaction allowed to stir overnight at 700 rpm. The following morning the solvent was removed by rotary evaporation, and the residue was partitioned between ethyl acetate and water. The ethyl acetate fraction was dried ($MgSO_4$), evaporated, and the residue, if solid, recrystallized from methanol.

***p*-Cyano-*m*-trifluoromethyl-α-bromoisobutyranilide (1).** *p*-Cyano-*m*-trifluoromethylaniline (3.96 g, 21.3 mmol) gave 7.02 g (21.1 mmol, 99% yield) of pure *p*-cyano-*m*-trifluoromethyl-α-bromoisobutyranilide (**1**).

Characterization data for **1** are provided in our 2014 publication[10] where it is given the correct IUPAC name of "2-bromo-*N*-[4-cyano-3-(trifluoromethyl)phenyl]-2-methylpropanamide".

α-Bromoisobutyranilide (5). Aniline (2.00 g, 21.5 mmol) gave 4.04 g (16.8 mmol, 78% yield) of pure α-bromoisobutyranilide (**5**) as white needles that looked like shredded coconut, m.p. 89–92 °C; R_f = 0.54 in 4 : 1 hexanes/EtOAc, 0.74 in 65 : 35 hexanes/EtOAc and 0.95 in 1 : 1 hexanes/EtOAc; IR(cm^{-1}): 3275, 3042, 2993, 2924, 1660 (C=O), 1594, 1551, 1513, 1461, 1401, 1372, 1355, 1318, 1295, 1234, 1187, 1141, 962, 900, 862, 815, 767, 738, 677; ^{1}H NMR (300 MHz, 26 mg: 0.4 mL $CDCl_3$): δ 2.06 (6H, s, CH_3), δ 7.15 (1H, tt, ArH^4, *J* 2, *J* 8), δ 7.36 (2H, tt, ArH^3, *J* 2, *J* 8), δ 7.54 (2H, dt, ArH^2, *J* 2, *J* 8), δ 8.46 (1H, br, s, NH); ^{13}C NMR (75 MHz, 137 mg: 0.4 mL $CDCl_3$): δ 32.8 (s, C-$3_{A/B}$), δ 63.2 (s, C-2), δ 120.3 (s, C-2′), δ 125.1 (s, C-4′), δ 129.3 (s, C-3′), δ 137.6 (s, C-1′), δ 170.2 (s, C-1); GC-(EI) TOF-HRMS: calcd *m*/*z* for $C_{10}H_{12}NOBr$: 241.0102, observed: 241.0095.

***p*-Methyl-α-bromoisobutyranilide (7).** *p*-Toluidine (2.30 g, 21.5 mmol) gave 4.72 g (18.5 mmol, 86% yield) of pure *p*-methyl-α-bromoisobutyranilide (**7**) as little amber prisms, m.p. 95–98 °C; R_f = 0.63 in 4 : 1 hexanes/EtOAc, 0.78 in 65 : 35 hexanes/EtOAc and 0.93 in 1 : 1 hexanes/EtOAc; IR(cm^{-1}): 3297, 3195, 3032, 3006, 2984, 2919, 1652 (C=O), 1601, 1533, 1512, 1470, 1404, 1319, 1297, 1236, 1193, 1164, 1100, 1022, 1009, 946, 938, 893, 813, 767, 755, 696; ^{1}H NMR (300 MHz, 35 mg: 0.4 mL $CDCl_3$): δ 2.05 (6H, s, CH_3), δ 2.33 (3H, s, $ArCH_3$), δ 7.15 (2H, d, ArH^3, *J* 8), δ 7.42 (2H, d, ArH^2, *J* 8), δ 8.40 (1H, br, s, NH); ^{13}C

NMR (75 MHz, 135 mg: 0.4 mL $CDCl_3$): δ 21.2 (s, $ArCH_3$), δ 32.8 (s, C-$3_{A/B}$), δ 63.4 (s, C-2), δ 120.3 (s, C-2′), δ 129.7 (s, C-3′), δ 134.8 (s, C-1′), δ 135.1 (s, C-4′), δ 170.1 (s, C-1); GC-(EI) TOF-HRMS: calcd m/z for $C_{11}H_{14}NOBr$: 255.0259, observed: 255.0254.

***o*-Carboethoxy-α-bromoisobutyranilide (9).** Ethyl anthranilate (3.60 g, 21.8 mmol) gave 6.26 g (20.1 mmol, 92% yield) of pure *o*-carboethoxy-α-bromoisobutyranilide (**9**) as little amber prisms, m.p. 59–61 °C; R_f = 0.63 in 4 : 1 hexanes/EtOAc, 0.82 in 65 : 35 hexanes/EtOAc and 0.95 in 1 : 1 hexanes/EtOAc; IR(cm^{-1}): 3189, 3117, 3076, 2974, 2937, 1696 (C=O), 1680 (C=O), 1605, 1592, 1467, 1449, 1365, 1298, 1271, 1239, 1199, 1170, 1144, 1105, 1086, 1050, 1016, 969, 947, 856, 763, 730, 700; ^{1}H NMR (300 MHz, 30 mg: 0.4 mL $CDCl_3$): δ 1.42 (3H, t, ethyl CH_3), δ 2.07 (6H, s, CH_3), δ 4.42 (2H, q, ethyl CH_2), δ 7.12 (1H, td, ArH^4, J 2, J 8), δ 7.56 (1H, td, ArH^5, J 2, J 8), δ 8.08 (1H, dd, ArH^6, J 2, J 8), δ 8.70 (1H, dd, ArH^3, J 2, J 8), δ 11.90 (1H, br, s, NH); ^{13}C NMR (75 MHz, 145 mg: 0.4 mL $CDCl_3$): δ 14.4 (s, ethyl CH_3), δ 32.1 (s, C-$3_{A/B}$), δ 60.5 (s, C-2), δ 61.8 (s, ethyl CH_2), δ 116.2 (s, C-2′), δ 120.5 (s, C-6′), δ 123.2 (s, C-4′), δ 131.2 (s, C-3′), δ 134.7 (s, C-5′), δ 141.4 (s, C-1′), δ 168.3 (s, ester C=O), δ 171.0 (s, C-1); GC-(EI) TOF-HRMS: calcd m/z for $C_{13}H_{15}NO_3Br$: 312.0235, observed: 312.0222.

***o*-Nitro-α-bromoisobutyranilide (11).** *o*-Nitroaniline (2.90 g, 21.0 mmol) gave 5.83 g (20.4 mmol, 97% yield) of pure *o*-nitro-α-bromoisobutyranilide (**11**) as bright yellow needles, m.p. 67–70 °C; R_f = 0.61 in 4 : 1 hexanes/EtOAc, 0.80 in 65 : 35 hexanes/EtOAc and 0.83 in 1 : 1 hexanes/EtOAc; IR(cm^{-1}): 3320, 3118, 2985, 1701 (C=O), 1606, 1584, 1544, 1496, 1458, 1427, 1391, 1374, 1335, 1268, 1221, 1145, 1112, 1077, 1044, 1009, 945, 891, 862, 787, 742, 681; ^{1}H NMR (300 MHz, 32 mg: 0.4 mL $CDCl_3$): δ 2.07 (6H, s, CH_3), δ 7.23 (1H, td, ArH^4, J 2, J 8), δ 7.68 (1H, td, ArH^5, J 2, J 8), δ 8.25 (1H, dd, ArH^3, J 2, J 8), δ 8.73 (1H, dd, ArH^6, J 2, J 8), δ 11.34 (1H, br, s, NH); ^{13}C NMR (75 MHz, 138 mg: 0.4 mL $CDCl_3$): δ 32.2 (s, C-$3_{A/B}$), δ 60.7 (s, C-2), δ 122.1 (s, C-3′), δ 124.0 (s, C-4′), δ 126.1 (s, C-6′), δ 134.7 (s, C-1′), δ 136.1 (s, C-5′), δ 137.0 (s, C-2′), δ 171.3 (s, C-1); GC-(EI) TOF-HRMS: calcd m/z for $C_{10}H_{11}N_2O_3Br$: 285.9953, observed: 285.9949.

***m*-Nitro-α-bromoisobutyranilide (13).** *m*-Nitroaniline (2.90 g, 21.0 mmol) gave 5.83 g (20.4 mmol, 97% yield) of pure *m*-nitro-α-bromoisobutyranilide (**13**) as yellowish shards, m.p. 98–101 °C; R_f = 0.44 in 4 : 1 hexanes/EtOAc, 0.69 in 65 : 35 hexanes/EtOAc and 0.92 in 1 : 1 hexanes/EtOAc; IR(cm^{-1}): 3370, 3090, 2980, 2931, 1694 (C=O), 1590, 1525, 1484, 1418, 1392, 1374, 1349, 1315, 1298, 1243, 1152, 1108, 1079, 1007, 958, 893, 874, 813, 735, 673, 692, 673; ^{1}H NMR (300 MHz, 45 mg: 0.4 mL $CDCl_3$): δ 2.06 (6H, s, CH_3), δ 7.51 (1H, t, ArH^5, J 8), δ 7.90 (1H, dd, ArH^6, J 2, J 8), δ 7.99 (1H, dd, ArH^4, J 2, J 8), δ 8.46 (1H, t, ArH^2, J 2), δ 8.66 (1H, br, s, NH); ^{13}C NMR (75 MHz, 138 mg: 0.4 mL $CDCl_3$): δ 32.4 (s, C-$3_{A/B}$), δ 61.9 (s, C-2), δ 115.2 (s, C-2′), δ 119.6 (s, C-4′), δ 126.1 (s, C-6′), δ 130.0 (s, C-5′), δ 138.8 (s, C-1′), δ 148.7 (s, C-3′), δ 170.8 (s, C-1); GC-(EI) TOF-HRMS: calcd m/z for $C_{10}H_{11}N_2O_3Br$: 285.9953, observed: 285.9963.

***p*-Nitro-α-bromoisobutyranilide (15).** *p*-Nitroaniline (2.90 g, 21.0 mmol) gave 5.35 g (18.7 mmol, 89% yield) of pure *p*-nitro-α-bromoisobutyranilide (**15**) as tiny yellow needles, m.p. 116–120 °C; R_f = 0.40 in 4 : 1 hexanes/EtOAc, 0.67 in 65 : 35 hexanes/EtOAc and 0.93 in 1 : 1 hexanes/EtOAc; IR(cm^{-1}): 3406, 3115, 2929, 2931, 1698 (C=O), 1612, 1596, 1534, 1496, 1404, 1334, 1300, 1243, 1194, 1177, 1142, 1101, 945, 882, 854, 831, 750, 691, 674; ^{1}H NMR (300 MHz, 30 mg: 0.4 mL $CDCl_3$): δ 2.05 (6H, s, CH_3), δ 7.74 (2H, dt, ArH^2, J 2, J 8), δ 8.23 (2H, dt, ArH^3, J 2, J 8), δ 8.72 (1H, br, s, NH); ^{13}C NMR (75 MHz, 122 mg: 0.4 mL $CDCl_3$): δ 32.4 (s, C-$3_{A/B}$), δ 62.1 (s, C-2), δ 119.7 (s, C-2′), δ 125.2 (s, C-3′), δ 143.5 (s, C-1′), δ 144.1 (s, C-4′), δ 170.7 (s, C-1); GC-(EI) TOF-HRMS: calcd m/z for $C_{10}H_{11}N_2O_3Br$: 285.9953, observed: 285.9929.

***o*-Bromo-α-bromoisobutyranilide (17).** *o*-Bromoaniline (3.70 g, 21.5 mmol) gave 6.79 g (21.3 mmol, 99% yield) of pure *o*-bromo-α-bromoisobutyranilide (**17**) as a clear, low-viscosity amber oil; R_f = 0.70 in 4 : 1 hexanes/EtOAc, 0.85 in 65 : 35 hexanes/EtOAc and 0.96 in 1 : 1 hexanes/EtOAc; IR(cm^{-1}): 3352, 2984, 2934, 1685 (C=O), 1588, 1520, 1434, 1300, 1155, 1110, 1025, 939, 745, 683; ^{1}H NMR (300 MHz, 144 mg: 0.4 mL $CDCl_3$): δ 2.06 (6H, s, CH_3), δ 7.01 (1H, td, ArH^4, J 2, J 8), δ 7.33 (1H, td, ArH^5, J 2, J 8), δ 7.56 (1H, dd, ArH^3, J 2, J 8), δ 8.32 (1H, dd, ArH^6, J 2, J 8), δ 9.04 (1H, br, s, NH); ^{13}C NMR (75 MHz, 144 mg: 0.4 mL $CDCl_3$): δ 32.7 (s, C-$3_{A/B}$), δ 62.7 (s, C-2), δ 114.4 (s, C-2′), δ 121.8 (s, C-6′), δ 125.9 (s, C-5′), δ 128.6 (s, C-3′), δ 132.6 (s, C-4′), δ 135.8 (s, C-1′), δ 170.3 (s, C-1); GC-(EI) TOF-HRMS: calcd m/z for $C_{10}H_{11}NOBr_2$: 318.9207, observed: 318.9194.

***o*-Chloro-α-bromoisobutyranilide (19).** *o*-Chloroaniline (2.75 g, 21.6 mmol) gave 5.23 g (18.9 mmol, 88% yield) of pure *o*-chloro-α-bromoisobutyranilide (**19**) as a clear, low-viscosity amber oil; R_f = 0.66 in 4 : 1 hexanes/EtOAc, 0.86 in 65 : 35 hexanes/EtOAc and 0.96 in 1 : 1 hexanes/EtOAc; IR(cm^{-1}): 3365, 2985, 2934, 1686 (C=O), 1593, 1514, 1439, 1304, 1154, 1111, 1054, 1034, 940, 746, 698; ^{1}H NMR (300 MHz, 139 mg: 0.4 mL $CDCl_3$): δ 2.04 (6H, s, CH_3), δ 7.04 (1H, td, ArH^4, J 2, J 8), δ 7.26 (1H, td, ArH^5, J 2, J 8), δ 7.36 (1H, dd, ArH^3, J 2, J 8), δ 8.30 (1H, dd, ArH^6, J 2, J 8), δ 9.04 (1H, br, s, NH); ^{13}C NMR (75 MHz, 139 mg: 0.4 mL $CDCl_3$): δ 32.8 (s, C-$3_{A/B}$), δ 62.9 (s, C-2), δ 121.5 (s, C-6′), δ 124.0 (s, C-2′), δ 125.4 (s, C-5′), δ 128.0 (s, C-3′), δ 129.4 (s, C-4′), δ 134.7 (s, C-1′), δ 170.4 (s, C-1); GC-(EI) TOF-HRMS: calcd m/z for $C_{10}H_{11}NOClBr$: 274.9713, observed: 274.9710.

***m*-Chloro-α-bromoisobutyranilide (21).** *m*-Chloroaniline (2.75 g, 21.6 mmol) gave 5.88 g (21.3 mmol, 99% yield) of pure *m*-chloro-α-bromoisobutyranilide (**21**) as white needles with a slight redness to them, m.p. 91–95 °C; R_f = 0.53 in 4 : 1 hexanes/EtOAc, 0.78 in 65 : 35 hexanes/EtOAc and 0.94 in 1 : 1 hexanes/EtOAc; IR(cm^{-1}): 3291, 2998, 2977, 2931, 1663 (C=O), 1593, 1521, 1424, 1285, 1244, 1162, 1109, 919, 875, 860, 782, 758, 697, 682; ^{1}H NMR (300 MHz, 31 mg: 0.4 mL $CDCl_3$): δ 2.06 (6H, s, CH_3), δ 7.14 (1H, dt, ArH^4, J 2, J 8), δ 7.28 (1H, t, ArH^5, J 8), δ 7.39 (1H, dq, ArH^6, J 2, J 8), δ 7.70 (1H, t, ArH^2, J 2), δ 8.47 (1H, br, s, NH); ^{13}C NMR (75 MHz, 136 mg: 0.4 mL $CDCl_3$): δ 32.8 (s, C-$3_{A/B}$), δ 62.9 (s, C-2), δ 118.5 (s, C-6′), δ 120.5 (s, C-2′), δ 125.3 (s, C-4′), δ 130.3 (s, C-5′), δ 135.1 (s, C-3′), δ 139.0 (s, C-1′), δ 170.6 (s, C-1); GC-(EI) TOF-HRMS: calcd m/z for $C_{10}H_{11}NOClBr$: 274.9713, observed: 274.9686.

***p*-Chloro-α-bromoisobutyranilide (23).** *p*-Chloroaniline (2.75 g, 21.6 mmol) gave 4.45 g (16.1 mmol, 75% yield) of pure *p*-chloro-α-bromoisobutyranilide (**23**) as colourless needles, m.p. 119–121 °C; R_f = 0.52 in 4 : 1 hexanes/EtOAc, 0.78 in 65 : 35

hexanes/EtOAc and 0.91 in 1 : 1 hexanes/EtOAc; IR(cm^{-1}): 3285, 3188, 3122, 3071, 2988, 2941, 2895, 1656 (C=O), 1591, 1552, 1529, 1478, 1459, 1418, 1398, 1372, 1351, 1305, 1287, 1254, 1240, 1187, 1142, 1092, 1074, 999, 962, 914, 904, 888, 864, 854, 792, 704, 683; ^{1}H NMR (300 MHz, 43 mg: 0.4 mL $CDCl_3$): δ 2.04 (6H, s, CH_3), δ 7.30 (2H, dt, ArH^3, *J* 2, *J* 8), δ 7.49 (2H, dt, ArH^2, *J* 2, *J* 8), δ 8.45 (1H, br, s, NH); ^{13}C NMR (75 MHz, 157 mg: 0.4 mL $CDCl_3$): δ 32.6 (s, C-$3_{A/B}$), δ 62.8 (s, C-2), δ 121.7 (s, C-2′), δ 129.3 (s, C-3′), δ 130.1 (s, C-4′), δ 136.2 (s, C-1′), δ 170.3 (s, C-1); GC-(EI) TOF-HRMS: calcd *m*/*z* for $C_{10}H_{11}NOClBr$: 274.9713, observed: 274.9706.

***o*-Chloro-α-bromoisobutyranilide (25).** *o*-Methoxyaniline (2.40 g, 21.6 mmol) gave 4.92 g (18.2 mmol, 84% yield) of pure *o*-chloro-α-bromoisobutyranilide (**25**) as a clear, brown-metallic oil; R_f = 0.60 in 4 : 1 hexanes/EtOAc, 0.81 in 65 : 35 hexanes/EtOAc and 0.93 in 1 : 1 hexanes/EtOAc; IR(cm^{-1}): 3380, 2983, 2936, 2839, 1677 (C=O), 1600, 1522, 1486, 1459, 1433, 1336, 1290, 1250, 1218, 1176, 1157, 1110, 1047, 1026, 940, 773, 744; ^{1}H NMR (300 MHz, 28 mg: 0.4 mL $CDCl_3$): δ 2.06 (6H, s, CH_3), δ 3.92 (3H, s, O–CH_3), δ 6.90 (1H, dd, ArH^3, *J* 2, *J* 8), δ 6.98 (1H, td, ArH^5, *J* 2, *J* 8), δ 7.08 (1H, td, ArH^4, *J* 2, *J* 8), δ 8.33 (1H, dd, ArH^6, *J* 2, *J* 8), δ 9.13 (1H, br, s, NH); ^{13}C NMR (75 MHz, 133 mg: 0.4 mL $CDCl_3$): δ 32.5 (s, C-$3_{A/B}$), δ 56.0 (s, O–CH_3), δ 62.8 (s, C-2), δ 110.2 (s, C-3′), δ 119.5 (s, C-6′), δ 121.0 (s, C-5′), δ 124.4 (s, C-4′), δ 127.4 (s, C-1′), δ 148.5 (s, C-2′), δ 169.9 (s, C-1); GC-(EI) TOF-HRMS: calcd *m*/*z* for $C_{11}H_{14}NO_2Br$: 271.0208, observed: 271.0195.

***m*-Chloro-α-bromoisobutyranilide (27).** *m*-Methoxyaniline (2.40 g, 21.6 mmol) gave 5.44 g (20.1 mmol, 93% yield) of pure *m*-chloro-α-bromoisobutyranilide (**27**) as white needles, m.p. 112–114 °C; R_f = 0.47 in 4 : 1 hexanes/EtOAc, 0.75 in 65 : 35 hexanes/EtOAc and 0.93 in 1 : 1 hexanes/EtOAc; IR(cm^{-1}): 3454, 3340, 3003, 2961, 2942, 2897, 1660 (C=O), 1597, 1546, 1528, 1510, 1462, 1442, 1414, 1375, 1355, 1299, 1232, 1183, 1172, 1141, 1111, 1032, 962, 902, 865, 823, 764; ^{1}H NMR (300 MHz, 31 mg: 0.4 mL $CDCl_3$): δ 2.10 (6H, s, CH_3), δ 3.86 (3H, s, O–CH_3), δ 6.75 (1H, dd, ArH^4, *J* 2, *J* 8), δ 7.05 (1H, dd, ArH^6, *J* 2, *J* 8), δ 7.30 (1H, dd, ArH^5, *J* 2, *J* 8), δ 7.37 (1H, t, ArH^2, *J* 2), δ 8.49 (1H, br, s, NH); ^{13}C NMR (75 MHz, 31 mg: 0.4 mL $CDCl_3$): δ 32.9 (s, C-$3_{A/B}$), δ 55.7 (s, O–CH_3), δ 63.5 (s, C-2), δ 105.8 (s, C-6′), δ 111.3 (s, C-2′), δ 112.4 (s, C-4′), δ 130.1 (s, C-5′), δ 139.0 (s, C-1′), δ 160.6 (s, C-3′), δ 170.3 (s, C-1); GC-(EI) TOF-HRMS: calcd *m*/*z* for $C_{11}H_{14}NO_2Br$: 271.0208, observed: 271.0216.

***p*-Chloro-α-bromoisobutyranilide (29).** *p*-Methoxyaniline (2.40 g, 21.6 mmol) gave 5.80 g (21.4 mmol, 99% yield) of pure *p*-chloro-α-bromoisobutyranilide (**29**) as white needles, m.p. 88–89 °C; R_f = 0.46 in 4 : 1 hexanes/EtOAc, 0.72 in 65 : 35 hexanes/EtOAc and 0.91 in 1 : 1 hexanes/EtOAc; IR(cm^{-1}): 3319, 3007, 2982, 2962, 2841, 1654 (C=O), 1601, 1539, 1508, 1468, 1444, 1412, 1372, 1316, 1300, 1273, 1232, 1223, 1197, 1184, 1164, 1106, 1031, 952, 933, 890, 831, 809, 763, 751, 675; ^{1}H NMR (300 MHz, 25 mg: 0.4 mL $CDCl_3$): δ 2.07 (6H, s, CH_3), δ 3.82 (3H, s, O–CH_3), δ 6.90 (2H, dt, ArH^3, *J* 2, *J* 8), δ 7.45 (2H, dt, ArH^2, *J* 2, *J* 8), δ 8.40 (1H, br, s, NH); ^{13}C NMR (75 MHz, 25 mg: 0.4 mL $CDCl_3$): δ 32.4 (s, C-$3_{A/B}$), δ 55.5 (s, O–CH_3), δ 63.3 (s, C-2), δ 114.6 (s, C-3′), δ 121.8 (s, C-2′), δ 130.5 (s, C-1′), δ 156.8 (s, C-4′), δ 169.9 (s, C-1); GC-(EI) TOF-HRMS: calcd *m*/*z* for $C_{11}H_{14}NO_2Br$: 271.0208, observed: 271.0197.

***N*-Benzyl-α-bromoisobutyramide (31).** Benzylamine (2.30 g, 21.5 mmol) gave 4.33 g (17.0 mmol, 79% yield) of pure *N*-benzyl-α-bromoisobutyramide (**31**) as a fine white powder, m.p. 77–80 °C; R_f = 0.38 in 4 : 1 hexanes/EtOAc, 0.64 in 65 : 35 hexanes/EtOAc and 0.90 in 1 : 1 hexanes/EtOAc; IR(cm^{-1}): 3300, 3065, 3030, 2973, 2939, 2920, 1642 (C=O), 1533, 1495, 1471, 1453, 1418, 1355, 1292, 1195, 1102, 1081, 1014, 922, 826, 752, 729, 699, 693; ^{1}H NMR (300 MHz, 23 mg: 0.4 mL $CDCl_3$): δ 1.99 (6H, s, CH_3), δ 4.47 (2H, d, CH_2 *J* 8), δ 7.02 (1H, br, s, NH), δ 7.30 (2H, m, ArH^2), δ 7.34 (2H, m, ArH^3), δ 7.36 (1H, m, ArH^4); ^{13}C NMR (75 MHz, 125 mg: 0.4 mL $CDCl_3$): δ 32.7 (s, C-$3_{A/B}$), δ 44.5 (s, CH_2), δ 62.9 (s, C-2), δ 127.7 (s, C-2′), δ 127.8 (s, C-4′), δ 129.0 (s, C-3′), δ 138.0 (s, C-1′), δ 172.2 (s, C-1); GC-(EI) TOF-HRMS: calcd *m*/*z* for $C_{11}H_{14}NOBr$: 255.0259, observed: 255.0265.

α-Bromo-*N*-butylisobutyramide (33). *n*-Butylamine (1.60 g, 21.9 mmol) gave 3.05 g (13.8 mmol, 63% yield) of pure α-bromo-*N*-butylisobutyramide (**33**) as a clear, pale yellow, low-viscosity oil; IR(cm^{-1}): 3348, 2959, 2932, 2873, 1649 (C=O), 1528, 1465, 1437, 1370, 1301, 1282, 1225, 1190, 1112, 738; ^{1}H NMR (300 MHz, 26 mg: 0.4 mL $CDCl_3$): δ 0.96 (3H, t, $alkyl^4$ *J* 8), δ 1.38 (2H, sextet, $alkyl^3$ *J* 8), δ 1.54 (2H, sextet, $alkyl^2$ *J* 8), δ 1.97 (6H, s, CH_3), δ 3.28 (2H, sextet, $alkyl^1$ *J* 8), δ 6.73 (1H, br, s, NH); ^{13}C NMR (75 MHz, 147 mg: 0.4 mL $CDCl_3$): δ 13.9 (s, C-4′), δ 20.2 (s, C-3′), δ 31.5 (s, C-2′), δ 32.8 (s, C-$3_{A/B}$), δ 40.3 (s, C-1′), δ 63.3 (s, C-2), δ 172.0 (s, C-1); GC-(EI) TOF-HRMS: calcd *m*/*z* for $C_8H_{16}NOBr$: 221.0415, observed: 221.0417.

Substitution reactions

Unless otherwise stated, reactions were carried out at room temperature using ~5 mmol (1–2 g) of the reactant bromo compound (1–2 g) with $NaNO_2$ (4.00 g, 44.9 mmol) in DMF (40 mL) and a magnetic stirrer at 700 rpm.

The rates were monitored by periodically removing 1 mL of the reacting mixture, placing it in dichloromethane (2 mL) and washing with water (4 × 3 mL) in a 5 mL screw cap vial. The dichloromethane layer was then dried ($MgSO_4$) and analysed by GC-MS.

The time between each aliquot was determined for each reaction by trial in an initial rough experiment.

For preparative reactions, apart from the preparation of **2**, which could be obtained by addition of water to the DMF reaction mixture, the substitutions were worked up on completion by the removal of DMF on a rotary evaporator with water bath at 70 °C and vacuum rigorously kept at 25 Torr, with Dow Corning high vacuum grease freshly applied to the joins and Keck clips used to hold the flask onto a non-reversible splash-guard. The residue was partitioned between water and ethyl acetate and the ethyl acetate fraction was evaporated. After TLC of the residue to determine a suitable eluent, the product was purified by column chromatography (40 mm diameter) on 43–60 μ silica (~150 g) with pre-adsorption on ~10 g of silica. This method typically produced 800–1300 mg of highly pure nitro substitution product as observed by NMR.

***p*-Cyano-*m*-trifluoromethyl-α-nitroisobutyranilide (2). 1** (*p*-Cyano-*m*-trifluoromethyl-α-bromoisobutyranilide) (1.68 g, 5.03 mmol) was added to $NaNO_2$ and DMF. The reaction was worked

up by addition of 20 mL of deionized water which caused the product to begin to precipitate. The flask was placed in a crystal fridge at 8 °C overnight and then the crystals collected by Büchner funnel filtration to give 1.88 g of intensely white needles 2 to 10 mm in length. These were found to be *p*-cyano-*m*-trifluoromethyl-α-nitroisobutyranilide (**2**) which was co-crystallized in a 1 : 1 ratio with DMF (86% yield when corrected for the DMF), m.p. 129–131 °C. A DMF free version of **2** could be prepared by repeated liquid/liquid extraction using water/ethyl acetate which provides a white amorphous powder of the same m.p. Characterization data for **2** are provided in our 2014 publication[10] where it is given the correct IUPAC name of "*N*-[4-cyano-3-(trifluoromethyl)phenyl]-2-methyl-2-nitropropanamide".

α-Nitroisobutyranilide (6). **5** (α-Bromoisobutyranilide) (1.20 g, 4.98 mmol) gave 870 mg (4.18 mmol, 84% yield) of pure α-nitroisobutyranilide (**6**) as an extremely shiny crystalline powder with a hint of orange, m.p. 104–107 °C; R_f = 0.32 in 4 : 1 hexanes/EtOAc, 0.56 in 65 : 35 hexanes/EtOAc and 0.87 in 1 : 1 hexanes/EtOAc; IR(cm^{-1}): 3256, 3199, 3136, 3076, 1655 (C=O), 1598, 1549, 1538, 1492, 1459, 1440, 1399, 1373, 1352, 1321, 1266, 1233, 1189, 1143, 963, 894, 859, 752, 695, 666; ^{1}H NMR (300 MHz, 26 mg: 0.4 mL $CDCl_3$): δ 1.94 (6H, s, CH_3), δ 7.17 (1H, tt, ArH^4, *J* 2, *J* 8), δ 7.34 (2H, tt, ArH^3, *J* 2, *J* 8), δ 7.48 (2H, dt, ArH^2, *J* 2, *J* 8), δ 7.98 (1H, br, s, NH); ^{13}C NMR (75 MHz, 26 mg: 0.4 mL $CDCl_3$): δ 24.9 (s, C-$3_{A/B}$), δ 91.6 (s, C-2), δ 120.8 (s, C-2′), δ 125.8 (s, C-4′), δ 129.5 (s, C-3′), δ 136.8 (s, C-1′), δ 164.7 (s, C-1); GC-(EI) TOF-HRMS: calcd *m*/*z* for $C_{10}H_{12}N_2O_3$: 208.0848, observed: 208.0846.

***p*-Methyl-α-nitroisobutyranilide (8).** **7** (*p*-Methyl-α-bromoisobutyranilide) (1.28 g, 5.02 mmol) gave 970 mg (4.37 mmol, 87% yield) of pure *p*-methyl-α-nitroisobutyranilide (**8**) as orange shards of various morphology, m.p. 115–118 °C; R_f = 0.38 in 4 : 1 hexanes/EtOAc, 0.61 in 65 : 35 hexanes/EtOAc and 0.87 in 1 : 1 hexanes/EtOAc; IR(cm^{-1}): 3274, 3120, 3042, 2993, 2924, 2893, 2860, 1660 (C=O), 1594, 1550, 1522, 1513, 1460, 1436, 1401, 1372, 1355, 1318, 1295, 1259, 1234, 1187, 1179, 1141, 961, 900, 862, 815, 770, 738, 678; ^{1}H NMR (300 MHz, 21 mg: 0.4 mL $CDCl_3$): δ 1.93 (6H, s, CH_3), δ 2.32 (3H, s, $ArCH_3$), δ 7.13 (2H, d, ArH^3, *J* 8), δ 7.35 (2H, d, ArH^2, *J* 8), δ 7.91 (1H, br, s, NH); ^{13}C NMR (75 MHz, 42 mg: 0.4 mL $CDCl_3$): δ 21.3 (s, $ArCH_3$), δ 24.9 (s, C-$3_{A/B}$), δ 91.6 (s, C-2), δ 121.1 (s, C-2′), δ 129.9 (s, C-3′), δ 134.3 (s, C-1′), δ 135.5 (s, C-4′), δ 164.9 (s, C-1); GC-(EI) TOF-HRMS: calcd *m*/*z* for $C_{11}H_{14}N_2O_3$: 222.1004, observed: 222.1006.

***o*-Carboethoxy-α-nitroisobutyranilide (10).** **9** (*o*-Carboethoxy-α-bromoisobutyranilide) (1.56 g, 5.00 mmol) gave 1381 mg (4.95 mmol, 99% yield) of pure *o*-carboethoxy-α-nitroisobutyranilide (**10**) as white, amorphous powder, m.p. 84–87 °C; R_f = 0.43 in 4 : 1 hexanes/EtOAc, 0.69 in 65 : 35 hexanes/EtOAc and 0.93 in 1 : 1 hexanes/EtOAc; IR(cm^{-1}): 3177, 3120, 3082, 2991, 1699 (C=O), 1685 (C=O), 1608, 1594, 1551, 1529, 1466, 1455, 1366, 1351, 1303, 1277, 1251, 1238, 1182, 1139, 1090, 1016, 857, 763, 700; ^{1}H NMR (300 MHz, 25 mg: 0.4 mL $CDCl_3$): δ 1.42 (3H, t, ethyl CH_3), δ 1.98 (6H, s, CH_3), δ 4.41 (2H, q, ethyl CH_2), δ 7.16 (1H, td, ArH^4, *J* 2, *J* 8), δ 7.57 (1H, td, ArH^5, *J* 2, *J* 8), δ 8.08 (1H, dd, ArH^6, *J* 2, *J* 8), δ 8.66 (1H, dd, ArH^3, *J* 2, *J* 8), δ 11.81 (1H, br, s, NH); ^{13}C NMR (75 MHz, 68 mg: 0.4 mL $CDCl_3$/0.1 mL d_6-DMSO): δ 14.9 (s, ethyl CH_3), δ 24.3 (s, C-$3_{A/B}$), δ 62.5 (s, ethyl CH_2), δ 92.3 (s, C-2), δ 118.9 (s, C-2′), δ 122.0 (s, C-6′), δ 125.2 (s, C-4′), δ 131.6 (s, C-3′), δ 135.1 (s, C-5′), δ 139.8 (s, C-1′), δ 166.5 (s, C-1), δ 168.2 (s, ester C=O); GC-(EI) TOF-HRMS: calcd *m*/*z* for $C_{13}H_{15}N_2O_5$: 279.0981, observed: 279.0972.

***o*-Nitro-α-nitroisobutyranilide (12).** **11** (*o*-Nitro-α-bromoisobutyranilide) (1.36 g, 4.74 mmol) gave 1000 mg (3.95 mmol, 83% yield) of pure *o*-nitro-α-nitroisobutyranilide (**12**) as a deep yellow, cauliflower-shaped crystalline nuggets, m.p. 82–84 °C; R_f = 0.38 in 4 : 1 hexanes/EtOAc, 0.70 in 65 : 35 hexanes/EtOAc and 0.90 in 1 : 1 hexanes/EtOAc; IR(cm^{-1}): 3392, 2924, 2854, 1706 (C=O), 1607, 1588, 1548, 1497, 1454, 1431, 1396, 1374, 1335, 1270, 1224, 1161, 1140, 1075, 898, 861, 854, 789, 742, 688; ^{1}H NMR (300 MHz, 18 mg: 0.4 mL $CDCl_3$): δ 2.00 (6H, s, CH_3), δ 7.28 (1H, td, ArH^4, *J* 2, *J* 8), δ 7.70 (1H, tt, ArH^5, *J* 2, *J* 8), δ 8.27 (1H, dd, ArH^3, *J* 2, *J* 8), δ 8.71 (1H, dd, ArH^6, *J* 2, *J* 8), δ 11.09 (1H, br, s, NH); ^{13}C NMR (75 MHz, 18 mg: 0.4 mL $CDCl_3$): δ 24.6 (s, C-$3_{A/B}$), δ 91.6 (s, C-2), δ 122.7 (s, C-3′), δ 124.9 (s, C-4′), δ 126.3 (s, C-6′), δ 134.1 (s, C-1′), δ 136.5 (s, C-5′), δ 137.2 (s, C-2′), δ 165.9 (s, C-1); GC-(EI) TOF-HRMS: calcd *m*/*z* for $C_{10}H_{11}N_3O_5$: 253.0699, observed: 253.0705.

***m*-Nitro-α-nitroisobutyranilide (14).** **13** (*m*-Nitro-α-bromoisobutyranilide) (1.43 g, 4.74 mmol) gave 1028 mg (4.06 mmol, 86% yield) of pure *m*-nitro-α-nitroisobutyranilide (**14**) as a pale yellow, clean looking crystalline powder, m.p. 135–136 °C; R_f = 0.27 in 4 : 1 hexanes/EtOAc, 0.57 in 65 : 35 hexanes/EtOAc and 0.84 in 1 : 1 hexanes/EtOAc; IR(cm^{-1}): 3347, 3093, 2923, 2854, 1659 (C=O), 1617, 1553, 1532, 1458, 1434, 1401, 1373, 1350, 1317, 1287, 1262, 1234, 1192, 1145, 1089, 1079, 970, 909, 882, 856, 824, 809, 734, 693, 671; ^{1}H NMR (300 MHz, 50 mg: 0.4 mL d_6-DMSO): δ 1.93 (6H, s, CH_3), δ 7.67 (1H, t, ArH^5, *J* 8), δ 8.01 (1H, dd, ArH^6, *J* 2, *J* 8), δ 8.07 (1H, dd, ArH^4, *J* 2, *J* 8), δ 8.61 (1H, t, ArH^6, *J* 2), δ 10.40 (1H, br, s, NH); ^{13}C NMR (75 MHz, 50 mg: 0.4 mL d_6-DMSO): δ 24.6 (s, C-$3_{A/B}$), δ 92.5 (s, C-2), δ 115.7 (s, C-2′), δ 119.8 (s, C-4′), δ 127.4 (s, C-6′), δ 131.3 (s, C-5′), δ 140.2 (s, C-1′), δ 148.8 (s, C-3′), δ 167.5 (s, C-1); GC-(EI) TOF-HRMS: calcd *m*/*z* for $C_{10}H_{11}N_3O_5$: 253.0699, observed: 253.0694.

***p*-Nitro-α-nitroisobutyranilide (16).** **15** (*p*-Nitro-α-bromoisobutyranilide) (1.43 g, 4.74 mmol) gave 980 mg (3.87 mmol, 82% yield) of pure *p*-nitro-α-nitroisobutyranilide (**16**) as a fine, white fluffy powder, m.p. 138–140 °C; R_f = 0.19 in 4 : 1 hexanes/EtOAc, 0.45 in 65 : 35 hexanes/EtOAc and 0.87 in 1 : 1 hexanes/EtOAc; IR(cm^{-1}): 3352, 1709 (C=O), 1615, 1597, 1547, 1506, 1464, 1409, 1400, 1374, 1346, 1307, 1249, 1221, 1181, 1160, 1142, 1115, 898, 848, 829, 816, 752, 691; ^{1}H NMR (300 MHz, 27 mg: 0.4 mL d_6-DMSO): δ 1.94 (6H, s, CH_3), δ 7.94 (2H, dt, ArH^2, *J* 2, *J* 8), δ 8.29 (2H, dt, ArH^3, *J* 2, *J* 8), δ 10.50 (1H, br, s, NH); ^{13}C NMR (75 MHz, 27 mg: 0.4 mL d_6-DMSO): δ 24.5 (s, C-$3_{A/B}$), δ 92.5 (s, C-2), δ 121.2 (s, C-2′), δ 125.7 (s, C-3′), δ 144.0 (s, C-4′), δ 145.1 (s, C-1′), δ 167.4 (s, C-1); GC-(EI) TOF-HRMS: calcd *m*/*z* for $C_{10}H_{11}N_3O_5$: 253.0699, observed: 253.0702.

***o*-Bromo-α-nitroisobutyranilide (18).** **17** (*o*-Bromo-α-bromoisobutyranilide) (1.61 g, 5.02 mmol) gave 1082 mg (3.77 mmol, 75% yield) of pure *o*-bromo-α-nitroisobutyranilide (**18**) as an amber oil; R_f = 0.48 in 4 : 1 hexanes/EtOAc, 0.69 in 65 : 35 hexanes/EtOAc and 0.91 in 1 : 1 hexanes/EtOAc; IR(cm^{-1}): 3398, 3339, 2997, 2925, 1699 (C=O), 1590, 1548, 1519, 1464, 1436, 1398, 1373, 1346, 1299, 1237, 1207, 1167, 1143, 1121, 1047,

1026, 896, 855, 750; ^{1}H NMR (300 MHz, 26 mg: 0.4 mL $CDCl_3$): δ 1.98 (6H, s, CH_3), δ 7.04 (1H, td, ArH^4, J 2, J 8), δ 7.34 (1H, td, ArH^5, J 2, J 8), δ 7.56 (1H, dd, ArH^3, J 2, J 8), δ 8.24 (1H, dd, ArH^6, J 2, J 8), δ 8.52 (1H, br, s, NH); ^{13}C NMR (75 MHz, 66 mg: 0.4 mL $CDCl_3$): δ 24.9 (s, C-3$_{A/B}$), δ 91.4 (s, C-2), δ 114.8 (s, C-2′), δ 122.6 (s, C-6′), δ 126.8 (s, C-5′), δ 128.9 (s, C-3′), δ 132.8 (s, C-4′), δ 134.9 (s, C-1′), δ 164.9 (s, C-1); GC-(EI) TOF-HRMS: calcd m/z for $C_{10}H_{11}N_2O_3Br$: 285.9953, observed: 285.9961.

***o*-Chloro-α-nitroisobutyranilide (20).** **19** (*o*-Chloro-α-bromoisobutyranilide) (1.38 g, 4.99 mmol) gave 955 mg (3.94 mmol, 79% yield) of pure *o*-chloro-α-nitroisobutyranilide (**20**) as an amber oil; R_f = 0.43 in 4 : 1 hexanes/EtOAc, 0.70 in 65 : 35 hexanes/EtOAc and 0.90 in 1 : 1 hexanes/EtOAc; IR(cm^{-1}): 3352, 2998, 2922, 2852, 1697 (C=O), 1594, 1549, 1518, 1467, 1441, 1398, 1373, 1347, 1302, 1238, 1168, 1144, 1128, 1055, 1035, 897, 856, 751, 690; ^{1}H NMR (300 MHz, 21 mg: 0.4 mL $CDCl_3$): δ 1.97 (6H, s, CH_3), δ 7.11 (1H, td, ArH^4, J 2, J 8), δ 7.30 (1H, td, ArH^5, J 2, J 8), δ 7.40 (1H, dd, ArH^3, J 2, J 8), δ 8.26 (1H, dd, ArH^6, J 2, J 8), δ 8.58 (1H, br, s, NH); ^{13}C NMR (75 MHz, 39 mg: 0.4 mL $CDCl_3$): δ 24.9 (s, C-3$_{A/B}$), δ 91.5 (s, C-2), δ 122.2 (s, C-6′), δ 124.2 (s, C-2′), δ 126.2 (s, C-5′), δ 128.2 (s, C-3′), δ 129.5 (s, C-4′), δ 133.8 (s, C-1′), δ 164.7 (s, C-1); GC-(EI) TOF-HRMS: calcd m/z for $C_{10}H_{11}N_2O_3Cl$: 242.0458, observed: 242.0462.

***m*-Chloro-α-nitroisobutyranilide (22).** **21** (*m*-Chloro-α-bromoisobutyranilide) (1.38 g, 4.99 mmol) gave 1135 mg (4.68 mmol, 94% yield) of pure *m*-chloro-α-nitroisobutyranilide (**22**) as a light orange crystalline mass with multiple nucleation points, m.p. 125–128 °C; R_f = 0.47 in 4 : 1 hexanes/EtOAc, 0.72 in 65 : 35 hexanes/EtOAc and 0.89 in 1 : 1 hexanes/EtOAc; IR(cm^{-1}): 3385, 3188, 3122, 3071, 2988, 2941, 2895, 1656 (C=O), 1590, 1552, 1528, 1478, 1459, 1418, 1398, 1372, 1351, 1304, 1287, 1254, 1240, 1231, 1187, 1142, 1092, 1074, 999, 914, 904, 888, 854, 791, 704, 682; ^{1}H NMR (300 MHz, 18 mg: 0.4 mL $CDCl_3$): δ 1.82 (6H, s, CH_3), δ 6.99 (1H, d, ArH^4, J 8), δ 7.14 (1H, td, ArH^5, J 2, J 8), δ 7.43 (1H, d, ArH^6, J 8), δ 7.64 (1H, m, ArH^2), δ 9.38 (1H, br, s, NH); ^{13}C NMR (75 MHz, 18 mg: 0.4 mL $CDCl_3$/2 drops d_6-DMSO): δ 24.7 (s, C-3$_{A/B}$), δ 91.2 (s, C-2), δ 118.9 (s, C-6′), δ 121.0 (s, C-2′), δ 124.7 (s, C-4′), δ 129.8 (s, C-5′), δ 134.2 (s, C-3′), δ 139.3 (s, C-1′), δ 165.8 (s, C-1); GC-(EI) TOF-HRMS: calcd m/z for $C_{10}H_{11}N_2O_3Cl$: 242.0458, observed: 242.0475.

***p*-Chloro-α-nitroisobutyranilide (24).** **23** (*p*-Chloro-α-bromoisobutyranilide) (1.38 g, 4.99 mmol) gave 1070 mg (4.41 mmol, 88% yield) of pure *p*-chloro-α-nitroisobutyranilide (**24**) as a pale yellow, clean looking crystalline powder, m.p. 124–127 °C; R_f = 0.38 in 4 : 1 hexanes/EtOAc, 0.67 in 65 : 35 hexanes/EtOAc and 0.90 in 1 : 1 hexanes/EtOAc; IR(cm^{-1}): 3303, 3195, 3126, 3057, 3002, 2924, 2854, 1664 (C=O), 1599, 1547, 1533, 1492, 1460, 1400, 1379, 1353, 1308, 1287, 1241, 1188, 1145, 1087, 1014, 960, 904, 864, 820, 747, 708, 695, 667; ^{1}H NMR (300 MHz, 21 mg: 0.4 mL $CDCl_3$): δ 1.94 (6H, s, CH_3), δ 7.30 (2H, d, ArH^3, J 8), δ 7.44 (2H, d, ArH^2, J 8), δ 8.01 (1H, br, s, NH); ^{13}C NMR (75 MHz, 21 mg: 0.4 mL $CDCl_3$): δ 25.0 (s, C-3$_{A/B}$), δ 91.7 (s, C-2), δ 122.3 (s, C-2′), δ 129.5 (s, C-3′), δ 131.0 (s, C-4′), δ 135.5 (s, C-1′), δ 164.8 (s, C-1); GC-(EI) TOF-HRMS: calcd m/z for $C_{10}H_{11}N_2O_3Cl$: 242.0458, observed: 242.0477.

***o*-Methoxy-α-nitroisobutyranilide (26).** **25** (*o*-Methoxy-α-bromoisobutyranilide) (1.40 g, 5.15 mmol) gave 868 mg (3.65 mmol, 71% yield) of pure *o*-methoxy-α-nitroisobutyranilide (**26**) as tiny, pretty, orange prisms or various morphology, m.p. 67–70 °C; R_f = 0.40 in 4 : 1 hexanes/EtOAc, 0.65 in 65 : 35 hexanes/EtOAc and 0.89 in 1 : 1 hexanes/EtOAc; IR(cm^{-1}): 3331, 3043, 3005, 2964, 2936, 2901, 2838, 1675 (C=O), 1594, 1553, 1521, 1493, 1460, 1432, 1403, 1375, 1357, 1322, 1287, 1262, 1220, 1177, 1142, 1112, 1042, 1025, 963, 899, 862, 849, 780, 748, 739, 724, 666; ^{1}H NMR (300 MHz, 19 mg: 0.4 mL $CDCl_3$): δ 1.95 (6H, s, CH_3), δ 3.91 (3H, s, O–CH_3), δ 6.90 (1H, dd, ArH^3, J 2, J 8), δ 6.97 (1H, td, ArH^5, J 2, J 8), δ 7.10 (1H, td, ArH^4, J 2, J 8), δ 8.28 (1H, dd, ArH^6, J 2, J 8), δ 8.62 (1H, br, s, NH); ^{13}C NMR (75 MHz, 57 mg: 0.4 mL $CDCl_3$): δ 24.9 (s, C-3$_{A/B}$), δ 56.2 (s, O–CH_3), δ 91.6 (s, C-2), δ 110.4 (s, C-3′), δ 120.3 (s, C-6′), δ 121.4 (s, C-5′), δ 125.3 (s, C-4′), δ 126.9 (s, C-1′), δ 148.7 (s, C-2′), δ 164.4 (s, C-1); GC-(EI) TOF-HRMS: calcd m/z for $C_{11}H_{14}N_2O_4$: 238.0954, observed: 238.0952.

***m*-Methoxy-α-nitroisobutyranilide (28).** **27** (*m*-Methoxy-α-bromoisobutyranilide) (1.40 g, 5.15 mmol) gave 981 mg (4.12 mmol, 80% yield) of pure *m*-methoxy-α-nitroisobutyranilide (**28**) as a crystalline mass of orange tipped needles, m.p. 97–99 °C; R_f = 0.29 in 4 : 1 hexanes/EtOAc, 0.55 in 65 : 35 hexanes/EtOAc and 0.85 in 1 : 1 hexanes/EtOAc; IR(cm^{-1}): 3276, 3223, 3154, 3007, 2943, 2838, 1665 (C=O), 1614, 1597, 1539, 1489, 1451, 1427, 1397, 1373, 1344, 1320, 1301, 1277, 1267, 1208, 1182, 1149, 1031, 953, 844, 788, 764, 749, 727, 686; ^{1}H NMR (300 MHz, 28 mg: 0.4 mL $CDCl_3$): δ 1.93 (6H, s, CH_3), δ 3.80 (3H, s, O–CH_3), δ 6.72 (1H, dd, ArH^4, J 2, J 8), δ 6.96 (1H, dd, ArH^6, J 2, J 8), δ 7.22 (1H, t, ArH^5, J 8), δ 7.26 (1H, d, ArH^2, J 2), δ 7.98 (1H, br, s, NH); ^{13}C NMR (75 MHz, 120 mg: 0.4 mL $CDCl_3$): δ 24.6 (s, C-3$_{A/B}$), δ 55.5 (s, O–CH_3), δ 91.5 (s, C-2), δ 106.8 (s, C-6′), δ 111.6 (s, C-2′), δ 113.2 (s, C-4′), δ 130.0 (s, C-5′), δ 138.0 (s, C-1′), δ 160.4 (s, C-3′), δ 165.2 (s, C-1); GC-(EI) TOF-HRMS: calcd m/z for $C_{11}H_{14}N_2O_4$: 238.0954, observed: 238.0954.

***p*-Methoxy-α-nitroisobutyranilide (30).** **29** (*p*-Methoxy-α-bromoisobutyranilide) (1.40 g, 5.15 mmol) gave 1078 mg (4.53 mmol, 77% yield) of pure *p*-methoxy-α-nitroisobutyranilide (**30**) as tiny, pretty, pale yellow needles, m.p. 69–71 °C; R_f = 0.16 in 4 : 1 hexanes/EtOAc, 0.48 in 65 : 35 hexanes/EtOAc and 0.80 in 1 : 1 hexanes/EtOAc; IR(cm^{-1}): 3346, 3003, 2961, 2939, 2898, 2840, 1660 (C=O), 1597, 1545, 1530, 1510, 1462, 1440, 1414, 1403, 1375, 1356, 1311, 1299, 1268, 1232, 1184, 1173, 1141, 1112, 1031, 962, 901, 863, 850, 824, 764; ^{1}H NMR (300 MHz, 28 mg: 0.4 mL $CDCl_3$): δ 1.92 (6H, s, CH_3), δ 3.79 (3H, s, O–CH_3), δ 6.86 (2H, d, ArH^3, J 8), δ 7.37 (2H, d, ArH^2, J 8), δ 7.87 (1H, br, s, NH); ^{13}C NMR (75 MHz, 120 mg: 0.4 mL $CDCl_3$): δ 24.9 (s, C-3$_{A/B}$), δ 55.8 (s, O–CH_3), δ 91.5 (s, C-2), δ 114.5 (s, C-3′), δ 122.9 (s, C-2′), δ 129.8 (s, C-1′), δ 157.5 (s, C-4′), δ 164.9 (s, C-1); GC-(EI) TOF-HRMS: calcd m/z for $C_{11}H_{14}N_2O_4$: 238.0954, observed: 238.0971.

***N*-Benzyl-α-nitroisobutyramide (32).** **31** (*N*-Benzyl-α-bromoisobutyramide) (1.40 g, 5.47 mmol) was added to $NaNO_2$ and DMF and the reaction heated at 120 °C for 4 h. After cooling the standard workup method gave 952 mg (4.29 mmol, 78% yield) of pure *N*-benzyl-α-nitroisobutyramide (**32**) as white, crystalline, cauliflower-shaped nodules, m.p. 87–88 °C; R_f = 0.23 in 4 : 1 hexanes/EtOAc, 0.49 in 65 : 35 hexanes/EtOAc and 0.76 in 1 : 1 hexanes/EtOAc; IR(cm^{-1}): 3295, 3088, 3028, 3003, 2930, 1652 (C=O), 1547, 1496, 1453, 1427, 1405, 1374, 1356, 1312, 1288,

1236, 1209, 1162, 1077, 1055, 1029, 1000, 865, 747, 732, 698, 671; ^{1}H NMR (300 MHz, 19 mg: 0.4 mL $CDCl_3$): δ 1.85 (6H, s, CH_3), δ 4.45 (2H, d, CH_2 J 8), δ 6.46 (1H, br, s, NH), δ 7.22–7.37 (5H, m, ArH^{2-6}); ^{13}C NMR (75 MHz, 55 mg: 0.4 mL $CDCl_3$): δ 24.8 (s, C-$3_{A/B}$), δ 44.4 (s, CH_2), δ 91.0 (s, C-2), δ 127.8 (s, C-2′), δ 128.1 (s, C-4′), δ 129.1 (s, C-3′), δ 137.5 (s, C-1′), δ 167.2 (s, C-1); GC-(EI) TOF-HRMS: calcd m/z for $C_{11}H_{14}N_2O_3$: 222.1004, observed: 222.1001.

***N*-Butyl-α-nitroisobutyramide (34).** **33** (*N*-Butyl-α-nitroisobutyramide) (1.30 g, 5.86 mmol) was added to $NaNO_2$ and DMF and the reaction heated at 120 °C for 4 h. After cooling the standard workup method gave 653 mg (3.47 mmol, 59% yield) of pure *N*-butyl-α-nitroisobutyramide (**34**) as orange, translucent, shard-shaped crystals, m.p. 61–64 °C; IR(cm^{-1}): 3322, 3085, 2957, 2934, 2874, 1654 (C=O), 1620, 1542, 1465, 1440, 1403, 1374, 1355, 1301, 1287, 1205, 1157, 867; ^{1}H NMR (300 MHz, 21 mg: 0.4 mL $CDCl_3$): δ 0.92 (3H, t, $alkyl^4$ J 8), δ 1.32 (2H, sextet, $alkyl^3$ J 8), δ 1.49 (2H, sextet, $alkyl^2$ J 8), δ 1.83 (6H, s, CH_3), δ 3.27 (2H, sextet, $alkyl^1$ J 8), δ 6.15 (1H, br, s, NH); ^{13}C NMR (75 MHz, 21 mg: 0.4 mL $CDCl_3$): δ 14.0 (s, C-4′), δ 20.2 (s, C-3′), δ 24.9 (s, C-$3_{A/B}$), δ 31.5 (s, C-2′), δ 40.3 (s, C-1′), δ 91.1 (s, C-2), δ 167.0 (s, C-1); GC-(EI) TOF-HRMS: calcd m/z for $C_8H_{16}N_2O_3$: 188.1161, observed: 188.1173.

Br–NO_2 substitution in the absence of O_2. Preparation of *p*-cyano-*m*-trifluoromethyl-α-nitroisobutyranilide (**2**) was carried out using two 100 mL Schlenk flasks. Into one flask was placed 1.68 g of *p*-cyano-*m*-trifluoromethyl-α-bromoisobutyranilide (**1**) and into the other was placed 4.00 g of $NaNO_2$. 20 mL of DMF was added to each flask which was then sealed with a rubber septum and placed under positive pressure of nitrogen. Nitrogen from the top of a liquid nitrogen tank was passed through a Dreschel bottle containing a solution of 5 g pyrogallol in 100 g KOH/100 mL water[107] and bubbled through both flasks for 30 min in order to displace any dissolved oxygen. The contents of the flask containing the dissolved compound (**1**) were then transferred to the flask containing the $NaNO_2$ using a 20 mL glass syringe under positive pressure of nitrogen. The reaction was monitored periodically by GC-MS and was seen to follow the same rate as that observed when the reaction was done under air.

Br–NO_2 substitution at low nitrite concentration. Preparation of *p*-cyano-*m*-trifluoromethyl-α-nitroisobutyranilide (**2**) was carried out in tandem in three 100 mL flasks of the same shape and all using the same shape magnetic stirrer, stirred at 700 rpm. The flasks were in the same room, on the same bench and the reaction started at the same time. The only difference was in the amount of sodium nitrite used. Each reaction used 35 mL of DMF which was taken from the same bottle immediately before use. As it was measured that at room temperature, 50 mL of DMF was required to dissolve 205 mg of $NaNO_2$, the saturated reaction used 144 mg of $NaNO_2$, the 75% and 50% saturation reactions used 108 mg and 72 mg respectively. As the 50% nitrite concentration contained 1.04 mmol of $NaNO_2$ and as an excess of nitrite in 4 : 1 or greater ratio was desired, 84 mg (0.025 mmol) of **1** was used in all three reactions. The reactions were monitored by GC-MS using the same extraction method and instrument as had been used to monitor the other substitution reactions. Aliquots were taken at ~1 h intervals to obtain five data points for each reaction; all fifteen GC-MS sample vials were run on the same GC-MS on the same day.

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